

expressed on T cells (such as CTLA-4 and PD-1) have demonstrated clinical activity across a variety of tumor types (Naidoo-et al., (2014) *British Journal of Cancer* 111, 2214–2219).

[0020] Cancer immune-therapy targeting tumor-associated macrophages (*e.g.*, M2-type macrophages) is an intense area of research. The presence of M2-macrophages in tumors is associated with poor prognosis.

[0021] Accordingly, there is also a need for antibodies that specifically bind TREM2 on a cell surface and modulate (*e.g.*, inhibit and/or otherwise reduce) ligand binding and/or one or more TREM2 activities in order to prevent, reduce the risk of, or treat cancer.

[0022] All references cited herein, including patent applications and publications, are hereby incorporated by reference in their entirety.

#### SUMMARY ~~OF THE PRESENT DISCLOSURE~~

[0023] The present disclosure is generally directed to compositions that include antibodies, *e.g.*, monoclonal, chimeric, humanized antibodies, antibody fragments, *etc.*, that specifically bind a TREM2 protein, *e.g.*, a mammalian TREM2 (*e.g.*, any non-human mammal) or human TREM2, and to methods of using such compositions. The antibodies of the present disclosure may include agonist, antagonist, or inert antibodies. The methods provided herein find use in preventing, reducing risk, or treating an individual having dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy 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, solid and blood cancer, 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 sclerosis, myeloid-derived tumors, tumors that express TREM2 and/or TREM2 ligands, 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. 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 antibody that binds to a 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 a control antibody.

**[0024]** In some **embodimentexamples**, 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 **embodimentexamples**, 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 **aspectexamples** 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 **embodimentexamples**, 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 **embodimentexamples**, 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 **embodimentexamples**, 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 **embodimentexamples**, the agonist antibodies may have increased safety and efficacy. In some **embodimentexamples**, 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 **embodimentexamples**, 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 **embodimentexamples**, the antagonist antibodies have increases safety and

efficacy. In some [embodimentexamples](#), the antagonist antibodies are incapable of activating TREM2 regardless of their configuration or their ability to cluster.

**[0028]** Accordingly, certain [aspectexamples](#) of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, 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. In some [embodimentexamples](#), the antibody enhances one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein, as compared to the one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein in the absence of the isolated antibody. In some [embodimentexamples](#), the antibody enhances the one or more TREM2 activities without blocking binding of the one or more TREM2 ligands to the TREM2 protein. In some [embodimentexamples](#), the antibody does not compete with the one or more TREM2 ligands for binding to the TREM2 protein. In some [embodimentexamples](#), the antibody enhances binding of the one or more TREM2 ligands to the TREM2 protein.

**[0029]** Other [aspectexamples](#) of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody induces one or more TREM2 activities without blocking binding of one or more TREM2 ligands to the TREM2 protein. In some [embodimentexamples](#), the antibody does not compete with the one or more TREM2 ligands for binding to the TREM2 protein. In some [embodimentexamples](#), the antibody enhances binding of the one or more TREM2 ligands to the TREM2 protein. In some [embodimentexamples](#), the antibody enhances one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein. In some [embodimentexamples](#), the antibody enhances one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein, as compared to the one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein in the absence of the isolated antibody.

**[0030]** In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody synergizes with the one or more TREM2 ligands to enhance the one or more TREM2 activities. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody synergizes with the one or more TREM2 ligands to enhance the one or more TREM2 activities. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody enhances the one or more TREM2 activities in the absence of cell surface clustering of TREM2. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody enhances the one or more TREM2 activities by inducing or retaining cell surface clustering of TREM2. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is clustered by an Fc-gamma receptor expressed on one or more immune cells. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the one or more immune cells are B cells or microglial cells. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the enhancement of the one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein is measured on primary cells selected from the

group consisting of dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, NK cells, osteoclasts, Langerhans cells of skin, and Kupffer cells, or on cell lines, and wherein the enhancement of the one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein is measured utilizing an *in vitro* cell assay. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody increases levels of soluble TREM2, increases half-life of soluble TREM2, or both. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the levels of soluble TREM2 are selected from the group consisting of serum levels of TREM2, cerebral spinal fluid (CSF) levels of TREM2, tissue levels of TREM2, and any combination thereof. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody does not bind to soluble TREM2. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody does not bind to soluble TREM2 *in vivo*. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the soluble TREM2 corresponds to amino acid residues selected from the group consisting of amino acid residues 19-160 of SEQ ID NO: 1, amino acid residues 19-159 of SEQ ID NO: 1, amino acid residues 19-158 of SEQ ID NO: 1, amino acid residues 19-157 of SEQ ID NO: 1, amino acid residues 19-156 of SEQ ID NO: 1, amino acid residues 19-155 of SEQ ID NO: 1, and amino acid residues 19-154 of SEQ ID NO: 1. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody decreases levels of TREM2 in one or more cells. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody decreases cell surface levels of TREM2, decreases intracellular levels of TREM2, decreases total levels of TREM2, or any combination thereof. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody induces TREM2 degradation, TREM2 cleavage, TREM2 internalization, TREM2 shedding, downregulation of TREM2 expression, or any combination thereof. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the levels of TREM2 in one or more cells are measured in primary cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, NK cells, osteoclasts, Langerhans cells of skin, and Kupffer cells, or on cell lines, and wherein the cellular levels of TREM2 are measured utilizing an *in vitro* cell assay. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a mammalian, such as a non-human mammal, protein or a human protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a wild-type protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a naturally occurring variant. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is expressed on human dendritic cells, human macrophages, human monocytes, human osteoclasts, human Langerhans cells of skin, human Kupffer cells, human microglia, or any combination thereof. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the one or more TREM2 activities are

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; (gg) modulating secretion of one or more pro-inflammatory mediators selected from the group consisting of IFN- $\beta$ , IL-1 $\alpha$ , IL-1 $\beta$ , CD86, TNF- $\alpha$ , IL-6, IL-8, CRP, 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, and 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; (hh) modulating secretion of one or more anti-inflammatory mediators selected from the group consisting of IL-4, IL-10, TGF- $\beta$ , IL-13, IL-35, IL-16, IFN-alpha, IL-1Ra, VEGF, G-CSF, YM, AXL, FLT1, and soluble receptors for TNF or IL-6, and 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; (ii) modulating expression of one or more proteins selected from the group consisting of C1qa, C1qb, C1qc, C1s, C1r, C4, C2, C3, ITGB2, HMOX1, LAT2, CASP1, CSTA, VSIG4, MS4A4A, C3AR1, GPX1, TyroBP, ALOX5AP, ITGAM, SLC7A7, CD4, ITGAX, PYCARD, and VEGF; (jj) increasing memory; and (kk) reducing cognitive deficit. In some [embedimentexamples](#) that may be combined with any of the preceding [embedimentexamples](#), 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- $\beta$ , IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , 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, and 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. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is of the IgG class the IgM class, or the IgA class. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody has an IgG2 isotype. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody comprises a human IgG2 constant region. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the human IgG2 constant region comprises an Fc region. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody enhances the one or more TREM2 activities independently of binding to an Fc receptor. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody binds an inhibitory Fc receptor. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#): (a) 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; (b) 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 DYFPEPTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS 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; (c) 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; (d) the a 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 (e) 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 or numbering. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody has an IgG4 isotype. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody comprises an S228P amino acid substitution at residue position 228, an F234A amino acid substitution at residue position 234, and an L235A amino acid substitution at residue position 235, wherein the numbering of the residue position is according to EU numbering.

**[0031]** In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: (i) amino acid residues 19-174 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 19-174 of SEQ ID NO: 1; (ii) amino acid residues 29-112 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 29-112 of SEQ ID NO: 1; (iii) amino acid residues 113-174 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 113-174 of SEQ ID NO: 1; (iv) amino acid residues 35-49 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 35-49 of SEQ ID NO: 1; (v) amino acid residues 35-49 and 140-150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 35-49 and 140-150 of SEQ ID NO: 1; (vi) amino acid residues 39-49 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 39-49 of SEQ ID NO: 1; (vii) amino acid residues 39-49 and 63-77 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 39-49 and 63-77 of SEQ ID NO: 1; (viii) amino acid residues 51-61 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 51-61 of SEQ ID NO: 1; (ix) amino acid residues 55-62 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-62 of SEQ ID NO: 1; (x) amino acid residues 55-62, 104-109, and 148-158 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-62, 104-109, and 148-158 of SEQ ID NO: 1; (xi) amino acid residues 55-62, 104-109, and 160-166 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-62, 104-109, and 160-166 of SEQ ID NO: 1; (xii) amino acid residues 55-65 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-65 of SEQ ID NO: 1; (xiii) amino acid residues 55-65 and 124-134 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-65 and 124-134 of SEQ ID NO: 1; (xiv) amino acid residues 63-73 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 63-73 of SEQ ID NO: 1; (xv) amino acid residues 63-77 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 63-77 of SEQ ID NO: 1; (xvi) amino acid residues 104-109 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues

104-109 of SEQ ID NO: 1; (xvii) amino acid residues 117-133 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 117-133 of SEQ ID NO: 1; (xviii) amino acid residues 124-134 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 124-134 of SEQ ID NO: 1; (xix) amino acid residues 137-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 137-146 of SEQ ID NO: 1; (xx) amino acid residues 139-147 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-147 of SEQ ID NO: 1; (xxi) amino acid residues 139-149 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-149 of SEQ ID NO: 1; (xxii) amino acid residues 140-150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-150 of SEQ ID NO: 1; (xxiii) amino acid residues 140-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-146 of SEQ ID NO: 1; (xxiv) amino acid residues 140-143 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-143 of SEQ ID NO: 1; (xxv) 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; (xxvi) amino acid residues 146-154 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 146-154 of SEQ ID NO: 1; (xxvii) amino acid residues 148-158 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 148-158 of SEQ ID NO: 1; (xxviii) amino acid residues 149-157 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 149-157 of SEQ ID NO: 1; (xxix) amino acid residues 149 and 150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 149 and 150 of SEQ ID NO: 1; (xxx) amino acid residues 151-155 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 151-155 of SEQ ID NO: 1; (xxxi) amino acid residues 154-161 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 154-161 of SEQ ID NO: 1; (xxxii) amino acid residues 156-170 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 156-170 of SEQ ID NO: 1; (xxxiii) amino acid residues 160-166 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 160-166 of SEQ ID NO: 1; and (xxxiv) amino acid residues 162-165 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 162-165 of SEQ ID NO: 1. In some **embodimentexamples** that may be combined with any of the preceding **embodimentexamples**, the antibody binds to one or more amino acid residues selected from the group consisting of K42, H43, W44, G45, H67, R77, T88, H114, E117, E151, D152, H154, and E156 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian TREM2 protein corresponding to an amino acid residue selected from the group consisting of K42, H43, W44, G45, H67, R77, T88, H114, E117, E151, D152, H154, and E156 of SEQ ID NO: 1. In some **embodimentexamples** that may be combined with any of the preceding **embodimentexamples**, the antibody binds to one or more

amino acid residues selected from the group consisting of E151, D152, H154, and E156 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian TREM2 protein corresponding to an amino acid residue selected from the group consisting of E151, D152, H154, and E156 of SEQ ID NO: 1. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody competes with one or more antibodies selected from the group consisting of 3B10, 7B3, 8F8, 9F5, 9G1, 9G3, 11A8, 12F9, 7E9, 7F6, 8C3, 2C5, 3C5, 4C12, 7D9, 2F6, 3A7, 7E5, 11H5, 1B4, 6H2, 7B11, 18D8, 18E4, 29F6, 40D5, 43B9, 44A8, 44B4, and any combination thereof for binding to TREM2.

**[0032]** In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain, or the heavy chain variable domain, or both comprise at least one, two, three, four, five, or six HVRs selected from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 of an antibody selected from the group consisting of: 4D11, 7C5, 6G12, 8F11, 8E10, 7E5, 7F8, 8F8, 1H7, 2H8, 3A2, 3A7, 3B10, 4F11, 6H6, 7A9, 7B3, 8A1, 9F5, 9G1, 9G3, 10A9, 11A8, 12D9, 12F9, 10C1, 7E9, 7F6, 8C3, 2C5, 3C5, 4C12, 7D9, 2F6, 11H5, B4, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, and 44B4v2. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#): (a) the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828; (b) the HVR-L2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743; (c) the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746; (d) the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835; (e) the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888; or (f) the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#): (a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 88; (b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 90; (c) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-

L3comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 88; (d) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 73, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 92; (e) the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 76, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 95; (f) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 60, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 78, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 97; (g) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 61, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 79, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 98; (h) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 62, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 80, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 99; (i) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 22, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 63, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 82, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 100; or (j) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 65, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 84, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 102. In some **embodimentexamples** that may be combined with any of the preceding **embodimentexamples**, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828; (b) an HVR-L2 comprising an amino acid sequence selected from

the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743; and (c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835; (b) an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888; and (c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 219-398, 602-634, 679-689, 724-730, 809-816, 821, 843, 844, 849, and 850; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 399-580, 635-678, 731-733, and 817-820, 822-825, and 845-847. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein: (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 333 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:521; (b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 850 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:521; (c) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 334 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:522; (d) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 335 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:523; (e) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 336 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:524; (f) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 337 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:525; (g) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 338 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:526; (h) the light chain variable domain comprises the amino

NO:729 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (vv) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:812 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:819; (ww) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:729 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:820; (xx) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 730 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (yy) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:813 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (zz) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:814 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:822; (aaa) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:815 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:824; or (bbb) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:816 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:825. In some **embodimentexamples** that may be combined with any of the preceding **embodimentexamples**, the antibody comprises a light chain variable domain of an antibody selected from the group consisting of: 3B10, 7B3, 8F8, 9F5, 9G1, 9G3, 11A8, 12F9, 7E9, 7F6, 8C3, 2C5, 3C5, 4C12, 7D9, 2F6, 3A7, 7E5, 11H5, 1B4v1, 1B4v2, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, and 44B4v2; and/or a heavy chain variable domain of an antibody selected from the group consisting of: 3B10, 7B3, 8F8, 9F5, 9G1, 9G3, 11A8, 12F9, 7E9, 7F6, 8C3, 2C5, 3C5, 4C12, 7D9, 2F6, 3A7, 7E5, 11H5, 1B4v1, 1B4v2, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, and 44B4v2. In some **embodimentexamples** that may be combined with any of the preceding **embodimentexamples**, the anti-TREM2 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises HVR-L1, HVR-L2, HVR-L3, the heavy chain variable domain comprises HVR-H1, HVR-H2, and HVR-H3, and wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770.

**[0033]** Other **aspectexamples** of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: (i) amino acid residues 19-174 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 19-174 of SEQ ID NO: 1; (ii) amino acid residues 29-112 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 29-112 of SEQ ID NO: 1; (iii) amino acid residues 113-174 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues

corresponding to amino acid residues 142-152 of SEQ ID NO: 1; (xxvi) amino acid residues 146-154 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 146-154 of SEQ ID NO: 1; (xxvii) amino acid residues 148-158 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 148-158 of SEQ ID NO: 1; (xxviii) amino acid residues 149-157 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 149-157 of SEQ ID NO: 1; (xxix) amino acid residues 149 and 150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 149 and 150 of SEQ ID NO: 1; (xxx) amino acid residues 151-155 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 151-155 of SEQ ID NO: 1; (xxxi) amino acid residues 154-161 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 154-161 of SEQ ID NO: 1; (xxxii) amino acid residues 156-170 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 156-170 of SEQ ID NO: 1; (xxxiii) amino acid residues 160-166 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 160-166 of SEQ ID NO: 1; and (xxxiv) amino acid residues 162-165 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 162-165 of SEQ ID NO: 1. In some

**embodimentexamples**, 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. In some **embodimentexamples**, the antibody further binds to one or more amino acid residues selected from the group consisting of: (i) amino acid residue Arg47 or Asp87 of SEQ ID NO: 1; (ii) amino acid residues 40-44 of SEQ ID NO: 1; (iii) amino acid residues 67-76 of SEQ ID NO: 1; and (iv) amino acid residues 114-118 of SEQ ID NO: 1.

**[0034]** Other **aspectexamples** of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody binds to one or more amino acid residues selected from the group consisting of K42, H43, W44, G45, H67, R77, T88, H114, E117, E151, D152, H154, and E156 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian TREM2 protein corresponding to an amino acid residue selected from the group consisting of K42, H43, W44, G45, H67, R77, T88, H114, E117, E151, D152, H154, and E156 of SEQ ID NO: 1. In some **embodimentexamples**, the antibody binds to one or more amino acid residues selected from the group consisting of E151, D152, H154, and E156 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian TREM2 protein corresponding to an amino acid residue selected from the group consisting of E151, D152, H154, and E156 of SEQ ID NO: 1. Other **aspectexamples** of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody binds to one or more amino acid residues selected from the group consisting of E151, D152, H154, and E156 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian TREM2 protein corresponding to an amino acid residue selected from the group consisting of E151, D152, H154, and E156 of SEQ ID NO: 1.

**[0035]** Other **aspeetexample**s of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody competes with one or more antibodies selected from the group consisting of 1A7, 3A2, 3B10, 6G12, 6H6, 7A9, 7B3, 8A1, 8E10, 8F11, 8F8, 9F5, 9G1, 9G3, 10A9, 10C1, 11A8, 12E2, 12F9, 12G6, 2C7, 2F5, 3C1, 4D7, 4D11, 6C11, 6G12, 7A3, 7C5, 7E9, 7F6, 7G1, 7H1, 8C3, 8F10, 12A1, 1E9, 2C5, 3C5, 4C12, 4F2, 5A2, 6B3, 7D1, 7D9, 11D8, 8A12, 10E7, 10B11, 10D2, 7D5, 2A7, 3G12, 6H9, 8G9, 9B4, 10A1, 11A8, 12F3, 2F8, 10E3, 1H7, 2F6, 2H8, 3A7, 7E5, 7F8, 11H5, 7C5, 4F11, 12D9, 1B4v1, 1B4v2, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, 44B4v2, and any combination thereof for binding to TREM2.

**[0036]** Other **aspeetexample**s of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain, or the heavy chain variable domain, or both comprise at least one, two, three, four, five, or six HVRs selected from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 of an antibody selected from the group consisting of: 1A7, 3A2, 3B10, 6G12, 6H6, 7A9, 7B3, 8A1, 8E10, 8F11, 8F8, 9F5, 9G1, 9G3, 10A9, 10C1, 11A8, 12E2, 12F9, 12G6, 2C7, 2F5, 3C1, 4D7, 4D11, 6C11, 6G12, 7A3, 7C5, 7E9, 7F6, 7G1, 7H1, 8C3, 8F10, 12A1, 1E9, 2C5, 3C5, 4C12, 4F2, 5A2, 6B3, 7D1, 7D9, 11D8, 8A12, 10E7, 10B11, 10D2, 7D5, 2A7, 3G12, 6H9, 8G9, 9B4, 10A1, 11A8, 12F3, 2F8, 10E3, 1H7, 2F6, 2H8, 3A7, 7E5, 7F8, 11H5, 7C5, 4F11, 12D9, 1B4v1, 1B4v2, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, and 44B4v2. In some **embodimentexample**s: (a) the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828; (b) the HVR-L2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743; (c) the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746; (d) the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835; (e) the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888; or (f) the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770. In some **embodimentexample**s: (a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 48, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 85; (b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 48, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3

comprises the amino acid sequence of SEQ ID NO: 80, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 99; (u) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 81, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 91; (v) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 22, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 63, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 82, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 100; (w) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 64, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 83, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 101; (x) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 65, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 84, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 102; (y) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 581, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 582, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 585, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 588; (z) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 586, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 86; or (aa) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 583, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 584, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 587, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 589. In some **embodiment examples**, the light chain variable domain comprises: (a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828; (b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743, or an amino acid sequence with at least

about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743; and (c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835; (b) an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888; and (c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770. In some [embodiment examples](#), the anti-TREM2 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises HVR-L1, HVR-L2, HVR-L3, the heavy chain variable domain comprises HVR-H1, HVR-H2, and HVR-H3, and wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770. In some [embodiment examples](#), the antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 219-398, 602-634, 679-689, 724-730, 809-816, 821, 843, 844, 849, and 850; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 399-580, 635-678, 731-733, 817-820, 822-825, and 845-847. In some [embodiment examples](#), the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein: (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 333 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 521; (b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 850 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 521; (c) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 334 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 522; (d) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 335 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 523; (e) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 336 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 524; (f) the light chain variable domain comprises

acid sequence of SEQ ID NO:810 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:818; (tt) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:811 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:733; (uu) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:729 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (vv) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:812 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:819; (ww) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:729 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:820; (xx) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 730 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (yy) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:813 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (zz) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:814 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:822; (aaa) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:815 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:824; or (bbb) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:816 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:825.

**[0037]** Other aspeetexamples of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 219-398, 602-634, 679-689, 724-730, 809-816, 821, 843, 844, 849, and 850; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 399-580, 635-678, 731-733, and 817-820, 822-825, and 845-847. In some embodimentexamples, the antibody comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO:843 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:845. In some embodimentexamples, the antibody comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO:843 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:846. In some embodimentexamples, the antibody comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO:843 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:847. In some embodimentexamples, the antibody comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO:844 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:847. In some embodimentexamples, the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein: (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 333 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID

comprises the amino acid sequence of SEQ ID NO: 726 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (pp) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 726 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:817; (qq) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 727 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (rr) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 728 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:733; (ss) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:810 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:818; (tt) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:811 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:733; (uu) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:729 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (vv) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:812 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:819; (ww) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:729 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:820; (xx) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 730 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (yy) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:813 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:731; (zz) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:814 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:822; (aaa) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:815 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:824; or (bbb) the light chain variable domain comprises the amino acid sequence of SEQ ID NO:816 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO:825.

**[0038]** Other aspeetexamples of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody comprises a light chain variable domain of an antibody selected from the group consisting of: 1A7, 3A2, 3B10, 6G12, 6H6, 7A9, 7B3, 8A1, 8E10, 8F11, 8F8, 9F5, 9G1, 9G3, 10A9, 10C1, 11A8, 12E2, 12F9, 12G6, 2C7, 2F5, 3C1, 4D7, 4D11, 6C11, 6G12, 7A3, 7C5, 7E9, 7F6, 7G1, 7H1, 8C3, 8F10, 12A1, 1E9, 2C5, 3C5, 4C12, 4F2, 5A2, 6B3, 7D1, 7D9, 11D8, 8A12, 10E7, 10B11, 10D2, 7D5, 2A7, 3G12, 6H9, 8G9, 9B4, 10A1, 11A8, 12F3, 2F8, 10E3, 1H7, 2F6, 2H8, 3A7, 7E5, 7F8, 11H5, 7C5, 4F11, 12D9, 1B4v1, 1B4v2, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, and 44B4v2; and/or a heavy chain variable domain of an antibody selected from the group consisting of: 1A7, 3A2, 3B10, 6G12, 6H6, 7A9, 7B3, 8A1, 8E10, 8F11, 8F8, 9F5, 9G1, 9G3, 10A9,

10C1, 11A8, 12E2, 12F9, 12G6, 2C7, 2F5, 3C1, 4D7, 4D11, 6C11, 6G12, 7A3, 7C5, 7E9, 7F6, 7G1, 7H1, 8C3, 8F10, 12A1, 1E9, 2C5, 3C5, 4C12, 4F2, 5A2, 6B3, 7D1, 7D9, 11D8, 8A12, 10E7, 10B11, 10D2, 7D5, 2A7, 3G12, 6H9, 8G9, 9B4, 10A1, 11A8, 12F3, 2F8, 10E3, 1H7, 2F6, 2H8, 3A7, 7E5, 7F8, 11H5, 7C5, 4F11, 12D9, 1B4v1, 1B4v2, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, and 44B4v2.

**[0039]** Other [aspectexamples](#) of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody binds essentially the same TREM2 epitope as an antibody selected from the group consisting of: 1A7, 3A2, 3B10, 6G12, 6H6, 7A9, 7B3, 8A1, 8E10, 8F11, 8F8, 9F5, 9G1, 9G3, 10A9, 10C1, 11A8, 12E2, 12F9, 12G6, 2C7, 2F5, 3C1, 4D7, 4D11, 6C11, 6G12, 7A3, 7C5, 7E9, 7F6, 7G1, 7H1, 8C3, 8F10, 12A1, 1E9, 2C5, 3C5, 4C12, 4F2, 5A2, 6B3, 7D1, 7D9, 11D8, 8A12, 10E7, 10B11, 10D2, 7D5, 2A7, 3G12, 6H9, 8G9, 9B4, 10A1, 11A8, 12F3, 2F8, 10E3, 1H7, 2F6, 2H8, 3A7, 7E5, 7F8, 11H5, 7C5, 4F11, 12D9, 1B4v1, 1B4v2, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, and 44B4v2.

**[0040]** Other [aspectexamples](#) of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828; (b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743; and (c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835; (b) an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888; and (c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID

NOs: 85-102, 588, 589, 709, 710, and 763-770. Other [aspectexamples](#) of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein, wherein the anti-TREM2 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises HVR-L1, HVR-L2, HVR-L3, the heavy chain variable domain comprises HVR-H1, HVR-H2, and HVR-H3, and wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770.

[0041] In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody competes with one or more TREM2 ligands for binding to the TREM2 protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody induces one or more TRME2 activities and enhances one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody induces one or more TRME2 activities without blocking binding of the one or more TREM2 ligands to the TREM2 protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody induces one or more TRME2 activities without blocking binding of one or more TREM2 ligands to the TREM2 protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody enhances the one or more TREM2 activities. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody does not compete with the one or more TREM2 ligands for binding of to the TREM2 protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody enhances binding of the one or more TREM2 ligands to the TREM2 protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody enhances one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein, as compared to the one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein in the absence of the isolated antibody. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody synergizes with the one or more TREM2 ligands to enhance the one or more TREM2 activities. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody enhances the one or more TREM2 activities in the absence of cell surface clustering of TREM2. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody enhances the one or more TREM2 activities by inducing or retaining cell surface clustering of TREM2. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is clustered by an Fc-gamma receptor expressed on one or more immune cells. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the one or more immune cells are B cells or microglial cells. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody increases levels of soluble TREM2, increases

half-life of soluble TREM2, or both. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the levels of soluble TREM2 are selected from the group consisting of serum levels of TREM2, cerebral spinal fluid (CSF) levels of TREM2, tissue levels of TREM2, and any combination thereof. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody decreases levels of TREM2 in one or more cells. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody decreases cell surface levels of TREM2, decreases intracellular levels of TREM2, decreases total levels of TREM2, or any combination thereof. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody induces TREM2 degradation, TREM2 cleavage, TREM2 internalization, TREM2 shedding, downregulation of TREM2 expression, or any combination thereof. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the levels of TREM2 in one or more cells are measured in primary cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, NK cells, osteoclasts, Langerhans cells of skin, and Kupffer cells, or on cell lines, and wherein the cellular levels of TREM2 are measured utilizing an *in vitro* cell assay. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a mammalian protein or a human protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a wild-type protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a naturally occurring variant. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is expressed on human dendritic cells, human macrophages, human monocytes, human osteoclasts, human Langerhans cells of skin, human Kupffer cells, human microglia, or any combination thereof. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the one or more TREM2 activities are selected from the group consisting of: (a) TREM2 binding to DAP12; (b) TREM2 phosphorylation; (c) DAP12 phosphorylation; (d) activation of one or more tyrosine kinases, optionally wherein the one or more tyrosine kinases comprise a Syk kinase, ZAP70 kinase, or both; (e) activation of phosphatidylinositol 3-kinase (PI3K); (f) activation of protein kinase B (Akt); (g) recruitment of phospholipase C-gamma (PLC-gamma) to a cellular plasma membrane, activation of PLC-gamma, or both; (h) recruitment of TEC-family kinase dVav to a cellular plasma membrane; (i) activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B); (j) inhibition of MAPK signaling; (k) phosphorylation of linker for activation of T cells (LAT), linker for activation of B cells (LAB), or both; (l) activation of IL-2-induced tyrosine kinase (Itk); (m) modulation of one or more pro-inflammatory mediators selected from the group consisting of IFN- $\beta$ , IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , 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,

consisting of C1qa, C1qb, C1qc, C1s, C1R, C4, C2, C3, ITGB2, HMOX1, LAT2, CASP1, CSTA, VSIG4, MS4A4A, C3AR1, GPX1, TyroBP, ALOX5AP, ITGAM, SLC7A7, CD4, ITGAX, PYCARD, and VEGF; (ii) increasing memory; and (jj) reducing cognitive deficit. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), 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- $\beta$ , IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , 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, and 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. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is of the IgG class the IgM class, or the IgA class. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody has an IgG2 isotype. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody comprises a human IgG2 constant region. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the human IgG2 constant region comprises an Fc region. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody enhances the one or more TREM2 activities independently of binding to an Fc receptor. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody binds an inhibitory Fc receptor. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (Fc $\gamma$ IIB). In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#): (a) 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; (b) 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 YTCNVDPKPS NTKVDKTVKCCVECPPCP (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; (c) 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; (d) 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 (e) 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 or, Kabat numbering. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is an inert antibody that binds to a TREM2 protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is an antagonist antibody that binds to a TREM2 protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a mammalian protein or a human protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a wild-type protein. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a naturally occurring variant. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the TREM2 protein is a disease variant. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody inhibits one or more TREM2 activities. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the one or more TREM2 activities are selected from the group consisting of: (a) TREM2 binding to DAP12; (b) TREM2 phosphorylation; (c) DAP12 phosphorylation; (d) activation of one or more tyrosine kinases, optionally wherein the one or more tyrosine kinases comprise a Syk

and any combination thereof; (x) increasing number of tumor-promoting myeloid immunosuppressor or tumor-promoting granulocytic immunosuppressor cells in a tumor, peripheral blood, lymphoid organ, or any combination thereof; (y) enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); (z) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are selected from the group consisting of TGF-beta, IL-10, and any combination thereof; (aa) increasing tumor infiltration of tumor-promoting FoxP3<sup>+</sup> regulatory T lymphocytes; (bb) decreasing activation of tumor-specific T lymphocytes with tumor-killing potential; (cc) decreasing infiltration of one of more cells selected from the group consisting of tumor-specific T lymphocytes with tumor killing potential, tumor-specific NK cells with tumor killing potential, tumor-specific B lymphocytes with potential to enhance immune response, and any combination thereof; (dd) increasing tumor volume; (ee) increasing tumor growth rate; (ff) increasing metastasis; (gg) increasing rate of tumor recurrence; (hh) decreasing efficacy of one or more immunotherapies that modulate anti-tumor T cell responses, optionally wherein the one or more immunotherapies are selected from the group consisting of PD1/PDL1 blockade, CTLA-4 blockade, and cancer vaccines; (ii) inhibition of PLCγ/PKC/calcium mobilization; and (jj) inhibition of PI3K/Akt, Ras/MAPK signaling. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), 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) recruitment of Syk to a DAP12/TREM2 complex; (e) 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; (f) increasing tumor volume; and (g) increasing tumor growth rate. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody inhibits interaction between TREM2 and one or more TREM2 ligands, inhibits TREM2 signal transduction, or both. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is incapable of binding an Fc-gamma receptor (FcγR). In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody has an IgG1, IgG2, IgG3, or IgG4 isotype. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#): (a) the 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, N297Q, D270A, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, 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; (b) the 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, H268E, V309L, N297A, N297Q, A330S, P331S, C232S, C233S,

M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or (c) the antibody has an IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: E233P, F234V, L234A/F234A, L235A, G237A, E318A, S228P, L236E, S241P, L248E, T394D, M252Y, S254T, T256E, N297A, N297Q, and any combination thereof, wherein the numbering of the residues is according to EU numbering. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#): (a) the Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of A330L, L234F; L235E, P331S, and any combination thereof, wherein the numbering of the residues is according to EU numbering; (b) the Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or (c) the Fc region further comprises a S228P amino acid substitution according to EU numbering. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, a naturally occurring variant of human TREM2, and a disease variant of human TREM2, and optionally wherein the antibody fragment is cross-linked to a second antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, a naturally occurring variant of human TREM2, and a disease variant of human TREM2. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the fragment is an Fab, Fab', Fab'-SH, F(ab')<sub>2</sub>, Fv or scFv fragment. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), 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. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is a murine antibody. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is a humanized antibody, a bispecific antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is a monoclonal antibody. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody is a bispecific antibody recognizing a first antigen and a second antigen. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the first antigen is human TREM2 or a naturally occurring variant thereof, and the second antigen is: (a) an antigen facilitating transport across the blood-brain-barrier; (b) an antigen facilitating transport across the blood-brain-barrier selected from the group consisting of

transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopeptide, and ANG1005; (c) a disease-causing agent selected from the group consisting of disease-causing peptides or proteins or, disease-causing nucleic acids, wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides; (d) ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA-4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG-3, and phosphatidylserine; and (e) a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells. In some **embodimentexamples** that may be combined with any of the preceding **embodimentexamples**, the antibody is used in combination with one or more antibodies that specifically bind a disease-causing agent selected from the group consisting of disease-causing peptides, disease-causing proteins, amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and any combination thereof; or with one or more antibodies that bind an immunomodulatory protein selected from the group consisting of: CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA-4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG-3, TREM1, TREM2, CD33, Siglec-5, Siglec-9, Siglec-11, phosphatidylserine, disease-causing nucleic acids, antisense GGCCCC (G2C4) repeat-expansion

RNA, and any combination thereof. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), when administered to an individual increases memory, reduces cognitive deficit, or both. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody binds specifically to both human TREM2 and mouse TREM2. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody has dissociation constant ( $K_D$ ) for human TREM2 and mouse TREM2 that ranges from about 12.8 nM to about 1.2 nM, or less than 1.2 nM. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody has dissociation constant ( $K_D$ ) for human TREM2 that ranges from about 12.8 nM to about 2.9 nM, or less than 2.9 nM. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody has dissociation constant ( $K_D$ ) for mouse TREM2 that ranges from about 10.4 nM to about 1.2 nM, or less than 1.2 nM. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the  $K_D$  is determined at a temperature of approximately 4°C. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody does not inhibit the growth of innate immune cells. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody binds to primary immune cells with a  $K_D$  of less than 1 nM. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 1% or more of the concentration of the antibody in the blood. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 2% or more of the concentration of the antibody in the blood. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 3% or more of the concentration of the antibody in the blood. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 4% or more of the concentration of the antibody in the blood.

**[0042]** Other [aspectexamples](#) of the present disclosure relate to an isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of the preceding [embodimentexamples](#). Other [aspectexamples](#) of the present disclosure relate to a vector comprising the nucleic acid of any of the preceding [embodimentexamples](#). Other [aspectexamples](#) of the present disclosure relate to an isolated host cell comprising the vector of any of the preceding [embodimentexamples](#). Other [aspectexamples](#) of the present disclosure relate to a method of producing an antibody that binds to TREM2, comprising culturing the host cell of any of the preceding [embodimentexamples](#) so that the antibody is produced. In some [embodimentexamples](#), the method further comprising recovering the antibody produced by the cell. Other [aspectexamples](#) of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to TREM2 produced by the method of any of the preceding [embodimentexamples](#). Other [aspectexamples](#) of the present disclosure relate to a

pharmaceutical composition comprising the antibody of any of the preceding embodiment 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 antibody that binds to TREM2, comprising culturing the host cell disclosed herein so that the antibody is produced.

[0042e] In one aspect, the present disclosure refers to an isolated antibody that binds to TREM2 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 aspect 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-sclerosis, 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 aspect 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,

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 myelosclerosis, 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. Other [aspectexamples](#) of the present disclosure relate to use of an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein in the manufacture of a medicament for 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 myelosclerosis, 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. Other [aspectexamples](#) 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, Nasu-Hakola disease, cognitive deficit, memory loss, spinal cord injury, traumatic brain injury, multiple sclerosis, chronic colitis, ulcerative colitis in and cancer, 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 [aspectexamples](#) 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, Nasu-Hakola disease, cognitive deficit, memory loss, spinal cord injury, traumatic brain injury, multiple sclerosis, chronic colitis, ulcerative colitis in and cancer. Other [aspectexamples](#) of the present disclosure relate to use of an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein in the manufacture of a medicament for 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, Nasu-Hakola disease, cognitive deficit, memory loss, spinal cord injury, traumatic brain injury, multiple sclerosis, chronic colitis, ulcerative colitis in and cancer. In some [embodimentexamples](#), the isolated antibody is: (a) an agonist antibody; (b) an inert antibody; or (c) an antagonist antibody. In some [embodimentexamples](#), the isolated antibody is the antibody of any of the preceding [embodimentexamples](#). In some [embodimentexamples](#), the disease, disorder, or injury is Alzheimer's disease. In some [embodimentexamples](#), the isolated antibody that binds to a TREM2 protein increases expression of one or more inflammatory mediators, wherein the one or more inflammatory mediators are selected from the group consisting of IL-1 $\beta$ , TNF- $\alpha$ , YM-1, CD86, CCL2, CCL3, CCL5, CCR2, CXCL10, Gata3, Rorc, and any combination thereof. In some [embodimentexamples](#), the isolated antibody that binds to a TREM2 protein decreases expression of one or more inflammatory mediators, wherein the one or more inflammatory mediators are selected from the group consisting of FLT1, OPN, CSF-1, CD11c, AXL, and any combination thereof. In some [embodimentexamples](#), the isolated antibody that binds to a TREM2 protein decreases levels of A $\beta$  peptide in the individual. In some [embodimentexamples](#), the isolated antibody that binds to a TREM2 protein increases the number of CD11b<sup>+</sup> microglial cells in the brain of the individual. In some [embodimentexamples](#), the isolated antibody that binds to a TREM2 protein increases memory of the individual. In some [embodimentexamples](#), the isolated antibody that binds to a TREM2 protein reduces cognitive deficit in the individual. In some [embodimentexamples](#), the isolated antibody that binds to a TREM2 protein increases motor coordination in the individual. In some [embodimentexamples](#), the method further comprises administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or another standard or investigational anti-cancer therapy. In some [embodimentexamples](#), the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the isolated antibody. In some [embodimentexamples](#), the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from the group consisting of an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-PD-

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 **embodimentexamples**, 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 **embodimentexamples**, the method further comprises administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some **embodimentexamples**, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the isolated antibody. In some **embodimentexamples**, 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 **embodimentexamples**, the method further comprises administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In some **embodimentexamples**, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the isolated antibody. In some **embodimentexamples**, 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 **embodimentexamples**, the method further comprises administering to the individual at least one stimulatory cytokine. In some **embodimentexamples**, the at least one stimulatory cytokine is administered in combination with the isolated antibody. In some **embodimentexamples**, the at least one stimulatory cytokine is selected from the group consisting of TNF- $\alpha$ , 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- $\alpha$ , IFN- $\beta$ , IL-2, IL-18, GM-CSF, G-CSF, and any combination thereof.

**[0043a]** In one aspect, the present disclosure refers to use of a therapeutically effective amount of the isolated antibody disclosed herein in the manufacture of a medicament for reducing risk of or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, cognitive deficit, memory loss, spinal cord injury, traumatic brain injury, chronic colitis, and ulcerative colitis.

**[0044]** Other **aspectexamples** 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 **aspectexamples** 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 **aspectexamples** of the present disclosure

relate to use of an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein in the manufacture of a medicament for 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. In some [embodimentexamples](#), the isolated antibody is the antibody of any of the preceding [embodimentexamples](#).

**[0045]** Other [aspectexamples](#) of the present disclosure relate to a method of inducing one or more TREM2 activities 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 [aspectexamples](#) of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein for use in inducing one or more TREM2 activities in an individual in need thereof. Other [aspectexamples](#) of the present disclosure relate to use of an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein in the manufacture of a medicament for inducing one or more TREM2 activities in an individual in need thereof. In some [embodimentexamples](#), the isolated antibody is the antibody of any of the preceding [embodimentexamples](#).

**[0046]** Other [aspectexamples](#) of the present disclosure relate to a method of inducing one or more TREM2 activities and 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 [aspectexamples](#) of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein for use in inducing one or more TREM2 activities and 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 [aspectexamples](#) of the present disclosure relate to use of an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein in the manufacture of a medicament for inducing one or more TREM2 activities and 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. In some [embodimentexamples](#), the isolated antibody is the antibody of any of the preceding [embodimentexamples](#).

**[0047]** Other [aspectexamples](#) of the present disclosure relate to a method of decreasing cellular levels of TREM2 in one or more cells 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 [aspectexamples](#) of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein for use in decreasing cellular levels of TREM2 in one or more cells in an individual in need thereof. Other [aspectexamples](#) of the present disclosure relate to use of an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein in the manufacture of a medicament for decreasing cellular levels of TREM2 in one or more cells in an individual in need thereof. In some [embodimentexamples](#), the isolated antibody is the antibody of any of the preceding [embodimentexamples](#).

**[0048]** In some embodimentexamples that may be combined with any of the preceding embodimentexamples, the individual has a heterozygous variant of TREM2, wherein the variant comprises one or more substitutions selected from the group consisting of: i. a glutamic acid to stop codon substitution in the nucleic acid sequence encoding amino acid residue Glu14 of SEQ ID NO: 1; ii. A glutamine to stop codon substitution in the nucleic acid sequence encoding amino acid residue Gln33 of SEQ ID NO: 1; iii. A tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue Trp44 of SEQ ID NO: 1; iv. An arginine to histidine amino acid substitution at an amino acid corresponding to amino acid residue Arg47 of SEQ ID NO: 1; v. a tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue Trp78 of SEQ ID NO: 1; vi. A valine to glycine amino acid substitution at an amino acid corresponding to amino acid residue Val126 of SEQ ID NO: 1; vii. An aspartic acid to glycine amino acid substitution at an amino acid corresponding to amino acid residue Asp134 of SEQ ID NO: 1; and viii. A lysine to asparagine amino acid substitution at an amino acid corresponding to amino acid residue Lys186 of SEQ ID NO: 1. In some embodimentexamples that may be combined with any of the preceding embodimentexamples, the individual has a heterozygous variant of TREM2, wherein the variant comprises a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G313 of the nucleic acid sequence encoding SEQ ID NO: 1; a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G267 of the nucleic acid sequence encoding SEQ ID NO: 1; or both. In some embodimentexamples that may be combined with any of the preceding embodimentexamples, the individual has a heterozygous variant of DAP12, wherein the variant comprises one or more variants selected from the group consisting of: i. a methionine to threonine substitution at an amino acid corresponding to amino acid residue Met1 of SEQ ID NO: 2; ii. A glycine to arginine amino acid substitution at an amino acid corresponding to amino acid residue Gly49 of SEQ ID NO: 2; iii. A deletion within exons 1-4 of the nucleic acid sequence encoding SEQ ID NO: 2; iv. An insertion of 14 amino acid residues at exon 3 of the nucleic acid sequence encoding SEQ ID NO: 2; and v. a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G141 of the nucleic acid sequence encoding SEQ ID NO: 2.

**[0049]** Other aspectexamples of the present disclosure relate to a method of inducing or promoting innate immune cell survival or wound healing 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 aspectexamples of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in inducing or promoting innate immune cell survival or wound healing an individual in need thereof. Other aspectexamples 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 inducing or promoting innate immune cell survival or wound healing an individual in need thereof. In some embodimentexamples, the isolated agonist antibody is the agonist antibody of any of the preceding embodimentexamples.

[0050] Other [aspectexamples](#) 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 [aspectexamples](#) 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 [aspectexamples](#) 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 [embodimentexamples](#), the isolated agonist antibody is the agonist antibody of any of the preceding [embodimentexamples](#).

[0051] Other [aspectexamples](#) 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 [aspectexamples](#) 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 [aspectexamples](#) 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 [embodimentexamples](#), the isolated agonist antibody is the agonist antibody of any of the preceding [embodimentexamples](#).

[0052] Other [aspectexamples](#) 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 [aspectexamples](#) 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 [aspectexamples](#) 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 an individual in need thereof. In some [embodimentexamples](#), the isolated agonist antibody is the agonist antibody of any of the preceding [embodimentexamples](#).

[0052a] In one aspect, the present disclosure refers to use of a therapeutically effective amount of the isolated antibody disclosed herein in the manufacture of a medicament for reducing Abeta peptide levels in an individual in need thereof.

[0053] Other [aspectexamples](#) of the present disclosure relate to a method of increasing the number of CD11b<sup>+</sup> 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 [aspectexamples](#) of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in increasing the number of CD11b<sup>+</sup> microglial cells in an individual in need thereof. Other [aspectexamples](#) 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<sup>+</sup> microglial cells in an individual in need thereof. In some [embodimentexamples](#), the isolated agonist antibody is the agonist antibody of any of the preceding [embodimentexamples](#).

[0054] Other [aspectexamples](#) 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

administering to the individual a therapeutically effective amount of an isolated agonist antibody that binds to a TREM2 protein. Other [aspectexamples](#) of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in increasing levels of one or more of FLT1, OPNCSF1, CD11c, and AXL in an individual in need thereof. Other [aspectexamples](#) 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 levels of one or more of FLT1, OPNCSF1, CD11c, and AXL in an individual in need thereof. In some [embodimentexamples](#), the isolated agonist antibody is the agonist antibody of any of the preceding [embodimentexamples](#).

**[0055]** Other [aspectexamples](#) of the present disclosure relate to a method of treating spinal cord injury 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 [aspectexamples](#) of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in treating spinal cord injury in an individual in need thereof. Other [aspectexamples](#) 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 treating spinal cord injury in an individual in need thereof. In some [embodimentexamples](#), the isolated agonist antibody is the agonist antibody of any of the preceding [embodimentexamples](#).

**[0056]** Other [aspectexamples](#) of the present disclosure relate to a method of treating s chronic colitis or ulcerative colitis 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 [aspectexamples](#) of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in treating chronic colitis or ulcerative colitis in an individual in need thereof. Other [aspectexamples](#) 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 treating chronic colitis or ulcerative colitis in an individual in need thereof. In some [embodimentexamples](#), the isolated agonist antibody is the agonist antibody of any of the preceding [embodimentexamples](#).

**[0057]** In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody does not inhibit the growth of innate immune cells. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody binds to primary immune cells with a  $K_D$  of less than 1 nM. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the  $K_D$  is determined at a temperature of approximately 4°C. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 1% or more of the concentration of the antibody in the blood. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 2% or more of the concentration of the antibody in the blood. In some [embodimentexamples](#) that may be combined with any of the preceding [embodimentexamples](#), the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 3% or more of the concentration of the

antibody in the blood. In some **embodimentexamples** that may be combined with any of the preceding **embodimentexamples**, the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 4% or more of the concentration of the antibody in the blood.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0058]** **FIG. 1A** shows an amino acid sequence alignment between the human TREM2 protein (SEQ ID NO: 1) and the human NCTR2 protein (SEQ ID NO: 851), depicting the homology between the two proteins. The consensus sequence is SEQ ID NO: 852.

**FIG. 1B** shows a structure-based sequence alignment between several TREM proteins and other members of the IgV family. The amino acid residue numbering is consistent with the mature sequence of the human TREM1 protein. The secondary structure elements of TREM1 are illustrated as arrows for the  $\beta$  strands and cylinders for  $\alpha$  helices. Amino acid residues involved in homo- and heterodimer formation are shown on black background. Cysteine residues that form disulfide bonds and that are conserved for the V-type Ig fold, are depicted in bold and marked with asterisks. Gaps are indicated by “-”. M-1 residues violating antibody-like dimer formation mode are marked with closed triangles as (*e.g.*, Radaev et al., (2003) Structure. 11(12):1527-1535). TREM-1\_human (SEQ ID NO: 853), TREM-2\_human (SEQ ID NO: 854), TREM-1\_mouse (SEQ ID NO: 855), TREM-2\_mouse (SEQ ID NO: 856), TREM-3\_mouse (SEQ ID NO: 857), NKp44 (SEQ ID NO: 858), aTCR\_human (SEQ ID NO: 859), bTCR\_human (SEQ ID NO: 860), gTCR\_human (SEQ ID NO: 861), dTCR\_human (SEQ ID NO: 862), Vd\_human (SEQ ID NO: 863), hIGG1\_mouse (SEQ ID NO: 864), lIGG1\_mouse (SEQ ID NO: 865), CD8\_human (SEQ ID NO: 866), and CTLA4\_human (SEQ ID NO: 867).

**[0059]** **FIG. 2** shows an amino acid sequence alignment between the human TREM1 protein (SEQ ID NO: 868) and the human TREM2 protein (SEQ ID NO: 1), depicting the homology between the two proteins. The consensus sequence is SEQ ID NO: 869.

**[0060]** **FIG. 3A** shows FACS histograms demonstrating binding of TREM2 antibodies 7E5 and 2H8 to a mouse cell line (BWZ) expressing recombinant mouse TREM2. **FIG. 3B** shows antibodies 7E5 and 2H8 binding to wild-type (TREM2 +/+) bone marrow derived mouse macrophages (BMMac) and TREM2-deficient (TREM2 -/-) BMMac. Antibody mIgG1 represents a negative isotype control. Shaded histograms represent the TREM2 negative cells population. Black outlined histograms represent the TREM2 positive cell population. **FIG. 3C** shows a dose response curve demonstrating dose-dependent binding of the TREM2 antibody 7E5 to BWZ cells expressing recombinant mouse TREM2 but not to parental BWZ cells. Antibody mIgG1 represents the negative isotype control.

**[0061]** **FIG. 4A** shows FACS histograms demonstrating binding of TREM2 antibodies 10A9, 10C1, and 8F8 to a human cell line (293) expressing a recombinant human TREM2-DAP12 fusion protein. Shaded histograms represent a TREM2 negative cell population. Black outlined histograms represent a TREM2 positive cell population. **FIG. 4B** shows antibodies 10A9, 10C1, and 8F8 binding to primary human dendritic cells (hDCs). Shaded histograms show binding of the isotype antibody

## CLAIMS

What is claimed is:

- ~~1. An isolated antibody that binds to a TREM2 protein, 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.~~
- ~~2. The isolated antibody of claim 1, wherein the antibody enhances one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein, as compared to the one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein in the absence of the isolated antibody.~~
- ~~3. The isolated antibody of claim 1 or claim 2, wherein the antibody enhances the one or more TREM2 activities without blocking binding of the one or more TREM2 ligands to the TREM2 protein.~~
- ~~4. The isolated antibody of claim 1 or claim 2, wherein the antibody does not compete with the one or more TREM2 ligands for binding to the TREM2 protein.~~
- ~~5. The isolated antibody of any one of claims 1-4, wherein the antibody enhances binding of the one or more TREM2 ligands to the TREM2 protein.~~
- ~~6. An isolated antibody that binds to a TREM2 protein, wherein the antibody induces one or more TREM2 activities without blocking binding of one or more TREM2 ligands to the TREM2 protein.~~
- ~~7. The isolated antibody of claim 6, wherein the antibody enhances binding of the one or more TREM2 ligands to the TREM2 protein.~~
- ~~8. The isolated antibody of any one of claims 6-7, wherein the antibody enhances one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein.~~
- ~~9. The isolated antibody of claim 8, wherein the antibody enhances one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein, as compared to the one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein in the absence of the isolated antibody.~~
- ~~10. The isolated antibody of any one of claims 1-9, wherein the antibody synergizes with the one or more TREM2 ligands to enhance the one or more TREM2 activities.~~
- ~~11. The isolated antibody of any one of claims 1-10, wherein the antibody enhances the one or more TREM2 activities in the absence of cell surface clustering of TREM2.~~
- ~~12. The isolated antibody of any one of claims 1-11, wherein the antibody enhances the one or more TREM2 activities by inducing or retaining cell surface clustering of TREM2.~~

- ~~13. — The isolated antibody of claim 12, wherein the antibody is clustered by an Fc gamma receptor expressed on one or more immune cells.~~
- ~~14. — The isolated antibody of claim 13, wherein the one or more immune cells are B cells or microglial cells.~~
- ~~15. — The isolated antibody of any one of claims 1-14, wherein the enhancement of the one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein is measured on primary cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, NK cells, osteoclasts, Langerhans cells of skin, and Kupffer cells, or on cell lines, and wherein the enhancement of the one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein is measured utilizing an *in vitro* cell assay.~~
- ~~16. — The isolated antibody of any one of claims 1-15, wherein the antibody increases levels of soluble TREM2, increases half life of soluble TREM2, or both.~~
- ~~17. — The isolated antibody of claim 16, wherein the levels of soluble TREM2 are selected from the group consisting of serum levels of TREM2, cerebral spinal fluid (CSF) levels of TREM2, tissue levels of TREM2, and any combination thereof.~~
- ~~18. — The isolated antibody of any one of claims 1-15, wherein the antibody does not bind to soluble TREM2.~~
- ~~19. — The isolated antibody of claim 18, wherein the antibody does not bind to soluble TREM2 *in vivo*.~~
- ~~20. — The isolated antibody of any one of claims 1-15, wherein the antibody decreases levels of TREM2 in one or more cells.~~
- ~~21. — The isolated antibody of 20, wherein the antibody decreases cell surface levels of TREM2, decreases intracellular levels of TREM2, decreases total levels of TREM2, or any combination thereof.~~
- ~~22. — The isolated antibody of 20 or claim 21, wherein the antibody induces TREM2 degradation, TREM2 cleavage, TREM2 internalization, TREM2 shedding, downregulation of TREM2 expression, or any combination thereof.~~
- ~~23. — The isolated antibody of any one of claims 20-22, wherein the levels of TREM2 in one or more cells are measured in primary cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, NK cells, osteoclasts, Langerhans cells of skin, and Kupffer cells, or on cell lines, and wherein the cellular levels of TREM2 are measured utilizing an *in vitro* cell assay.~~

24. ~~The isolated antibody of any one of claims 1-23, wherein the TREM2 protein is a mammalian protein or a human protein.~~

25. ~~The isolated antibody of claim 24, wherein the TREM2 protein is a wild-type protein.~~

26. ~~The isolated antibody of claim 24, wherein the TREM2 protein is a naturally-occurring variant.~~

27. ~~The isolated antibody of any one of claims 1-26, wherein the TREM2 protein is expressed on human dendritic cells, human macrophages, human monocytes, human osteoclasts, human Langerhans cells of skin, human Kupffer cells, human microglia, or any combination thereof.~~

28. ~~The isolated antibody of any one of claims 1-27, 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- $\beta$ , IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , 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, and 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.~~

29. ~~The isolated antibody of any one of claims 1-28, wherein the antibody is of the IgG class the IgM class, or the IgA class.~~

- ~~30. — The isolated antibody of claim 29, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.~~
- ~~31. — The isolated antibody of claim 30, wherein the antibody has an IgG2 isotype.~~
- ~~32. — The isolated antibody of claim 30 or claim 31, wherein the antibody comprises a human IgG2 constant region.~~
- ~~33. — The isolated antibody of claim 32, wherein the human IgG2 constant region comprises an Fe region.~~
- ~~34. — The isolated antibody of any one of claims 29-33, wherein the antibody enhances the one or more TREM2 activities independently of binding to an Fe receptor.~~
- ~~35. — The isolated antibody of any one of claims 30-34, wherein the antibody binds an inhibitory Fe receptor.~~
- ~~36. — The isolated antibody of claim 35, wherein the inhibitory Fe receptor is inhibitory Fe-gamma receptor IIB (FcγRIIB).~~
- ~~37. — The isolated antibody of claim 36, wherein:~~
- ~~(a) — the isolated antibody has a human or mouse IgG1 isotype and comprises one or more amino acid substitutions in the Fe 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 Fe region at a position corresponding to glycine 236;~~
  - ~~(b) — 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 YTCNVDPKPS NTKVDKTVERKCCVECPPCP (SEQ ID NO: 886), and optionally wherein the antibody Fe 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;~~
  - ~~(c) — the isolated antibody has an IgG2 isotype and comprises one or more amino acid substitutions in the Fe 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;~~

- ~~(d) — 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~~
- ~~(e) — 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.~~

~~38. — The isolated antibody of any one of claims 1-28, wherein the antibody has an IgG4 isotype.~~

~~39. — The isolated antibody of claim 38, wherein the antibody comprises an S228P amino acid substitution at residue position 228, an F234A amino acid substitution at residue position 234, and an L235A amino acid substitution at residue position 235, wherein the numbering of the residue position is according to EU numbering.~~

~~40. — The isolated antibody of any one of claims 1-39, wherein the antibody binds to one or more amino acids within amino acid residues selected from the group consisting of:~~

- ~~i. — amino acid residues 19-174 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 19-174 of SEQ ID NO: 1;~~
- ~~ii. — amino acid residues 29-112 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 29-112 of SEQ ID NO: 1;~~
- ~~iii. — amino acid residues 113-174 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 113-174 of SEQ ID NO: 1;~~
- ~~iv. — amino acid residues 35-49 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 35-49 of SEQ ID NO: 1;~~
- ~~v. — amino acid residues 35-49 and 140-150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 35-49 and 140-150 of SEQ ID NO: 1;~~
- ~~vi. — amino acid residues 39-49 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 39-49 of SEQ ID NO: 1;~~
- ~~vii. — amino acid residues 39-49 and 63-77 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 39-49 and 63-77 of SEQ ID NO: 1;~~

- ~~viii. amino acid residues 51-61 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 51-61 of SEQ ID NO: 1;~~
- ~~ix. amino acid residues 55-62 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-62 of SEQ ID NO: 1;~~
- ~~x. amino acid residues 55-62, 104-109, and 148-158 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-62, 104-109, and 148-158 of SEQ ID NO: 1;~~
- ~~xi. amino acid residues 55-62, 104-109, and 160-166 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-62, 104-109, and 160-166 of SEQ ID NO: 1;~~
- ~~xii. amino acid residues 55-65 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-65 of SEQ ID NO: 1;~~
- ~~xiii. amino acid residues 55-65 and 124-134 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-65 and 124-134 of SEQ ID NO: 1;~~
- ~~xiv. amino acid residues 63-73 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 63-73 of SEQ ID NO: 1;~~
- ~~xv. amino acid residues 63-77 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 63-77 of SEQ ID NO: 1;~~
- ~~xvi. amino acid residues 104-109 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 104-109 of SEQ ID NO: 1;~~
- ~~xvii. amino acid residues 117-133 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 117-133 of SEQ ID NO: 1;~~
- ~~xviii. amino acid residues 124-134 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 124-134 of SEQ ID NO: 1;~~
- ~~xix. amino acid residues 137-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 137-146 of SEQ ID NO: 1;~~
- ~~xx. amino acid residues 139-147 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-147 of SEQ ID NO: 1;~~
- ~~xxi. amino acid residues 139-149 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-149 of SEQ ID NO: 1;~~
- ~~xxii. amino acid residues 140-150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-150 of SEQ ID NO: 1;~~
- ~~xxiii. amino acid residues 140-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-146 of SEQ ID NO: 1;~~
- ~~xxiv. amino acid residues 140-143 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-143 of SEQ ID NO: 1;~~

~~xxv. 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;~~

~~xxvi. amino acid residues 146-154 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 146-154 of SEQ ID NO: 1;~~

~~xxvii. amino acid residues 148-158 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 148-158 of SEQ ID NO: 1;~~

~~xxviii. amino acid residues 149-157 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 149-157 of SEQ ID NO: 1;~~

~~xxix. amino acid residues 149 and 150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 149 and 150 of SEQ ID NO: 1;~~

~~xxx. amino acid residues 151-155 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 151-155 of SEQ ID NO: 1;~~

~~xxxi. amino acid residues 154-161 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 154-161 of SEQ ID NO: 1;~~

~~xxxii. amino acid residues 156-170 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 156-170 of SEQ ID NO: 1;~~

~~xxxiii. amino acid residues 160-166 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 160-166 of SEQ ID NO: 1; and~~

~~xxxiv. amino acid residues 162-165 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 162-165 of SEQ ID NO: 1.~~

41. — The isolated antibody of any one of claims 1-39, wherein the antibody binds to one or more amino acid residues selected from the group consisting of K42, H43, W44, G45, H67, R77, T88, H114, E117, E151, D152, H154, and E156 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian TREM2 protein corresponding to an amino acid residue selected from the group consisting of K42, H43, W44, G45, H67, R77, T88, H114, E117, E151, D152, H154, and E156 of SEQ ID NO: 1.

42. — The isolated antibody of any one of claims 1-41, wherein the antibody competes with one or more antibodies selected from the group consisting of 3B10, 7B3, 8F8, 9F5, 9G1, 9G3, 11A8, 12F9, 7E9, 7F6, 8C3, 2C5, 3C5, 4C12, 7D9, 2F6, 3A7, 7E5, 11H5, 1B4, 6H2, 7B11, 18D8, 18E4, 29F6, 40D5, 43B9, 44A8, 44B4, and any combination thereof for binding to TREM2.

43. — The isolated antibody of any one of claims 1-41, wherein the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain, or the heavy chain variable domain, or both comprise at least one, two, three, four, five, or six HVRs selected from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 of an antibody selected from the group consisting of: 4D11, 7C5, 6G12, 8F11, 8E10, 7E5, 7F8, 8F8, 1H7, 2H8, 3A2, 3A7,

3B10, 4F11, 6H6, 7A9, 7B3, 8A1, 9F5, 9G1, 9G3, 10A9, 11A8, 12D9, 12F9, 10C1, 7E9, 7F6, 8C3, 2C5, 3C5, 4C12, 7D9, 2F6, 11H5, B4, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, and 44B4v2.

44. ~~The isolated antibody of claim 43, wherein:~~

- ~~(a) the HVR L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828;~~
- ~~(b) the HVR L2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743;~~
- ~~(c) the HVR L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746;~~
- ~~(d) the HVR H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835;~~
- ~~(e) the HVR H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888; or~~
- ~~(f) the HVR H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770.~~

45. ~~The isolated antibody of claim 43, wherein:~~

- ~~(a) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 36, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 88;~~
- ~~(b) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 90;~~
- ~~(c) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 35, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 73, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 92;~~

- ~~(d) — the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 76, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 95;~~
- ~~(e) — the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 60, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 78, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 97;~~
- ~~(f) — the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 60, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 888, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 97;~~
- ~~(g) — the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 61, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 79, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 98;~~
- ~~(h) — the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 62, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 80, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 99;~~
- ~~(i) — the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 22, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 63, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 82, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 100; or~~
- ~~(j) — the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 65, the HVR-H2 comprises the amino acid sequence of~~

~~SEQ ID NO: 84, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 102.~~

~~46. The isolated antibody of any one of claims 1-41, wherein the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises:~~

- ~~(a) an HVR L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828;~~
- ~~(b) an HVR L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743; and~~
- ~~(c) an HVR L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746; and~~

~~wherein the heavy chain variable domain comprises:~~

- ~~(a) an HVR H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835;~~
- ~~(b) an HVR H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888; and~~
- ~~(c) an HVR H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770.~~

~~47. The isolated antibody of any one of claims 1-41, wherein the antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 219-398, 602-634, 679-689, 724-730, 809-816, 821, 843, 844, 849, and 850; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 399-580, 635-678, 731-733, 817-820, 822-825, and 845-847.~~

48. ~~An isolated antibody that binds to a TREM2 protein, wherein the antibody binds to one or more amino acids within amino acid residues selected from the group consisting of:~~

- ~~i. amino acid residues 19-174 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 19-174 of SEQ ID NO: 1;~~
- ~~ii. amino acid residues 29-112 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 29-112 of SEQ ID NO: 1;~~
- ~~iii. amino acid residues 113-174 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 113-174 of SEQ ID NO: 1;~~
- ~~iv. amino acid residues 35-49 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 35-49 of SEQ ID NO: 1;~~
- ~~v. amino acid residues 35-49 and 140-150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 35-49 and 140-150 of SEQ ID NO: 1;~~
- ~~vi. amino acid residues 39-49 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 39-49 of SEQ ID NO: 1;~~
- ~~vii. amino acid residues 39-49 and 63-77 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 39-49 and 63-77 of SEQ ID NO: 1;~~
- ~~viii. amino acid residues 51-61 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 51-61 of SEQ ID NO: 1;~~
- ~~ix. amino acid residues 55-62 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-62 of SEQ ID NO: 1;~~
- ~~x. amino acid residues 55-62, 104-109, and 148-158 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-62, 104-109, and 148-158 of SEQ ID NO: 1;~~
- ~~xi. amino acid residues 55-62, 104-109, and 160-166 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-62, 104-109, and 160-166 of SEQ ID NO: 1;~~
- ~~xii. amino acid residues 55-65 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-65 of SEQ ID NO: 1;~~
- ~~xiii. amino acid residues 55-65 and 124-134 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 55-65 and 124-134 of SEQ ID NO: 1;~~
- ~~xiv. amino acid residues 63-73 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 63-73 of SEQ ID NO: 1;~~
- ~~xv. amino acid residues 63-77 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 63-77 of SEQ ID NO: 1;~~

- ~~xvi. amino acid residues 104-109 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 104-109 of SEQ ID NO: 1;~~
- ~~xvii. amino acid residues 117-133 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 117-133 of SEQ ID NO: 1;~~
- ~~xviii. amino acid residues 124-134 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 124-134 of SEQ ID NO: 1;~~
- ~~xix. amino acid residues 137-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 137-146 of SEQ ID NO: 1;~~
- ~~xx. amino acid residues 139-147 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-147 of SEQ ID NO: 1;~~
- ~~xxi. amino acid residues 139-149 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-149 of SEQ ID NO: 1;~~
- ~~xxii. amino acid residues 140-150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-150 of SEQ ID NO: 1;~~
- ~~xxiii. amino acid residues 140-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-146 of SEQ ID NO: 1;~~
- ~~xxiv. amino acid residues 140-143 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-143 of SEQ ID NO: 1;~~
- ~~xxv. 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;~~
- ~~xxvi. amino acid residues 146-154 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 146-154 of SEQ ID NO: 1;~~
- ~~xxvii. amino acid residues 148-158 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 148-158 of SEQ ID NO: 1;~~
- ~~xxviii. amino acid residues 149-157 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 149-157 of SEQ ID NO: 1;~~
- ~~xxix. amino acid residues 149 and 150 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 149 and 150 of SEQ ID NO: 1;~~
- ~~xxx. amino acid residues 151-155 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 151-155 of SEQ ID NO: 1;~~
- ~~xxxi. amino acid residues 154-161 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 154-161 of SEQ ID NO: 1;~~
- ~~xxxii. amino acid residues 156-170 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 156-170 of SEQ ID NO: 1;~~
- ~~xxxiii. amino acid residues 160-166 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 160-166 of SEQ ID NO: 1; and~~

~~xxxiv. amino acid residues 162-165 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 162-165 of SEQ ID NO: 1.~~

~~49. The isolated antibody of claim 48, 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.~~

~~50. The isolated antibody of claim 48 or claim 49, wherein the antibody further binds to one or more amino acid residues selected from the group consisting of:~~

- ~~i. amino acid residue Arg47 or Asp87 of SEQ ID NO: 1;~~
- ~~ii. amino acid residues 40-44 of SEQ ID NO: 1;~~
- ~~iii. amino acid residues 67-76 of SEQ ID NO: 1; and~~
- ~~iv. amino acid residues 114-118 of SEQ ID NO: 1.~~

~~51. An isolated antibody that binds to a TREM2 protein, wherein the antibody binds to one or more amino acid residues selected from the group consisting of K42, H43, W44, G45, H67, R77, T88, H114, E117, E151, D152, H154, and E156 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian TREM2 protein corresponding to an amino acid residue selected from the group consisting of K42, H43, W44, G45, H67, R77, T88, H114, E117, E151, D152, H154, and E156 of SEQ ID NO: 1.~~

~~52. An isolated antibody that binds to a TREM2 protein, wherein the antibody competes with one or more antibodies selected from the group consisting of 1A7, 3A2, 3B10, 6G12, 6H6, 7A9, 7B3, 8A1, 8E10, 8F11, 8F8, 9F5, 9G1, 9G3, 10A9, 10C1, 11A8, 12E2, 12F9, 12G6, 2C7, 2F5, 3C1, 4D7, 4D11, 6C11, 6G12, 7A3, 7C5, 7E9, 7F6, 7G1, 7H1, 8C3, 8F10, 12A1, 1E9, 2C5, 3C5, 4C12, 4F2, 5A2, 6B3, 7D1, 7D9, 11D8, 8A12, 10E7, 10B11, 10D2, 7D5, 2A7, 3G12, 6H9, 8G9, 9B4, 10A1, 11A8, 12F3, 2F8, 10E3, 1H7, 2F6, 2H8, 3A7, 7E5, 7F8, 11H5, 7C5, 4F11, 12D9, 1B4v1, 1B4v2, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, 44B4v2, and any combination thereof for binding to TREM2.~~

~~53. An isolated antibody that binds to a TREM2 protein, wherein the antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain, or the heavy chain variable domain, or both comprise at least one, two, three, four, five, or six HVRs selected from HVR L1, HVR L2, HVR L3, HVR H1, HVR H2, and HVR H3 of an antibody selected from the group consisting of: 1A7, 3A2, 3B10, 6G12, 6H6, 7A9, 7B3, 8A1, 8E10, 8F11, 8F8, 9F5, 9G1, 9G3, 10A9, 10C1, 11A8, 12E2, 12F9, 12G6, 2C7, 2F5, 3C1, 4D7, 4D11, 6C11, 6G12, 7A3, 7C5, 7E9, 7F6, 7G1, 7H1, 8C3, 8F10, 12A1, 1E9, 2C5, 3C5, 4C12, 4F2, 5A2, 6B3, 7D1, 7D9, 11D8, 8A12, 10E7, 10B11, 10D2, 7D5, 2A7, 3G12, 6H9, 8G9, 9B4, 10A1, 11A8, 12F3, 2F8, 10E3, 1H7, 2F6, 2H8, 3A7, 7E5, 7F8, 11H5, 7C5, 4F11, 12D9, 1B4v1, 1B4v2, 6H2, 7B11v1, 7B11v2, 18D8, 18E4v1, 18E4v2, 29F6v1, 29F6v2, 40D5v1, 40D5v2, 43B9, 44A8v1, 44A8v2, 44B4v1, and 44B4v2.~~

~~54. The isolated antibody of claim 53, wherein:~~

- ~~(a) the HVR L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828;~~
- ~~(b) the HVR L2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743;~~
- ~~(c) the HVR L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746;~~
- ~~(d) the HVR H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835;~~
- ~~(e) the HVR H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888; or~~
- ~~(f) the HVR H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770.~~

~~55. The isolated antibody of claim 53 or claim 54, wherein:~~

- ~~(a) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 34, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 48, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 85;~~
- ~~(b) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 25, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 35, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 67, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 86;~~
- ~~(c) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 12, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 37, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 50, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 68, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 87;~~
- ~~(d) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 36, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR H2 comprises the amino acid sequence of~~

~~SEQ ID NO: 69, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 88;~~

- ~~(e) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 13, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 38, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 52, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 89;~~
- ~~(f) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 90;~~
- ~~(g) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 40, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 72, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 91;~~
- ~~(h) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 35, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 73, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 92;~~
- ~~(i) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 581, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 582, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 74, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 93;~~
- ~~(j) the HVR L1 comprises the amino acid sequence of SEQ ID NO: 17, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 30, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 41, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR H2 comprises the amino acid sequence of~~

~~SEQ ID NO: 75, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 94;~~

- ~~(k) — the HVR H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 76, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 95;~~
- ~~(l) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 42, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 59, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 77, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 96;~~
- ~~(m) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 43, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 60, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 78, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 97;~~
- ~~(n) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 43, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 60, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 888, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 97;~~
- ~~(o) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 20, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 44, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 61, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 79, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 98;~~
- ~~(p) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 21, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 45, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 62, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 80, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 99;~~
- ~~(q) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR L3 comprises the~~

- ~~amino acid sequence of SEQ ID NO: 40, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 81, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 91;~~
- ~~(r) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 22, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 46, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 63, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 82, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 100;~~
- ~~(s) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 23, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 47, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 64, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 83, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 101;~~
- ~~(t) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 35, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 65, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 84, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 102;~~
- ~~(u) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 581, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 582, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 585, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 588;~~
- ~~(v) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 35, the HVR H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 586, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 86; or~~
- ~~(w) — the HVR L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR L3 comprises the amino acid sequence of SEQ ID NO: 583, the HVR H1 comprises the amino acid~~

sequence of SEQ ID NO: 584, the HVR H2 comprises the amino acid sequence of SEQ ID NO: 587, and the HVR H3 comprises the amino acid sequence of SEQ ID NO: 589.

56. — The isolated antibody of claim 53, wherein the light chain variable domain comprises:

- (a) — an HVR L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-23, 581, 690-694, 734-738, and 826-828;
- (b) — an HVR L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-33, 695-697, and 739-743; and
- (c) — an HVR L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-47, 582, 583, 698-702, and 744-746; and

wherein the heavy chain variable domain comprises:

- (a) — an HVR H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-65, 584, 703-705, 747-754, and 829-835;
- (b) — an HVR H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-84, 585-587, 706-708, 755-762, 836-842, and 888; and
- (c) — an HVR H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-102, 588, 589, 709, 710, and 763-770.

57. — The isolated antibody of any one of claims 53-56, wherein the antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 219-398, 602-634, 679-689, 724-730, 809-816, 821, 843, 844, 849, and 850; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 399-580, 635-678, 731-733, 817-820, 822-825, and 845-847.

~~58. — The isolated antibody of any one of claims 48-57, wherein the antibody competes with one or more TREM2 ligands for binding to the TREM2 protein.~~

~~59. — The isolated antibody of any one of claims 48-58, wherein the antibody is an inert antibody that binds to a TREM2 protein.~~

~~60. — The isolated antibody of any one of claims 48-58, wherein the antibody is an antagonist antibody that binds to a TREM2 protein.~~

~~61. — The isolated antibody of claim 59 or claim 60, wherein the TREM2 protein is a mammalian protein or a human protein.~~

~~62. — The isolated antibody of claim 61, wherein the TREM2 protein is a wild-type protein.~~

~~63. — The isolated antibody of claim 61, wherein the TREM2 protein is a naturally occurring variant.~~

~~64. — The isolated antibody of claim 61, wherein the TREM2 protein is a disease variant.~~

~~65. — The isolated antibody of any one of claims 60-64, wherein the antibody inhibits one or more TREM2 activities.~~

~~66. — The isolated antibody of claim 65, 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) — recruitment of Syk to a DAP12/TREM2 complex;~~

~~(e) — 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;~~

~~(f) — increasing tumor volume; and~~

~~(g) — increasing tumor growth rate.~~

~~67. — The isolated antibody of any one of claims 60-66, wherein the antibody inhibits interaction between TREM2 and one or more TREM2 ligands, inhibits TREM2 signal transduction, or both.~~

~~68. — The isolated antibody of any one of claims 60-67, wherein the antibody is incapable of binding an Fc-gamma receptor (FcγR).~~

~~69. — The isolated antibody of any one of claims 59-68, wherein the antibody has an IgG1, IgG2, IgG3, or IgG4 isotype.~~

~~70. The isolated antibody of claim 69, wherein:~~

- ~~(a) the 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, N297Q, D270A, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, 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;~~
- ~~(b) the 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, H268E, V309L, N297A, N297Q, A330S, P331S, C232S, C233S, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or~~
- ~~(c) the antibody has an IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: E233P, F234V, L234A/F234A, L235A, G237A, E318A, S228P, L236E, S241P, L248E, T394D, M252Y, S254T, T256E, N297A, N297Q, and any combination thereof, wherein the numbering of the residues is according to EU numbering.~~

~~71. The isolated antibody of claim 70, wherein:~~

- ~~(a) the Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of A330L, L234F, L235E, P331S, and any combination thereof, wherein the numbering of the residues is according to EU numbering;~~
- ~~(b) the Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or~~
- ~~(c) the Fc region further comprises a S228P amino acid substitution according to EU numbering.~~

~~72. The isolated antibody of any one of claims 1-71, wherein the antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, a naturally occurring variant of human TREM2, and a disease variant of human TREM2, and optionally wherein the antibody fragment is cross-linked to a second antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, a naturally occurring variant of human TREM2, and a disease variant of human TREM2.~~

~~73. — The isolated antibody of claim 72, wherein the fragment is an Fab, Fab', Fab' SH, F(ab')<sub>2</sub>, Fv or scFv fragment.~~

~~74. — The isolated antibody of any one of claims 1-73, 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.~~

~~75. — The isolated antibody of any one of claims 1-74, wherein the antibody is a murine antibody.~~

~~76. — The isolated antibody of any one of claims 1-74, wherein the antibody is a humanized antibody, a bispecific antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody.~~

~~77. — The isolated antibody of any one of claims 1-76, wherein the antibody is a monoclonal antibody.~~

~~78. — The isolated antibody of any one of claims 1-77, wherein the antibody is a bispecific antibody recognizing a first antigen and a second antigen.~~

~~79. — The isolated antibody of claim 78, wherein the first antigen is human TREM2 or a naturally occurring variant thereof, and the second antigen is:~~

- ~~(a) — an antigen facilitating transport across the blood-brain barrier;~~
- ~~(b) — an antigen facilitating transport across the blood-brain barrier selected from the group consisting of transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopeptide, and ANG1005;~~
- ~~(c) — a disease-causing agent selected from the group consisting of disease-causing peptides or proteins or, disease-causing nucleic acids, wherein the disease-causing nucleic acids are antisense GGCCC (G2C4) repeat expansion RNA, the disease-causing proteins are selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrP<sup>Sc</sup>, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin-1, ataxin-2, ataxin-3, ataxin-7, ataxin-8, ataxin-10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta-2~~

microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides;

(d) — ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA-4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG-3, and phosphatidylserine; and

(e) — a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells.

80. — The isolated antibody of any one of claims 1-79, wherein the antibody is used in combination with one or more antibodies that specifically bind a disease-causing agent selected from the group consisting of disease-causing peptides, disease-causing proteins, amyloid-beta, oligomeric amyloid-beta, amyloid-beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open-reading frame 72), prion protein, PrP<sup>Sc</sup>, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin-1, ataxin-2, ataxin-3, ataxin-7, ataxin-8, ataxin-10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta-2-microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and any combination thereof; or with one or more antibodies that bind an immunomodulatory protein selected from the group consisting of: CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA-4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG-3, TREM1, TREM2, CD33, Siglec-5, Siglec-9, Siglec-11, phosphatidylserine, disease-causing nucleic acids, antisense GGCCCC (G2C4) repeat expansion RNA, and any combination thereof.

81. — The isolated antibody of any one of the preceding claims, wherein when administered to an individual increases memory, reduces cognitive deficit, or both.

82. — The isolated antibody of any one of the preceding claims, wherein the antibody binds specifically to both human TREM2 and mouse TREM2.

83. — The isolated antibody of any one of the preceding claims, wherein the antibody has dissociation constant ( $K_D$ ) for human TREM2 and mouse TREM2 that ranges from about 12.8 nM to about 1.2 nM, or less than 1.2 nM, wherein the  $K_D$  is determined at a temperature of approximately 4°C.

~~84. The isolated antibody of any one of the preceding claims, wherein the antibody has dissociation constant ( $K_D$ ) for human TREM2 that ranges from about 12.8 nM to about 2.9 nM, or less than 2.9 nM, wherein the  $K_D$  is determined at a temperature of approximately 4°C.~~

~~85. The isolated antibody of any one of the preceding claims, wherein the antibody has dissociation constant ( $K_D$ ) for mouse TREM2 that ranges from about 10.4 nM to about 1.2 nM, or less than 1.2 nM, wherein the  $K_D$  is determined at a temperature of approximately 4°C.~~

~~86. The isolated antibody of any one of the preceding claims, wherein the antibody does not inhibit the growth of innate immune cells.~~

~~87. The isolated antibody of any one of the preceding claims, wherein the antibody binds to primary immune cells with a  $K_D$  of less than 1 nM, wherein the  $K_D$  is determined at a temperature of approximately 4°C.~~

~~88. The isolated antibody of any one of the preceding claims, wherein the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 1% or more of the concentration of the antibody in the blood.~~

~~89. The isolated antibody of any one of the preceding claims, wherein the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 2% or more of the concentration of the antibody in the blood.~~

~~90. The isolated antibody of any one of the preceding claims, wherein the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 3% or more of the concentration of the antibody in the blood.~~

~~91. The isolated antibody of any one of the preceding claims, wherein the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 4% or more of the concentration of the antibody in the blood.~~

1. An isolated antibody that binds to a 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 a control antibody.

2. The isolated 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 a control antibody.

3. The isolated 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 a control antibody.

4. The isolated 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 a control antibody.
5. The isolated 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 a control antibody.
6. The isolated 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 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 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 a 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 a control antibody.
9. The isolated antibody of any one of claims 1-8, wherein the Abeta peptide is Abeta42 or Abeta40.
10. The isolated 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 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 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 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 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 antibody of any one of claims 1-14, wherein the TREM2 protein is: (a) a non-human mammalian TREM2 protein or a human TREM2 protein; and/or (b) a wild-type protein, a naturally occurring variant, or a disease variant.

16. The isolated 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- $\beta$ , IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , 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 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 NTKVDKTVERKCCVECPCP (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 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 antibody of any one of claims 1-18, wherein the 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 antibody of any one of claims 1-19, wherein the 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 antibody of any one of claims 1-20, wherein:

(a) the antibody is an antibody fragment and the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')<sub>2</sub>, Fv or scFv fragment;

(b) the antibody is a murine antibody, a humanized antibody, a bispecific antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody; and/or

(c) the antibody is a monoclonal antibody.

22. The isolated antibody of any one of claims 1-21, wherein the antibody binds specifically to both human TREM2 and mouse TREM2.

23. The isolated antibody of any one of claims 1-22, 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.

92.24. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of ~~the preceding~~ claims 1-23.

93.25. A vector comprising the nucleic acid of claim ~~24~~92.

94.26. An isolated host cell comprising the vector of claim ~~25~~93.

95.27. A method of producing an antibody that binds to TREM2, comprising culturing the host cell of claim ~~26~~94 so that the antibody is produced.

96. ~~The method of claim 95, further comprising recovering the antibody produced by the cell.~~

97.28. An isolated antibody that binds to TREM2 produced by the method of claim ~~95 or~~ ~~claim 96~~ 27.

98.29. A pharmaceutical composition comprising the antibody of any one of claims 1-~~23~~94 and a pharmaceutically acceptable carrier.

99.30. Use of a therapeutically effective amount of the isolated antibody of any one of claims 1-23 in ~~the manufacture of a medicament for~~ A method of preventing, reducing risk ~~of~~, or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, ~~Nasu-Hakola disease~~, cognitive deficit, memory loss, spinal cord injury, traumatic brain injury, ~~multiple sclerosis~~, chronic colitis, and ulcerative colitis, ~~and cancer, comprising administering to an individual in need thereof a therapeutically effective amount of an isolated antibody that binds to a TREM2 protein.~~

100. ~~The method of claim 99, wherein the isolated antibody is:~~

(a) ~~an agonist antibody;~~

(b) ~~an inert antibody; or~~

(c) ~~an antagonist antibody.~~

101. The method of claim 99 or claim 100, wherein the isolated antibody is the antibody of any ~~one of claims 1-91.~~

~~102.31. The use of claim 30 method of any one of claims 99-101, wherein the disease, disorder, or injury is Alzheimer's disease.~~

~~103.—The method of any one of claims 99-102, wherein the isolated antibody that binds to a TREM2 protein increases expression of one or more inflammatory mediators, wherein the one or more inflammatory mediators are selected from the group consisting of IL-1 $\beta$ , TNF- $\alpha$ , YM-1, CD86, CCL2, CCL3, CCL5, CCR2, CXCL10, Gata3, Rorc, and any combination thereof.~~

~~104.—The method of any one of claims 99-102, wherein the isolated antibody that binds to a TREM2 protein decreases expression of one or more inflammatory mediators, wherein the one or more inflammatory mediators are selected from the group consisting of FLT1, OPN, CSF-1, CD11c, AXL, and any combination thereof.~~

~~105.—The method of any one of claims 99-104, wherein the isolated antibody that binds to a TREM2 protein decreases levels of Abeta peptide in the individual.~~

~~106.—The method of any one of claims 99-105, wherein the isolated antibody that binds to a TREM2 protein increases the number of CD11b<sup>+</sup> microglial cells in the brain of the individual.~~

~~107.—The method of any one of claims 99-106, wherein the isolated antibody that binds to a TREM2 protein increases memory of the individual.~~

~~108.—The method of any one of claims 99-107, wherein the isolated antibody that binds to a TREM2 protein reduces cognitive deficit in the individual.~~

~~109.—The method of any one of claims 99-108, wherein the isolated antibody that binds to a TREM2 protein increases motor coordination in the individual.~~

~~110.—The method of any one of claims 99-109, further comprising administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or another standard or investigational anti-cancer therapy.~~

~~111.—The method of claim 110, wherein the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the isolated antibody.~~

~~112.—The method of claim 110 or claim 111, wherein the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from the group consisting of an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-PD-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.~~

113. —The method of claim 110, wherein 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.

114. —The method of any one of claims 99-113, further comprising administering to the individual at least one antibody that specifically binds to an inhibitory cytokine.

115. —The method of claim 114, wherein the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the isolated antibody.

116. —The method of claim 114 or claim 115, wherein 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.

117. —The method of any one of claims 99-116, further comprising administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein.

118. —The method of claim 117, wherein the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the isolated antibody.

119. —The method of claim 117 or claim 118, wherein 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.

120. —The method of any one of claims 99-119, further comprising administering to the individual at least one stimulatory cytokine.

121. —The method of claim 120, wherein the at least one stimulatory cytokine is administered in combination with the isolated antibody.

122. —The method of claim 120 or claim 121, wherein the at least one stimulatory cytokine is selected from the group consisting of TNF- $\alpha$ , 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- $\alpha$ , IFN- $\beta$ , IL-2, IL-18, GM-CSF, G-CSF, and any combination thereof.

~~123. — 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 antibody that binds to a TREM2 protein.~~

~~124. — A method of inducing one or more TREM2 activities in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated antibody that binds to a TREM2 protein.~~

~~125. — A method of inducing one or more TREM2 activities and 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 antibody that binds to a TREM2 protein.~~

~~126. — A method of decreasing cellular levels of TREM2 on one or more cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated antibody that binds to a TREM2 protein.~~

~~127. — The method of any one of claims 123–126, wherein the isolated antibody is the antibody of any one of claims 1–91.~~

~~128. — The method of any one of claims 99–127, wherein the individual has a heterozygous variant of TREM2, wherein the variant comprises one or more substitutions selected from the group consisting of:~~

- ~~i. — a glutamic acid to stop codon substitution in the nucleic acid sequence encoding amino acid residue Glu14 of SEQ ID NO: 1;~~
- ~~ii. — a glutamine to stop codon substitution in the nucleic acid sequence encoding amino acid residue Gln33 of SEQ ID NO: 1;~~
- ~~iii. — a tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue Trp44 of SEQ ID NO: 1;~~
- ~~iv. — an arginine to histidine amino acid substitution at an amino acid corresponding to amino acid residue Arg47 of SEQ ID NO: 1;~~
- ~~v. — a tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue Trp78 of SEQ ID NO: 1;~~
- ~~vi. — a valine to glycine amino acid substitution at an amino acid corresponding to amino acid residue Val126 of SEQ ID NO: 1;~~
- ~~vii. — an aspartic acid to glycine amino acid substitution at an amino acid corresponding to amino acid residue Asp134 of SEQ ID NO: 1; and~~
- ~~viii. — a lysine to asparagine amino acid substitution at an amino acid corresponding to amino acid residue Lys186 of SEQ ID NO: 1.~~

~~129. —The method of any one of claims 99-128, wherein the individual has a heterozygous variant of TREM2, wherein the variant comprises a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G313 of the nucleic acid sequence encoding SEQ ID NO: 1; a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G267 of the nucleic acid sequence encoding SEQ ID NO: 1; or both.~~

~~130. —The method of any one of claims 99-129, wherein the individual has a heterozygous variant of DAP12, wherein the variant comprises one or more variants selected from the group consisting of:~~

- ~~i. —a methionine to threonine substitution at an amino acid corresponding to amino acid residue Met1 of SEQ ID NO: 2;~~
- ~~ii. —a glycine to arginine amino acid substitution at an amino acid corresponding to amino acid residue Gly49 of SEQ ID NO: 2;~~
- ~~iii. —a deletion within exons 1-4 of the nucleic acid sequence encoding SEQ ID NO: 2;~~
- ~~iv. —an insertion of 14 amino acid residues at exon 3 of the nucleic acid sequence encoding SEQ ID NO: 2; and~~
- ~~v. —a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G141 of the nucleic acid sequence encoding SEQ ID NO: 2.~~

~~131. —A method of inducing or promoting innate immune cell survival or wound healing 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.~~

~~132. —The method of claim 131, wherein the isolated antibody is the antibody of any one of claims 1-58 and 72-91.~~

~~133. —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.~~

~~134. —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.~~

~~135.~~ 32. Use of a therapeutically effective amount of the isolated antibody of any one of claims 1-23 in the manufacture of a medicament for ~~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.

33. —The use of claim 32, wherein Abeta peptide levels are reduced in the brain of the individual.

34. —The use of any one of claims 30-33, wherein:

(a) the individual has a heterozygous variant of TREM2, wherein:

1) the variant comprises one or more substitutions selected from the group consisting of:

- i) a glutamic acid to stop codon substitution in the nucleic acid sequence encoding amino acid residue Glu14 of SEQ ID NO: 1,
- ii) a glutamine to stop codon substitution in the nucleic acid sequence encoding amino acid residue Gln33 of SEQ ID NO: 1,
- iii) a tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue Trp44 of SEQ ID NO: 1,
- iv) an arginine to histidine amino acid substitution at an amino acid corresponding to amino acid residue Arg47 of SEQ ID NO: 1,
- v) a tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue Trp78 of SEQ ID NO: 1,
- vi) a valine to glycine amino acid substitution at an amino acid corresponding to amino acid residue Val126 of SEQ ID NO: 1,
- vii) an aspartic acid to glycine amino acid substitution at an amino acid corresponding to amino acid residue Asp134 of SEQ ID NO: 1, and
- viii) a lysine to asparagine amino acid substitution at an amino acid corresponding to amino acid residue Lys186 of SEQ ID NO: 1; and/or

2) the variant comprises:

- i) a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G313 of the nucleic acid sequence encoding SEQ ID NO: 1, and/or
- ii) a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G267 of the nucleic acid sequence encoding SEQ ID NO: 1; and/or

(b) the individual has a heterozygous variant of DAP12, wherein the variant comprises one or more variants selected from the group consisting of:

- i) a methionine to threonine substitution at an amino acid corresponding to amino acid residue Met1 of SEQ ID NO: 887;
- ii) a glycine to arginine amino acid substitution at an amino acid corresponding to amino acid residue Gly49 of SEQ ID NO: 887;
- iii) a deletion within exons 1-4 of the nucleic acid sequence encoding SEQ ID NO: 887;
- iv) an insertion of 14 amino acid residues at exon 3 of the nucleic acid sequence encoding SEQ ID NO: 887; and
- v) a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G141 of the nucleic acid sequence encoding SEQ ID NO: 887.

136. — ~~A method of increasing the number of CD11b<sup>+</sup> 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.~~
137. — ~~A method of increasing levels of one or more of FLT1, OPNCSF1, CD11c, and AXL 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.~~
138. — ~~A method of treating spinal cord injury 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.~~
139. — ~~A method of treating chronic colitis or ulcerative colitis 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.~~
140. — ~~The method of claim of any one of claims 133-139, wherein the isolated antibody is the antibody of any one of claims 1-91.~~
141. — ~~The method of claim of any one of the preceding claims, wherein the antibody does not inhibit the growth of innate immune cells.~~
142. — ~~The method of claim of any one of the preceding claims, wherein the antibody binds to primary immune cells with a K<sub>D</sub> of less than 1 nM, wherein the K<sub>D</sub> is determined at a temperature of approximately 4°C.~~
143. — ~~The method of claim of any one of the preceding claims, wherein the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 1% or more of the concentration of the antibody in the blood.~~
144. — ~~The method of claim of any one of the preceding claims, wherein the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 2% or more of the concentration of the antibody in the blood.~~
145. — ~~The method of claim of any one of the preceding claims, wherein the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 3% or more of the concentration of the antibody in the blood.~~
146. — ~~The method of claim of any one of the preceding claims, wherein the antibody accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 4% or more of the concentration of the antibody in the blood.~~