

[0021] Moreover, the tumor microenvironment is composed of a heterogeneous immune infiltrate, which include T lymphocytes, macrophages and cells of myeloid/granulocytic lineage. Therapeutic approaches that modulate specific subsets of immune cells are changing the standard of care. “Checkpoint blocking” antibodies targeting immune-modulatory molecules 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).

[0022] 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. Accordingly, there is a need for antibodies that specifically bind TREM2 and/or DAP12 and (*e.g.*, activate or inhibit) one or more TREM2 and/or DAP12 activities in tumor-associated immune cells, such as macrophages, dendritic cells, myeloid/granulocytic cells, T cells, and monocytes.

[0023] All references cited herein, including patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[0024] The present disclosure is generally directed to methods and compositions that include antibodies, *e.g.*, monoclonal antibodies, chimeric antibodies, bispecific antibodies, humanized antibodies, antibody fragments, *etc.*, that specifically bind a TREM2 protein and/or its signaling adaptor molecule DAP12, *e.g.*, a mammalian TREM2, a human TREM2, a mammalian DAP12, or a human DAP12, including wild-type proteins and naturally occurring variants thereof. The antibodies of the present disclosure may include agonist antibodies, inert antibodies, and/or antagonist antibodies. The methods provided herein find use in preventing, reducing risk, or treating an individual having dementia, frontotemporal dementia, Alzheimer’s disease, Nasu-Hakola disease, or multiple sclerosis; in inducing or promoting innate immune cell survival in an individual in need thereof, and/or in decreasing innate immune cell survival in an individual in need thereof.

[0024a] In an aspect of the present disclosure, there is provided an isolated antibody that binds to a TREM2 protein and is a TREM2 antagonist.

[0024b] In another aspect of the present disclosure, there is provided an isolated nucleic acid encoding the antibody disclosed herein.

[0024c] In a further aspect of the present disclosure, there is provided a vector comprising the nucleic acid disclosed herein.

[0024d] In another aspect of the present disclosure, there is provided an isolated host cell comprising the vector disclosed herein.

[0024e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody disclosed herein and a pharmaceutically acceptable carrier.

[0024f] In another aspect of the present disclosure, there is provided a use of an isolated antibody disclosed herein, in the manufacture of a medicament for decreasing expression of one or more TREM2-dependent genes in an individual in need thereof.

[0024g] In a further aspect of the present disclosure, there is provided a use of an isolated antibody disclosed herein, in the manufacture of a medicament for decreasing innate immune cell survival in an individual in need thereof.

[0024h] In another aspect of the present disclosure, there is provided a use of an isolated antibody disclosed herein, in the manufacture of a medicament for preventing, reducing risk of, or treating a disease, disorder or injury.

[0024i] In a further aspect of the present disclosure, there is provided an isolated antibody disclosed herein, for use in therapy.

[0025] Certain examples of the present disclosure relate to different classes of anti-TREM2 antibodies. In some examples, anti-TREM2 antibodies are agonist antibodies that bind to

TREM2 and activate, induce, promote, stimulate, or otherwise increase one or more TREM2 activities, survival of one or more innate immune cells, and/or expression of IL-6. In some examples, agonist anti-TREM2 antibodies of the present disclosure compete with TREM2 ligands for binding to TREM2 expressed on a cell surface. In some examples, agonist anti-TREM2 antibodies of the present disclosure do not compete with TREM2 ligands for binding to TREM2 expressed on a cell surface. In some examples, anti-TREM2 antibodies are inert or antagonist antibodies that bind to TREM2 and decrease, inhibit, or otherwise reduce one or more TREM2 activities and/or survival of one or more innate immune cells. In some examples, inert or antagonist anti-TREM2 antibodies of the present disclosure block or otherwise inhibit ligand binding to TREM2 expressed on a cell surface.

[0026] Other examples of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein, a DAP12 protein, or both, wherein the antibody induces one or more TREM2 activities, DAP12 activities, or both.

[0027] In certain examples that may be combined with any of the preceding examples, the TREM2 protein, the DAP12 protein, or both is a mammalian protein or a human protein. In certain examples that may be combined with any of the preceding examples, the TREM2 protein, the DAP12 protein, or both is a wild-type protein. In certain examples that may be combined with any of the preceding examples, the TREM2 protein, the DAP12 protein, or both is a naturally occurring variant. In certain examples that may be combined with any of the preceding examples, the TREM2 protein, the DAP12 protein, or both is expressed on human dendritic cells, human macrophages, human monocytes, human osteoclasts, human Langerhans cells of skin, human Kupffer cells, and/or human microglia. In certain examples that may be combined with any of the preceding examples, the isolated antibody induces or retains TREM2 clustering, DAP12 clustering, or both on a cell surface. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities comprise TREM2 binding to DAP12. In certain examples that may be combined with any of the preceding examples, the one or more DAP12 activities comprise DAP12 binding to TREM2. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12

activities, or both comprise DAP12 phosphorylation, TREM2 phosphorylation, or both. In certain examples that may be combined with any of the preceding examples, DAP12 phosphorylation, TREM2 phosphorylation, or both is induced by one or more SRC family tyrosine kinases. In certain examples that may be combined with any of the preceding examples, the one or more SRC family tyrosine kinases comprise a Syk kinase. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise PI3K activation. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise increased expression of one or more anti-inflammatory cytokines. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise increased expression of one or more anti-inflammatory mediators (e.g., cytokines) selected from the group consisting of IL-12p70, IL-6, and IL-10. In certain examples that may be combined with any of the preceding examples, the increased expression occurs in one or more cells selected from the group consisting of macrophages, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and microglial cells. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise reduced expression of one or more pro-inflammatory cytokines. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise reduced expression of one or more pro-inflammatory mediators selected from the group consisting of IFN- α 4, IFN- β , IL-6, IL-12 p70, IL-1 β , TNF, TNF- α , IL-10, IL-8, CRP, TGF- β members of the chemokine protein families, IL-20 family members, IL-33, LIF, IFN- γ , OSM, CNTF, TGF- β , GM-CSF, IL-11, IL-12, IL-17, IL-18, and CRP. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise reduced expression of TNF- α , IL-6, or both. In certain examples that may be combined with any of the preceding examples, the reduced expression of the one or more pro-inflammatory mediators occurs in one or more cells selected from the group consisting of macrophages, dendritic cells, monocytes, osteoclasts, Langerhans

cells of skin, Kupffer cells, and microglial cells. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise extracellular signal-regulated kinase (ERK) phosphorylation. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise increased expression of C-C chemokine receptor 7 (CCR7). In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise induction of microglial cell chemotaxis toward CCL19 and CCL21 expressing cells. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise an enhancement, normalization, or both of the ability of bone marrow-derived dendritic cells to induce antigen-specific T-cell proliferation. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise induction of osteoclast production, increased rate of osteoclastogenesis, or both. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise increasing the survival of macrophages, microglial cells, or both. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise increasing the function of macrophages, microglial cells, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, and/or Kupffer cells. In certain examples that may be combined with any of the preceding examples, the macrophages are M1 macrophages and/or microglia, M2 macrophages and/or microglia, or both. In certain examples that may be combined with any of the preceding examples, the M1 macrophages and/or microglia are activated M1 macrophages and/or microglia. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise induction of one or more types of clearance selected from the group consisting of apoptotic neuron clearance, nerve tissue debris clearance, non-nerve tissue debris clearance, bacteria or other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, and disease-causing nucleic acid clearance. In certain examples that may be combined with any

of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise induction of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, or disease-causing nucleic acid. In certain examples that may be combined with any of the preceding examples, the disease-causing protein is selected from the group consisting of amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and proline-arginine (PR) repeat peptides. In certain examples that may be combined with any of the preceding examples, the disease-causing nucleic acid is antisense GGCCCC (G2C4) repeat-expansion RNA. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise normalization of disrupted TREM2/DAP12-dependent gene expression. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise recruitment of Syk, ZAP70, or both to a DAP12/TREM2 complex. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise Syk phosphorylation. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise increased expression of CD83 and/or CD86 on dendritic cells, macrophages, and/or monocytes. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise reduced secretion of one or more inflammatory cytokines. In certain examples that may be combined with any of the preceding examples, the one or more inflammatory cytokines are selected from the group consisting of TNF- α , IL-10, IL-6, MCP-1, IFN- α 4, IFN- β , IL-1 β , IL-8, CRP, TGF-beta members

of the chemokine protein families, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, TGF-beta, GM-CSF, IL-11, IL-12, IL-17, IL-18, and CRP. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise reduced expression of one or more inflammatory receptors. In certain examples that may be combined with any of the preceding examples, the one or more inflammatory receptors comprise CD86. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise increasing phagocytosis by macrophages, dendritic cells, monocytes, and/or microglia under conditions of reduced levels of MCSF. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise decreasing phagocytosis by macrophages, dendritic cells, monocytes, and/or microglia in the presence of normal levels of MCSF. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise increasing activity of one or more TREM2-dependent genes. In certain examples that may be combined with any of the preceding examples, the one or more TREM2-dependent genes comprise one or more nuclear factor of activated T-cells (NFAT) transcription factors. In certain examples that may be combined with any of the preceding examples, the antibody is of the IgG class the IgM class, or the IgA class. In certain examples that may be combined with any of the preceding examples, the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG2 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG2 constant region. In certain examples that may be combined with any of the preceding examples, the e human IgG2 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the antibody induces the one or more TREM2 activities, DAP12 activities, or both independently of binding to an Fc receptor. In certain examples that may be combined with any of the preceding examples, the antibody binds an inhibitory Fc receptor. In certain examples that may be combined with any of the preceding examples, the inhibitory Fc receptor is inhibitory Fc-

gamma receptor IIB (FcγRIIB). In certain examples that may be combined with any of the preceding examples, the human IgG2 constant region comprises an Fc region that comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the human IgG2 constant region comprises a light chain constant region comprising a C214S amino acid substitution, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG1 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG1 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG1 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the antibody binds an inhibitory Fc receptor. In certain examples that may be combined with any of the preceding examples, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγRIIB). In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of N297A, D265A, L234A, L235A, G237A, C226S, C229S, E233P, L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody comprises an IgG2 isotype heavy chain constant domain 1(CH1) and

hinge region. In certain examples that may be combined with any of the preceding examples, the IgG2 isotype CH1 and hinge region comprise the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDPHKPS NTKVDKTVRKCCVECPPCP (SEQ ID NO: 397). In certain examples that may be combined with any of the preceding examples, the antibody Fc region comprises a S267E amino acid substitution, a L328F a L328F amino acid substitution, or both, and/or a N297A or N297Q amino acid substitution, wherein the numbering of the residues on IgG1 is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody comprises a mouse IgG1 constant region. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG4 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG4 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG4 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the antibody binds an inhibitory Fc receptor. In certain examples that may be combined with any of the preceding examples, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of L235A, G237A, S228P, L236E, S267E, E318A, L328F, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody has a hybrid IgG2/4 isotype. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, the antibody comprises a mouse IgG4 constant region. In certain examples that may be combined with any of the preceding examples, the isolated 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, human DAP12, and naturally occurring variant of human DAP12, and 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, human DAP12, and naturally occurring variant of human DAP12. In certain examples that may be combined with any of the preceding examples, the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment.

[0028] Other examples of the present disclosure relate to an isolated inert antibody that binds to a TREM2 protein. Other examples of the present disclosure relate to an isolated antagonist antibody that binds to a TREM2 protein.

[0029] In certain examples that may be combined with any of the preceding examples, the TREM2 protein, the DAP12 protein, or both is a mammalian protein or a human protein. In certain examples that may be combined with any of the preceding examples, the TREM2 protein, the DAP12 protein, or both is a wild-type protein. In certain examples that may be combined with any of the preceding examples, the TREM2 protein, the DAP12 protein, or both is a naturally occurring variant. In certain examples that may be combined with any of the preceding examples, the isolated antibody inhibits one or more TREM2 activities, DAP12 activities, or both. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise decreasing activity of one or more TREM2-dependent genes. In certain examples that may be combined with any of the preceding examples, the one or more TREM2-dependent genes comprise one or more nuclear factor of activated T-cells (NFAT) transcription factors. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both comprise decreasing the survival of macrophages, microglial cells, M1 macrophages, M1 microglial cells, M2

macrophages, M2 microglial cells, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or dendritic cells. In certain examples that may be combined with any of the preceding examples, the isolated antibody inhibits interaction between TREM2 and one or more TREM2 ligands, inhibits TREM2 signal transduction, or both. In certain examples that may be combined with any of the preceding examples, the antibody is incapable of binding an Fc-gamma receptor (FcγR). In certain examples that may be combined with any of the preceding examples, the antibody has an IgG1 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG1 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG1 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of N297A, N297Q, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the Fc region further comprises an amino acid deletion at a position corresponding to glycine 236 according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody comprises a mouse IgG1 constant region. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG2 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG2 constant region. In certain examples that may be combined with any of the preceding examples, the e human IgG2 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding

examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of V234A, G237A, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG4 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG4 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG4 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of E233P, F234V, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the isolated 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, human DAP12, and naturally occurring variant of human DAP12. In certain examples that may be combined with any of the preceding examples, the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment.

[0030] In certain examples that may be combined with any of the preceding examples, 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, w wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the Fc region further comprises a S228P amino acid substitution according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the isolated antibody competes for binding of TREM2 with one or more TREM2 ligands. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 ligands are selected from the group consisting of *E. coli* cells, apoptotic cells, nucleic acids, anionic lipids, zwitterionic lipids, negatively charged phospholipids, phosphatidylserine, sulfatides, phosphatidylcholin, sphingomyelin, membrane phospholipids, lipidated proteins, proteolipids, lipidated peptides, and lipidated amyloid beta peptide. In certain examples that may be combined with any of the preceding examples, the isolated antibody is a human antibody, a humanized antibody, a bispecific antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody. In certain examples that may be combined with any of the preceding examples, the isolated antibody is a bispecific antibody recognizing a first antigen and a second antigen. In certain examples that may be combined with any of the preceding examples, the first antigen is human TREM2 or a naturally occurring variant thereof, and the second antigen is a disease-causing protein selected from the group consisting of amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and proline-arginine (PR) repeat peptides; a blood brain barrier targeting protein selected from the group consisting of: transferin receptor, insulin receptor, insulin like growth factor receptor, LRP-1, and LRP1; or ligands and/or proteins expressed on immune cells. In certain examples that may be combined with any of the preceding examples, the isolated

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, human DAP12, and naturally occurring variant of human DAP12; and wherein the antibody is used in combination with one or more antibodies that specifically bind a disease-causing protein selected from the group consisting of: amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and proline-arginine (PR) repeat peptides, and any combination thereof. In certain examples that may be combined with any of the preceding examples, the antibody is a monoclonal antibody.

[0031] In certain examples that may be combined with any of the preceding examples, the isolated antibody binds to a linear epitope on TREM2. In certain examples that may be combined with any of the preceding examples, the linear epitope on TREM2 is located within the extracellular domain of TREM2. In certain examples that may be combined with any of the preceding examples, the linear epitope on TREM2 is located within the extracellular immunoglobulin-like variable-type (IgV) domain of TREM2. In certain examples that may be combined with any of the preceding examples, the isolated antibody binds to a TREM2 protein, and wherein the isolated antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. 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; ii amino acid residues 29-41 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 29-41 of SEQ ID NO: 1; iii. amino acid residues 40-44 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 40-44 of SEQ ID NO: 1; iv. amino acid residues 47-69 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino

acid residues 47-69 of SEQ ID NO: 1; v. amino acid residues 67-76 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 67-76 of SEQ ID NO: 1; vi. amino acid residues 76-86 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 76-86 of SEQ ID NO: 1; vii. amino acid residues 91-100 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 91-100 of SEQ ID NO: 1; viii. amino acid residues 99-115 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 99-115 of SEQ ID NO: 1; ix. amino acid residues 104-112 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 104-112 of SEQ ID NO: 1; and x. amino acid residues 114-118 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 114-118 of SEQ ID NO: 1. In certain examples that may be combined with any of the preceding examples, the isolated antibody binds to one or more amino acids within amino acid residues 43-50 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 43-50 of SEQ ID NO: 1. In certain examples that may be combined with any of the preceding examples, the isolated antibody binds to one or more amino acids within amino acid residues 49-57 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 49-57 of SEQ ID NO: 1. In certain examples that may be combined with any of the preceding examples, the isolated antibody binds to an epitope comprising one or more amino acids within amino acid residues 43-50 of SEQ ID NO: 1. In certain examples that may be combined with any of the preceding examples, the isolated antibody binds to an epitope comprising one or more amino acids within amino acid residues 43-50 of SEQ ID NO: 1. In certain examples that may be combined with any of the preceding examples, the isolated antibody binds to an epitope comprising 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. In certain examples that may be combined with any of the preceding examples, the isolated antibody binds to one or more amino acids within amino acid residues 22-40 of SEQ ID NO: 2, or amino acid residues on a DAP12 protein corresponding to amino acid residues 22-

40 of SEQ ID NO: 2. In certain examples that may be combined with any of the preceding examples, the isolated antibody is a bispecific antibody that binds to one or more amino acids selected from the group consisting of: i. one or more amino acid residues of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues of SEQ ID NO: 1; and ii. one or more amino acid residues of SEQ ID NO: 2, or amino acid residues on a DAP12 protein corresponding to amino acid residues of SEQ ID NO: 2.

[0032] In certain examples that may be combined with any of the preceding examples, the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and/or HVR-H3 of the monoclonal antibody Ab52; and/or wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and/or HVR-L3 of the monoclonal antibody Ab52. In certain examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:398. In certain examples that may be combined with any of the preceding examples, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:399. In certain examples that may be combined with any of the preceding examples, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:400. In certain examples that may be combined with any of the preceding examples, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:401. In certain examples that may be combined with any of the preceding examples, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:402. In certain examples that may be combined with any of the preceding examples, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:403. In certain examples that may be combined with any of the preceding examples, the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:398, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:398; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:399, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:399; and; and/or (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:400, or an amino acid sequence with at least about 95% homology to the amino acid

sequence of SEQ ID NO:400; and/or wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:401, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:401; (b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:402, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:402; and/or (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:403, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:403. In certain examples that may be combined with any of the preceding examples, the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and/or HVR-H3 of the monoclonal antibody Ab21; and/or wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and/or HVR-L3 of the monoclonal antibody Ab21. In certain examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:404. In certain examples that may be combined with any of the preceding examples, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:405. In certain examples that may be combined with any of the preceding examples, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:406. In certain examples that may be combined with any of the preceding examples, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:407. In certain examples that may be combined with any of the preceding examples, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:408. In certain examples that may be combined with any of the preceding examples, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:409. In certain examples that may be combined with any of the preceding examples, the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:404, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:404; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:405, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:405; and/or (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:406, or an amino acid

sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:406, and/or wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:407, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:407; (b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:408, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:408; and/or (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:409, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:409.

[0033] Other examples of the present disclosure relate to an isolated anti-human TREM2 antibody, wherein the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and/or HVR-H3 of the monoclonal antibody Ab52; and/or wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and/or HVR-L3 of the monoclonal antibody Ab52. In certain examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:398. In certain examples that may be combined with any of the preceding examples, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:399. In certain examples that may be combined with any of the preceding examples, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:400. In certain examples that may be combined with any of the preceding examples, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:401. In certain examples that may be combined with any of the preceding examples, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:402. In certain examples that may be combined with any of the preceding examples, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:403. In certain examples that may be combined with any of the preceding examples, the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:398, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:399, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:400, and/or wherein the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:401,

an HVR-L2 comprising the amino acid sequence of SEQ ID NO:402, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:403.

[0034] Other examples of the present disclosure relate to an isolated anti-human TREM2 antibody, wherein the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:398, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:398; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:399, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:399; and; and/or (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:400, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:400; and/or wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:401, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:401; (b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:402, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:402; and/or (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:403, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:403.

[0035] Other examples of the present disclosure relate to an isolated anti-human TREM2 antibody, wherein the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and/or HVR-H3 of the monoclonal antibody Ab21; and/or wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and/or HVR-L3 of the monoclonal antibody Ab21. In certain examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:404. In certain examples that may be combined with any of the preceding examples, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:405. In certain examples that may be combined with any of the preceding examples, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:406. In certain examples that may be combined with any of the preceding examples, the HVR-

L1 comprises the amino acid sequence of SEQ ID NO:407. In certain examples that may be combined with any of the preceding examples, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:408. In certain examples that may be combined with any of the preceding examples, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:409. In certain examples that may be combined with any of the preceding examples, the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:404, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:405, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:406, and/or wherein the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:407, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:408, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:409.

[0036] Other examples of the present disclosure relate to an isolated anti-human TREM2 antibody, wherein the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:404, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:404; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:405, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:405; and/or (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:406, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:406, and/or wherein the light chain variable domain comprises: (a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:407, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:407; (b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:408, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:408; and/or (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:409, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:409.

[0037] Other examples of the present disclosure relate to an isolated anti-human TREM2 antibody which binds essentially the same TREM2 epitope as the antibody Ab52. Other examples of the present disclosure relate to an isolated anti-human TREM2 antibody which binds essentially the same TREM2 epitope as the antibody Ab21.

[0038] In certain examples that may be combined with any of the preceding examples, the antibody is an agonist antibody, and wherein the antibody induces one or more TREM2 activities, DAP12 activities, or both. In certain examples that may be combined with any of the preceding examples, the isolated antibody induces or retains TREM2 clustering, DAP12 clustering, or both on a cell surface. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities, DAP12 activities, or both are selected from the group consisting of TREM2 binding to DAP12; DAP12 binding to TREM2; TREM2 phosphorylation, DAP12 phosphorylation; PI3K activation; increased expression of one or more anti-inflammatory mediators (e.g., cytokines) selected from the group consisting of IL-12p70, IL-6, and IL-10; reduced expression of one or more pro-inflammatory mediators selected from the group consisting of IFN- α 4, IFN- β , IL-6, IL-12 p70, IL-1 β , TNF, TNF- α , IL-10, IL-8, CRP, TGF- β members of the chemokine protein families, IL-20 family members, IL-33, LIF, IFN- γ , OSM, CNTF, TGF- β , GM-CSF, IL-11, IL-12, IL-17, IL-18, and CRP; reduced expression of TNF- α , IL-6, or both; extracellular signal-regulated kinase (ERK) phosphorylation; increased expression of C-C chemokine receptor 7 (CCR7); induction of microglial cell chemotaxis toward CCL19 and CCL21 expressing cells; an increase, normalization, or both of the ability of bone marrow-derived dendritic cells to induce antigen-specific T-cell proliferation; induction of osteoclast production, increased rate of osteoclastogenesis, or both; increasing the survival and/or function of one or more of dendritic cells, macrophages, microglial cells, M1 macrophages and/or microglial cells, activated M1 macrophages and/or microglial cells, M2 macrophages and/or microglial cells, monocytes, osteoclasts, Langerhans cells of skin, and Kupffer cells; induction of one or more types of clearance selected from the group consisting of apoptotic neuron clearance, nerve tissue debris clearance, non-nerve tissue debris clearance, bacteria or other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, and disease-causing nucleic acid

clearance; induction of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, or disease-causing nucleic acids; normalization of disrupted TREM2/DAP12-dependent gene expression; recruitment of Syk, ZAP70, or both to the TREM2/DAP12 complex; Syk phosphorylation; increased expression of CD83 and/or CD86 on dendritic cells, macrophages, monocytes, and/or microglia; reduced secretion of one or more inflammatory cytokines selected from the group consisting of TNF- α , IL-10, IL-6, MCP-1, IFN- α 4, IFN- β , IL-1 β , IL-8, CRP, TGF- β members of the chemokine protein families, IL-20 family members, IL-33, LIF, IFN- γ , OSM, CNTF, TGF- β , GM-CSF, IL-11, IL-12, IL-17, IL-18, and CRP; reduced expression of one or more inflammatory receptors; increasing phagocytosis by macrophages, dendritic cells, monocytes, and/or microglia under conditions of reduced levels of MCSF; decreasing phagocytosis by macrophages, dendritic cells, monocytes, and/or microglia in the presence of normal levels of MCSF; increasing activity of one or more TREM2-dependent genes; and any combination thereof. In certain examples that may be combined with any of the preceding examples, the antibody is of the IgG class the IgM class, or the IgA class. In certain examples that may be combined with any of the preceding examples, the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG2 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG2 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG2 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the antibody induces the one or more TREM2 activities, DAP12 activities, or both independently of binding to an Fc receptor. In certain examples that may be combined with any of the preceding examples, the antibody binds an inhibitory Fc receptor. In certain examples that may be combined with any of the preceding examples, the inhibitory Fc receptor is inhibitory Fc- γ receptor IIB (Fc γ IIB). In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region

comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the human IgG2 constant region comprises a light chain constant region comprising a C214S amino acid substitution, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG1 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG1 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG1 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the antibody binds an inhibitory Fc receptor. In certain examples that may be combined with any of the preceding examples, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγRIIB). In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of N297A, D265A, L234A, L235A, G237A, C226S, C229S, E233P, L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody comprises an IgG2 isotype heavy chain constant domain 1(CH1) and hinge region. In certain examples that may be combined with any of the preceding examples, the IgG2 isotype CH1 and hinge region comprise the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS

WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDPHKPS
NTKVDKTVKCCVECP (SEQ ID NO: 397). In certain examples that may be combined with any of the preceding examples, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody comprises a mouse IgG1 constant region. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG4 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG4 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG4 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the antibody binds an inhibitory Fc receptor. In certain examples that may be combined with any of the preceding examples, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of L235A, G237A, S228P, L236E, S267E, E318A, L328F, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody has a hybrid IgG2/4 isotype. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, the antibody comprises a mouse IgG4 constant region. In certain examples that may be combined with any of the preceding examples, the isolated

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, human DAP12, and naturally occurring variant of human DAP12, and 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, human DAP12, and naturally occurring variant of human DAP12. In certain examples that may be combined with any of the preceding examples, the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an inert antibody. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an antagonist antibody. In certain examples that may be combined with any of the preceding examples, the isolated antibody inhibits one or more TREM2 activities. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities are selected from the group consisting of decreasing activity of one or more TREM2-dependent genes; decreasing activity of one or more nuclear factor of activated T-cells (NFAT) transcription factors; decreasing the survival of macrophages, microglial cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or dendritic cells; and any combination thereof. In certain examples that may be combined with any of the preceding examples, the isolated antibody inhibits interaction between TREM2 and one or more TREM2 ligands, inhibits TREM2 signal transduction, or both. In certain examples that may be combined with any of the preceding examples, the antibody is incapable of binding an Fc-gamma receptor (FcγR). In certain examples that may be combined with any of the preceding examples, the antibody has an IgG1 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG1 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG1 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the

preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of N297A, N297Q, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the Fc region further comprises an amino acid deletion at a position corresponding to glycine 236 according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody comprises a mouse IgG1 constant region. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG2 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG2 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG2 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of V234A, G237A, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG4 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG4 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG4 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more modifications. In certain examples that may be combined with any of the preceding examples, the Fc region comprises one or more amino acid substitutions. In certain examples that may be combined with any of the

preceding examples, the one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of E233P, F234V, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the isolated 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, human DAP12, and naturally occurring variant of human DAP12. In certain examples that may be combined with any of the preceding examples, the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment. In certain examples that may be combined with any of the preceding examples, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the Fc region further comprises a S228P amino acid substitution according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody is a human antibody, a humanized antibody, a bispecific antibody, a multivalent antibody, or a chimeric antibody. In certain examples that may be combined with any of the preceding examples, the antibody is a bispecific antibody recognizing a first antigen and a second antigen. In certain examples that may be combined with any of the preceding examples, the antibody is a monoclonal antibody.

[0039] Other examples of the present disclosure relate to an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody promotes survival of one or more innate immune cells. Other examples of the present disclosure relate to an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody increases expression of IL-6. Other examples of the

present disclosure relate to an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody promotes survival of one or more innate immune cells or increases expression of IL-6. Other examples of the present disclosure relate to an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody promotes survival of one or more innate immune cells and increases expression of IL-6. In certain examples, the one or more innate immune cells are selected from the group consisting of macrophages, microglial cells, M1 microglial cells, activated M1 microglial cells, M2 microglial cells, dendritic cells, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and any combination thereof. In certain examples, the one or more innate immune cells are macrophages. In certain examples, the one or more innate immune cells are microglial cells. In certain examples, the one or more innate immune cells are M1 microglial cells. In certain examples, the one or more innate immune cells are activated M1 microglial cells. In certain examples, the one or more innate immune cells are M2 microglial cells. In certain examples, the one or more innate immune cells are dendritic cells (DCs). In certain examples, the one or more innate immune cells are M1 macrophages. In certain examples, the one or more innate immune cells are activated M1 macrophages. In certain examples, the one or more innate immune cells are M2 macrophages. In certain examples, the one or more innate immune cells are monocytes. In certain examples, the one or more innate immune cells are osteoclasts. In certain examples, the one or more innate immune cells are Langerhans cells of skin. In certain examples, the one or more innate immune cells are Kupffer cells.

[0040] Other examples of the present disclosure relate to an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. 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; ii. amino acid residues 29-41 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 29-41 of SEQ ID NO: 1; iii. amino acid residues 40-44 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 40-44 of SEQ ID NO: 1; iv. amino acid residues 43-50 of SEQ ID NO: 1, or

amino acid residues on a TREM2 protein corresponding to amino acid residues 43-50 of SEQ ID NO: 1; v. amino acid residues 49-57 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 49-57 of SEQ ID NO: 1; vi. amino acid residues 47-69 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 47-69 of SEQ ID NO: 1; vii. amino acid residues 67-76 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 67-76 of SEQ ID NO: 1; viii. amino acid residues 76-86 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 76-86 of SEQ ID NO: 1; ix. amino acid residues 91-100 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 91-100 of SEQ ID NO: 1; x. amino acid residues 99-115 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 99-115 of SEQ ID NO: 1; xi. amino acid residues 104-112 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 104-112 of SEQ ID NO: 1; xii. amino acid residues 114-118 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 114-118 of SEQ ID NO: 1; xiii. amino acid residues 130-171 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 130-171 of SEQ ID NO: 1; xiv. amino acid residues 139-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-146 of SEQ ID NO: 1; xv. amino acid residues 140-153 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-153 of SEQ ID NO: 1; xvi. amino acid residues 130-144 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 130-144 of SEQ ID NO: 1; and xvii. amino acid residues 158-171 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 158-171 of SEQ ID NO: 1. In certain examples, the isolated antibody binds to one or more amino acids within amino acid residues 43-50 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 43-50 of SEQ ID NO: 1. In certain examples, the isolated antibody binds to one or more amino acids within amino acid residues 49-57 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 49-57 of SEQ ID NO: 1. In certain examples, the isolated antibody binds to one or more amino acids within amino

acid residues 139-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 49-57 of SEQ ID NO: 1. In certain examples, the isolated antibody binds to one or more amino acids within amino acid residues 140-153 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-153 of SEQ ID NO: 1. In certain examples, the isolated antibody binds to an epitope comprising one or more amino acids within amino acid residues 43-50 of SEQ ID NO: 1. In certain examples, the isolated antibody binds to an epitope comprising one or more amino acids within amino acid residues 49-57 of SEQ ID NO: 1. In certain examples, the isolated antibody binds to an epitope comprising one or more amino acids within amino acid residues 139-146 of SEQ ID NO: 1. In certain examples, the isolated antibody binds to an epitope comprising one or more amino acids within amino acid residues 140-153 of SEQ ID NO: 1.

[0041] In certain examples that may be combined with any of the preceding examples, the TREM2 protein is a mammalian protein or a human protein. In certain examples that may be combined with any of the preceding examples, the TREM2 protein is a wild-type protein. In certain examples that may be combined with any of the preceding examples, the TREM2 protein is a naturally occurring variant. In certain examples that may be combined with any of the preceding examples, the antibody is an agonist antibody, and wherein the antibody induces one or more TREM2 activities. In certain examples that may be combined with any of the preceding examples, the isolated antibody induces or retains TREM2 clustering on a cell surface. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities are selected from the group consisting of: i. TREM2 binding to DAP12; ii. DAP12 phosphorylation; iii. increasing the survival of macrophages, microglial cells, M1 microglial cells, activated M1 microglial cells, M2 microglial cells, dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, osteoclasts, Langerhans cells of skin, and/or Kupffer cells; iv. Syk phosphorylation; v. increased expression of CD83 and/or CD86 on dendritic cells; vi. increasing phagocytosis by macrophages, dendritic cells, monocytes, and/or microglia; vii. increasing activity of one or more TREM2-dependent genes, optionally wherein the one or more TREM2-dependent genes comprise one or more nuclear factor of activated T-cells (NFAT) transcription

factors; and viii. increasing expression of one or more mediators selected from the group consisting of IL-12p70, IL-6, and IL-10. In certain examples that may be combined with any of the preceding examples, the antibody is of the IgG class the IgM class, or the IgA class. In certain examples that may be combined with any of the preceding examples, the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG2 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG2 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG2 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the antibody induces the one or more TREM2 activities independently of binding to an Fc receptor. In certain examples that may be combined with any of the preceding examples, the antibody binds an inhibitory Fc receptor. In certain examples that may be combined with any of the preceding examples, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In certain examples that may be combined with any of the preceding examples: i. the isolated antibody has a human IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; ii. the isolated antibody has a human IgG2 isotype, wherein the human IgG2 comprises a constant region, and wherein the human IgG2 constant region comprises a light chain constant region comprising a C214S amino acid substitution, wherein the numbering of the residues is according to EU or Kabat numbering; iii. 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, L234A, L235A, G237A, C226S, C229S, E233P, L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; iv. 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 comprise the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDPHKPS NTKVDKTVERKCCVECPPCP (SEQ ID NO: 397), 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 or Kabat numbering; v. 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, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; or vi. the isolated antibody has a hybrid IgG2/4 isotype, 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 certain examples that may be combined with any of the preceding examples, the isolated antibody is an inert antibody. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an antagonist antibody. In certain examples that may be combined with any of the preceding examples, the isolated antibody inhibits one or more TREM2 activities. In certain examples that may be combined with any of the preceding examples, the inhibited one or more TREM2 activities are selected from the group consisting of decreasing activity of one or more TREM2-dependent genes; decreasing activity of one or more nuclear factor of activated T-cells (NFAT) transcription factors; decreasing the survival of macrophages, microglial cells, M1 macrophages, M1microglial cells, M2 macrophages, M2 microglial cells, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or dendritic cells; decreased expression of one or more mediators selected from the group consisting of IL-12p70, IL-6, and IL-10; and any combination thereof. In certain examples that may be combined with any of the preceding examples, the isolated antibody inhibits interaction between TREM2 and one or more TREM2 ligands, inhibits TREM2 signal transduction, or both. In certain examples that may be combined with any of the preceding examples, the antibody is incapable of binding an Fc-gamma receptor (Fc γ R). In certain examples that may

be combined with any of the preceding examples: i. the isolated antibody has a human or mouse IgG1 isotype and comprises one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of N297A, N297Q, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering, optionally wherein the Fc region further comprises an amino acid deletion at a position corresponding to glycine 236 according to EU or Kabat numbering; ii. the isolated antibody has a human IgG2 isotype and comprises one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of V234A, G237A, 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 or Kabat numbering; or iii. the isolated antibody has a human or mouse IgG4 isotype and comprises one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of E233P, F234V, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the Fc region further comprises a S228P amino acid substitution according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, and a naturally occurring variant of human TREM2, and

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, human DAP12, and naturally occurring variant of human DAP12. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an antibody fragment, and wherein the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment. In certain examples that may be combined with any of the preceding examples, the isolated antibody competes for binding of TREM2 with one or more TREM2 ligands. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 ligands are selected from the group consisting of *E. coli* cells, apoptotic cells, nucleic acids, anionic lipids, zwitterionic lipids, negatively charged phospholipids, phosphatidylserine, sulfatides, phosphatidylcholin, sphingomyelin, membrane phospholipids, lipidated proteins, proteolipids, lipidated peptides, and lipidated amyloid beta peptide. In certain examples that may be combined with any of the preceding examples, the isolated antibody is a human antibody, a humanized antibody, a bispecific antibody, a multivalent antibody, or a chimeric antibody. In certain examples that may be combined with any of the preceding examples, the isolated antibody is a bispecific antibody recognizing a first antigen and a second antigen. In certain examples that may be combined with any of the preceding examples, the first antigen is human TREM2 or a naturally occurring variant thereof, and the second antigen is a disease-causing protein selected from the group consisting of amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and proline-arginine (PR) repeat peptides; or a blood brain barrier targeting protein selected from the group consisting of: transferin receptor, insulin receptor, insulin like growth factor receptor, LRP-1, and LRP1. In certain examples that may be

combined with any of the preceding examples, the isolated antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, and a naturally occurring variant of human TREM2; and wherein the antibody is used in combination with one or more antibodies that specifically bind a disease-causing protein selected from the group consisting of: amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and proline-arginine (PR) repeat peptides, and any combination thereof. In certain examples that may be combined with any of the preceding examples, the antibody is a monoclonal antibody. In certain examples that may be combined with any of the preceding examples, the isolated antibody is a bispecific antibody that binds to TREM2 and DAP12.

[0042] In certain examples that may be combined with any of the preceding examples, the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, 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:3-24, 398, and 404; an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:25-49, 399, and 405; and (c) an HVR-H3 c comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:50-119, 400, and 406; and/or wherein the light chain variable domain comprises: (a) an HVR-L1 c comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:120-137, 401, and 407; (b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:138-152, 402, and 408; and (c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:153-236, 403, and 409.

[0043] Other examples of the present disclosure relate to an isolated anti-human TREM2 antibody, wherein the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, 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:3-24, 398, and 404; an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:25-49, 399, and 405; and (c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:50-119, 400, and 406; and/or 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:120-137, 401, and 407; (b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:138-152, 402, and 408; and (c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:153-236, 403, and 409. Other examples of the present disclosure relate to an isolated anti-human TREM2 antibody which binds essentially the same TREM2 epitope as a monoclonal antibody selected from the group consisting of: Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54, Ab55, Ab56, Ab57, Ab58, Ab59, Ab60, Ab61, Ab62, Ab63, Ab64, Ab65, Ab66, Ab67, Ab68, Ab69, Ab70, Ab71, Ab72, Ab73, Ab74, Ab75, Ab76, Ab77, Ab78, Ab79, Ab80, Ab81, Ab82, Ab83, Ab84, Ab85, Ab86, and Ab87. Other examples of the present disclosure relate to an isolated anti-human TREM2 antibody which competes with a monoclonal antibody selected from the group consisting of: Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54, Ab55, Ab56, Ab57, Ab58, Ab59, Ab60, Ab61, Ab62, Ab63, Ab64, Ab65, Ab66, Ab67, Ab68, Ab69, Ab70, Ab71, Ab72, Ab73, Ab74, Ab75, Ab76, Ab77, Ab78, Ab79, Ab80, Ab81, Ab82, Ab83, Ab84, Ab85, Ab86, and Ab87 for binding to TREM2.

[0044] In certain examples that may be combined with any of the preceding examples, the antibody is an agonist antibody, and wherein the antibody induces one or more TREM2 activities. In certain examples that may be combined with any of the preceding examples, the isolated antibody induces or retains TREM2 clustering on a cell surface. In certain examples that may be combined with any of the preceding examples, the one or more TREM2 activities are selected from the group consisting of TREM2 binding to DAP12; DAP12 phosphorylation; increasing the survival of macrophages, microglial cells, M1 microglial cells, activated M1 microglial cells, M2 microglial cells, dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, osteoclasts, Langerhans cells of skin, and/or Kupffer cells; increased expression of IL-6; Syk phosphorylation; increased expression of CD83 and/or CD86 on dendritic cells; increasing phagocytosis by macrophages, dendritic cells, monocytes, and/or microglia; and increasing activity of one or more TREM2-dependent genes, optionally wherein the one or more TREM2-dependent genes comprise one or more nuclear factor of activated T-cells (NFAT) transcription factors; and any combination thereof. In certain examples that may be combined with any of the preceding examples, the antibody is of the IgG class the IgM class, or the IgA class. In certain examples that may be combined with any of the preceding examples, the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In certain examples that may be combined with any of the preceding examples, the antibody has an IgG2 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises a human IgG2 constant region. In certain examples that may be combined with any of the preceding examples, the human IgG2 constant region comprises an Fc region. In certain examples that may be combined with any of the preceding examples, the antibody induces the one or more TREM2 activities independently of binding to an Fc receptor. In certain examples that may be combined with any of the preceding examples, the antibody binds an inhibitory Fc receptor. In certain examples that may be combined with any of the preceding examples, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In certain examples that may be combined with any of the preceding examples: i. the isolated antibody has a human IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a

residue position selected from the group consisting of V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; ii. the isolated antibody has a human IgG2 isotype, wherein the human IgG2 comprises a constant region, and wherein the human IgG2 constant region comprises a light chain constant region comprising a C214S amino acid substitution, wherein the numbering of the residues is according to EU or Kabat numbering; iii. 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, L234A, L235A, G237A, C226S, C229S, E233P, L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; iv. 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 comprise the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDPHKPS NTKVDKTVRKCCVECPPCP (SEQ ID NO: 397), 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 or Kabat numbering; v. 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 L235A, G237A, S228P, L236E, S267E, E318A, L328F, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; or vi. the isolated antibody has a hybrid IgG2/4 isotype, 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 certain examples that may be combined with any of the preceding examples, the isolated antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, and a naturally occurring variant of human TREM2, and 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, human DAP12, and naturally occurring variant of human DAP12. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an antibody fragment, and wherein the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an inert antibody. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an antagonist antibody. In certain examples that may be combined with any of the preceding examples, the isolated antibody inhibits one or more TREM2 activities. In certain examples that may be combined with any of the preceding examples, the inhibited one or more TREM2 activities are selected from the group consisting of decreasing activity of one or more TREM2-dependent genes; decreasing activity of one or more nuclear factor of activated T-cells (NFAT) transcription factors; decreasing the survival of macrophages, microglial cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or dendritic cells; decreased expression of one or more mediators selected from the group consisting of IL-12p70, IL-6, and IL-10; and any combination thereof. In certain examples that may be combined with any of the preceding examples, the isolated antibody inhibits interaction between TREM2 and one or more TREM2 ligands, inhibits TREM2 signal transduction, or both. In certain examples that may be combined with any of the preceding examples, the antibody is incapable of binding an Fc-gamma receptor (FcγR). In certain examples that may be combined with any of the preceding examples: i. the isolated antibody has a human or mouse IgG1 isotype and comprises one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of N297A, N297Q, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering, optionally wherein the Fc region further comprises an amino acid deletion at a position corresponding to glycine 236 according to EU or Kabat numbering; ii. the isolated antibody has a human IgG2 isotype and comprises one or more

amino acid substitutions in the Fc region are at a residue position selected from the group consisting of V234A, G237A, 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 or Kabat numbering; or iii. the isolated antibody has a human or mouse IgG4 isotype and comprises one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of E233P, F234V, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, and a naturally occurring variant of human TREM2. In certain examples that may be combined with any of the preceding examples, the isolated antibody is an antibody fragment, and wherein the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment. In certain examples that may be combined with any of the preceding examples, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the Fc region further comprises a S228P amino acid substitution according to EU or Kabat numbering. In certain examples that may be combined with any of the preceding examples, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the antibody is a human antibody, a humanized antibody, a bispecific antibody, a multivalent antibody, or a chimeric antibody. In certain examples that may be combined with any of the preceding examples, the antibody is a bispecific antibody recognizing a first antigen and a second antigen. In certain examples that may be combined with any of the preceding examples, the antibody is a monoclonal antibody.

[0045] In certain examples that may be combined with any of the preceding examples, the isolated antibody binds specifically to both human TREM2 and mouse TREM2. In certain examples that may be combined with any of the preceding examples, the isolated antibody has dissociation constant (K_D) for human TREM2 and mouse TREM2 that ranges from less than about 5.75 nM to less than about 0.09 nM. In certain examples that may be combined with any of the preceding examples, the isolated antibody has dissociation constant (K_D) for human TREM2-Fc fusion protein that ranges from less than about 1.51 nM to less than about 0.35 nM. In certain examples that may be combined with any of the preceding examples, the isolated antibody has dissociation constant (K_D) for human monomeric TREM2 protein that ranges from less than about 5.75 nM to less than about 1.15 nM. In certain examples that may be combined with any of the preceding examples, the isolated antibody has dissociation constant (K_D) for mouse TREM2-Fc fusion protein that ranges from less than about 0.23 nM to less than about 0.09 nM. In certain examples that may be combined with any of the preceding examples, the isolated antibody has dissociation constant (K_D) for human TREM2 and mouse TREM2 that ranges from less than about 6.70 nM to less than about 0.23 nM. In certain examples that may be combined with any of the preceding examples, the isolated antibody has dissociation constant (K_D) for human TREM2-Fc fusion protein that ranges from less than about 0.71 nM to less than about 0.23 nM. In certain examples that may be combined with any of the preceding examples, the isolated antibody has dissociation constant (K_D) for human monomeric TREM2 protein that ranges from less than about 6.70 nM to less than about 0.66 nM. In certain examples that may be combined with any of the preceding examples, the isolated antibody has dissociation constant (K_D) for mouse TREM2-Fc fusion protein that ranges from less than about 4.90 nM to less than about 0.35 nM.

[0046] Other examples of the present disclosure relate to an isolated nucleic acid encoding the antibody of any one of the preceding examples. Other examples of the present disclosure relate to a vector comprising the nucleic acid of any one of the preceding examples. Other examples of the present disclosure relate to a host cell comprising the vector of any one of the preceding examples. Other examples of the present disclosure relate to an isolated host cell comprising

the vector of any one of the preceding examples. Other examples of the present disclosure relate to a method of producing an antibody, comprising culturing the cell of any one of the preceding examples so that the antibody is produced. In certain examples, the method further comprises recovering the antibody produced by the cell. Other examples of the present disclosure relate to an isolated antibody produced by any of the preceding methods of producing an antibody. Other examples of the present disclosure relate to a pharmaceutical composition comprising the antibody of any one of the preceding examples and a pharmaceutically acceptable carrier.

[0047] Other examples of the present disclosure relate to a method of preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, Nasu-Hakola disease, and multiple sclerosis, comprising administering to the individual a therapeutically effective amount of an isolated agonist antibody of any one of the preceding examples. Other examples of the present disclosure relate to an isolated agonist antibody of any one of the preceding examples 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, and multiple sclerosis. Other examples of the present disclosure relate to use of an isolated agonist antibody of any one of the preceding examples 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, and multiple sclerosis. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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.

[0048] Other examples of the present disclosure relate to a method of inducing or promoting innate immune cell survival in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated agonist antibody of any one of the preceding examples. Other examples of the present disclosure relate to an isolated agonist antibody of any one of the preceding examples for use in inducing or promoting innate immune cell survival in an individual in need thereof. Other examples of the present disclosure relate to use of an isolated agonist antibody of any one of the preceding examples in the manufacture of a medicament for inducing or promoting innate immune cell survival in an individual in need thereof. Other examples of the present disclosure relate to a method of inducing or promoting 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. Other examples of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in inducing or promoting wound healing in an individual in need thereof. Other examples of the present disclosure relate to use of an isolated agonist antibody that binds to a TREM2 protein in the manufacture of a medicament for inducing or promoting wound healing in an individual in need thereof.

[0049] Other examples of the present disclosure relate to a method of decreasing innate immune cell survival in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated antagonist antibody of any one of the preceding examples. Other examples of the present disclosure relate to an isolated antagonist antibody of any one of the preceding examples for use in decreasing innate immune cell survival in an individual in need thereof. Other examples of the present disclosure relate to use of an isolated antagonist antibody of any one of the preceding examples in the manufacture of a medicament for decreasing innate immune cell survival in an individual in need thereof.

[0050] Other examples of the present disclosure relate to a method of preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, Taupathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, lupus, acute and chronic colitis, 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, and cancer, comprising administering to the individual a therapeutically effective amount of an isolated antibody of any

one of the preceding examples. Other examples of the present disclosure relate to an isolated antibody of any one of the preceding examples 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, lupus, acute and chronic colitis, 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, and cancer. Other examples of the present disclosure relate to use of an isolated antibody of any one of the preceding examples 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, lupus, acute and chronic colitis, 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, and cancer.

[0051] In certain examples that may be combined with any of the preceding examples, the isolated antibody is: (a) an agonist antibody; (b) an inert antibody; or an (c) an antagonist antibody. In certain examples that may be combined with any of the preceding examples, (a) the antibody is of the IgG class the IgM class, or the IgA class; and/or(b) the antibody has an IgG1, IgG2, IgG3, or IgG4 isotype. In certain examples that may be combined with any of the preceding examples, the antibody comprises one or more amino acid substitutions in the Fc region are at a residue position selected from the group consisting of:(a) V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, T256E, and any combination thereof; (b) N297A, D265A, L234A, L235A, G237A, C226S, C229S, E233P, L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, and any combination thereof; (c) L235A, G237A, S228P, L236E, S267E, E318A, L328F, M252Y, S254T, T256E, and any combination thereof; (d) N297A, N297Q, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof; (e) V234A, G237A, H268E, V309L, N297A, N297Q, A330S, P331S, C232S, C233S, M252Y, S254T, T256E, and any combination thereof; or (f) E233P, F234V, 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 or Kabat numbering. In certain examples that may be combined with any of the preceding examples, the isolated antibody: (a) binds to one or more amino acids within amino acid residues 43-50 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 43-50 of SEQ ID NO: 1; or (b) one or more amino acids within amino acid residues 49-57 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 49-57 of SEQ ID NO: 1. In certain examples that may be combined with any of the preceding examples, the isolated antibody: (a) binds essentially the same TREM2 epitope as the antibody Ab52; (b) comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2,

least about 95% homology to the amino acid sequence of SEQ ID NO:407, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:408, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:408, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:409, or an amino acid sequence with at least about 95% homology to the amino acid sequence of SEQ ID NO:409. In certain examples that may be combined with any of the preceding examples, the isolated antibody is the isolated antibody of any one of the preceding examples. In certain examples that may be combined with any of the preceding examples, the isolated agonist antibody is the isolated agonist antibody of any one of the preceding examples. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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.

[0052] In certain examples that may be combined with any of the preceding examples, the cancer is selected from the group consisting of 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, and thyroid cancer. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the isolated antibody. In certain examples that may be combined with any of the preceding examples, 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-CTLA4 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 certain examples that may be combined with any of the preceding examples, the standard or investigational anti-cancer therapy is one or more therapies selected from the group consisting of radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib (Gleevec®), trastuzumab (Herceptin®), adoptive cell transfer (ACT), chimeric antigen receptor T cell transfer (CAR-T), vaccine therapy, and cytokine

therapy. In certain examples that may be combined with any of the preceding examples, the method further comprises administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In certain examples that may be combined with any of the preceding examples, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the isolated antibody. In certain examples that may be combined with any of the preceding examples, the at least one antibody that specifically binds to an inhibitory cytokine is selected from the group consisting of an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof. In certain examples that may be combined with any of the preceding examples, the method further comprises administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In certain examples that may be combined with any of the preceding examples, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the isolated antibody. In certain examples that may be combined with any of the preceding examples, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from the group consisting of an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, and any combination thereof. In certain examples that may be combined with any of the preceding examples, the method further comprises administering to the individual at least one stimulatory cytokine. In certain examples that may be combined with any of the preceding examples, the at least one stimulatory cytokine is administered in combination with the isolated antibody. In certain examples that may be combined with any of the preceding examples, the at least one stimulatory cytokine is selected from the group consisting of TNF- α , IL-10, IL-6, IL-8, CRP, TGF-beta members of the chemokine protein families, IL20 family member, IL-33, LIF, OSM, CNTF, TGF-beta, IL-11, IL-12, IL-17, IL-8, CRP, IFN- α , IFN- β , IL-2, IL-18, GM-CSF, G-CSF, and any combination thereof.

CLAIMS

What is claimed is:

1. An isolated antibody that binds to a TREM2 protein and is a TREM2 antagonist.
2. The isolated antibody of claim 1, wherein the antibody inhibits one or more TREM2 activities.
3. The isolated antibody of claim 2, wherein the antibody inhibits the one or more TREM2 activities when the antibody is not cross-linked or plate-bound.
4. The isolated antibody of claim 2 or claim 3, wherein the one or more TREM2 activities inhibited by the antibody comprise: (a) survival of macrophages, and/or (b) expression of one or more TREM2-dependent genes.
5. The isolated antibody of claim 4, wherein the antibody inhibits expression of one or more TREM2-dependent genes when the antibody is not cross-linked or plate-bound.
6. The isolated antibody of claim 4 or claim 5, wherein the one or more TREM2-dependent genes comprise nuclear factor of activated T-cells (NFAT) transcription factors.
7. The isolated antibody of any one of claims 4-6, wherein said inhibition of expression of one or more TREM2-dependent genes is assessed by a luciferase-based reporter assay using a luciferase reporter gene under the control of a nuclear factor of activated T-cells (NFAT) promoter to measure TREM2-dependent gene expression in BW5147.G.1.4 cells expressing mouse TREM2 and DAP12, wherein a decrease in luciferase reporter gene expression in the presence of the antibody compared to the level of luciferase reporter gene expression in the absence of the antibody indicates inhibition of TREM2-dependent gene expression.
8. The isolated antibody of any one of claims 4-7, wherein the antibody inhibits survival of macrophages when the antibody is not cross-linked or plate-bound.
9. The isolated antibody of any one of claims 1-8, wherein the antibody competes for binding of TREM2 with one or more TREM2 ligands.
10. The isolated antibody of claim 9, wherein the one or more TREM2 ligands are selected from the group consisting of: one or more TREM2 ligands expressed on *E. coli* cells, phosphatidylserine, and sphingomyelin.
11. The isolated antibody of any one of claims 1-10, wherein the antibody binds to one or more amino acids within amino acid residues selected from the group consisting of:
amino acid residues 43-50 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 43-50 of SEQ ID NO: 1;

amino acid residues 49-57 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 49-57 of SEQ ID NO: 1;

amino acid residues 139-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-146 of SEQ ID NO: 1; or amino acid residues 140-153 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 140-153 of SEQ ID NO: 1.

12. The isolated antibody of any one of claims 1-11, wherein the antibody:
 - i. has a dissociation constant (K_D) for human TREM2-Fc fusion protein that ranges from 0.23 nM to 1.51 nM; and/or
 - ii. has a dissociation constant (K_D) for human monomeric TREM2 protein that ranges from 0.66 nM to 6.70 nM.
13. The isolated antibody of any one of claims 1-12, wherein the antibody binds specifically to both human TREM2 and mouse TREM2.
14. The isolated antibody of any one of claims 1-13, wherein the antibody comprises a heavy chain variable domain and a light chain variable domain, wherein :
 - (a) the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 9, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33 or an amino acid sequence having at least about 95% homology to SEQ ID NO:33, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 58 or an amino acid sequence having at least about 95% homology to SEQ ID NO:58, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 124 or an amino acid sequence having at least about 95% homology to SEQ ID NO:124, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 144 or an amino acid sequence having at least about 95% homology to SEQ ID NO:144, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 161 or an amino acid sequence having at least about 95% homology to SEQ ID NO:161;
 - (b) the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 13 or an amino acid sequence having at least about 95% homology to SEQ ID NO:13, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36 or an amino acid sequence having at least about 95% homology to SEQ ID NO:36, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence having at least about 95% homology to SEQ ID NO:63,

and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122 or an amino acid sequence having at least about 95% homology to SEQ ID NO:122, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 146 or an amino acid sequence having at least about 95% homology to SEQ ID NO:146, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 166 or an amino acid sequence having at least about 95% homology to SEQ ID NO:166;

- (c) the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7 or an amino acid sequence having at least about 95% homology to SEQ ID NO:7, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 29 or an amino acid sequence having at least about 95% homology to SEQ ID NO:29, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 87 or an amino acid sequence having at least about 95% homology to SEQ ID NO:87, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 120 or an amino acid sequence having at least about 95% homology to SEQ ID NO:120, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 138 or an amino acid sequence having at least about 95% homology to SEQ ID NO:138, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 196 or an amino acid sequence having at least about 95% homology to SEQ ID NO:196; or
- (d) the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 398 or an amino acid sequence having at least about 95% homology to SEQ ID NO:398, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 399 or an amino acid sequence having at least about 95% homology to SEQ ID NO:399, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 400 or an amino acid sequence having at least about 95% homology to SEQ ID NO:400, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 401 or an amino acid sequence having at least about 95% homology to SEQ ID NO:401, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 402 or an amino acid sequence having at least about 95% homology to SEQ ID NO:402, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 403 or an amino acid sequence having at least about 95% homology to SEQ ID NO:403.

15. The isolated antibody of any one of claims 1-14, wherein the antibody comprises a heavy chain variable domain and a light chain variable domain, wherein:

- (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 258 or an amino acid sequence of SEQ ID NO: 258 having one or more conservative amino acid substitutions, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 259 or an amino acid sequence of SEQ ID NO: 259 having one or more conservative amino acid substitutions;
- (b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 268 or an amino acid sequence of SEQ ID NO: 268 having one or more conservative amino acid substitutions, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 269 or an amino acid sequence of SEQ ID NO: 269 having one or more conservative amino acid substitutions;
- (c) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 322 or an amino acid sequence of SEQ ID NO: 322 having one or more conservative amino acid substitutions, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 323 or an amino acid sequence of SEQ ID NO: 323 having one or more conservative amino acid substitutions; or
- (d) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 412 or an amino acid sequence of SEQ ID NO: 412 having one or more conservative amino acid substitutions, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 413 or an amino acid sequence of SEQ ID NO: 413 having one or more conservative amino acid substitutions.

16. The isolated antibody of any one of claims 1-15, wherein the antibody binds to an epitope of human TREM2 that is the same as the TREM2 epitope bound by a reference anti-TREM2 antibody, wherein the reference anti-TREM2 antibody comprises a heavy chain variable domain and a light chain variable domain, wherein:

- (a) the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 9, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 58, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 124, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 144, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 161;
- (b) the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 13, an HVR-H2 comprising the amino acid sequence of SEQ ID

NO: 36, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 146, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 166;

(c) the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 29, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 87, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 120, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 138, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 196; or

(d) the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 398, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 399, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 400, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 401, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 402, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 403.

17. The isolated antibody of any one of claims 1-16, wherein the antibody binds to an epitope of human TREM2 that is the same as the TREM2 epitope bound by a reference anti-TREM2 antibody, wherein the reference anti-TREM2 antibody comprises a heavy chain variable domain and a light chain variable domain, wherein:

(a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 258, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 259;

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 268, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 269;

(c) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 322, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 323;

or

(d) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 412, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 413.

18. The isolated antibody of any one of claims 1-7 and 9-13, wherein the antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 404 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 404, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 405 or an amino

acid sequence having at least about 95% homology to SEQ ID NO: 405, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 406 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 406, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 407 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 407, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 408 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 408, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 409 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 409.

19. The isolated antibody of any one of claims 1-7, 9-13 and 18, wherein the antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 410 or an amino acid sequence of SEQ ID NO: 410 having one or more conservative amino acid substitutions, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 411 or an amino acid sequence of SEQ ID NO: 411 having one or more conservative amino acid substitutions

20. The isolated antibody of any one of claims 1-7, 9-13 and 18-19, wherein the antibody binds to an epitope of human TREM2 that is the same as the TREM2 epitope bound by a reference anti-TREM2 antibody, wherein the reference anti-TREM2 antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 404, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 405, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 406, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 407, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 408, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 409.

21. The isolated antibody of any one of claims 1-7, 9-13 and 18-20, wherein the antibody binds to an epitope of human TREM2 that is the same as the TREM2 epitope bound by a reference anti-TREM2 antibody, wherein the reference anti-TREM2 antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 410, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 411.

22. The isolated antibody of any one of claims 1-3 and 9-13, wherein the antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the

heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 11, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 34 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 34, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 60, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 123 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 123, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 141 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 141, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 173 or an amino acid sequence having at least about 95% homology to SEQ ID NO: 173.

23. The isolated antibody of any one of claims 1-3, 9-13 and 22, wherein the antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 262 or an amino acid sequence of SEQ ID NO: 262 having one or more conservative amino acid substitutions, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 279 or an amino acid sequence of SEQ ID NO: 279 having one or more conservative amino acid substitutions.

24. The isolated antibody of any one of claims 1-3, 9-13 and 22-23, wherein the antibody binds to an epitope of human TREM2 that is the same as the TREM2 epitope bound by a reference anti-TREM2 antibody, wherein the reference anti-TREM2 antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 34, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 60, and the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 123, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 141, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 173.

25. The isolated antibody of any one of claims 1-3, 9-13 and 22-24, wherein the antibody binds to an epitope of human TREM2 that is the same as the TREM2 epitope bound by a reference anti-TREM2 antibody, wherein the reference anti-TREM2 antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain

variable domain comprises the amino acid sequence of SEQ ID NO: 262, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 279.

26. The isolated antibody of any one of claims 1-25, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

27. The isolated antibody of claim 26, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.

28. The isolated antibody of any one of claims 1-27, wherein the antibody is incapable of binding an Fc-gamma receptor (FcγR).

29. The isolated antibody of any one of claims 1-28, wherein the antibody is incapable of inducing or retaining clustering of TREM2.

30. The isolated antibody of any one of claims 27-29, wherein:

i. 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, D265A, L234A, L235A, C220S, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering, optionally wherein the Fc region further comprises an amino acid deletion at a position corresponding to glycine 236 according to EU numbering, and further optionally wherein 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;

ii. the antibody has a human IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of V234A, G237A, 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

iii. the 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 E233P, F234V, 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, optionally wherein the Fc region further comprises a S228P amino acid substitution according to EU numbering;

optionally wherein 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.

31. The isolated antibody of any one of claims 1-30, wherein the antibody is an antibody fragment, and wherein the antibody fragment is a Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment.

32. The isolated antibody of any one of claims 1-31, wherein the antibody is a human antibody, a humanized antibody, a bispecific antibody, a multivalent antibody, or a chimeric antibody.

33. The isolated antibody of any one of claims 1-32, wherein the antibody is a monoclonal antibody.

34. The isolated antibody of any one of claims 1-33, wherein the antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of a wild-type human TREM2 and a naturally occurring variant of human TREM2, and 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 a wild-type human TREM2, a naturally occurring variant of human TREM2, a wild-type human DAP12, and a naturally occurring variant of human DAP12.

35. The isolated antibody of any one of claims 1-33, wherein the antibody is a bispecific antibody recognizing a first antigen and a second antigen, wherein the first antigen is a wild-type human TREM2 or a naturally occurring variant thereof, and the second antigen is (a) DAP12; (b) a disease-causing protein selected from the group consisting of amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrP^{Sc}, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and proline-arginine (PR) repeat peptides; or (c) a blood brain barrier targeting protein selected from the group consisting of transferrin receptor, insulin receptor, insulin like growth factor receptor, LRP-1, and LRP1.

36. The isolated antibody of any one of claims 1-33, wherein the antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of a wild-type human TREM2, and a naturally occurring variant of human TREM2; and wherein the antibody is used in combination with one or more antibodies that specifically bind a disease-causing protein selected from the group consisting of: amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and proline-arginine (PR) repeat peptides, and any combination thereof.
37. An isolated nucleic acid encoding the antibody of any one of claims 1-36.
38. A vector comprising the nucleic acid of claim 37.
39. An isolated host cell comprising the vector of claim 38.
40. A pharmaceutical composition comprising the antibody of any one of claims 1-36 and a pharmaceutically acceptable carrier.
41. Use of an isolated antibody of any one of claims 1-36, in the manufacture of a medicament for decreasing expression of one or more TREM2-dependent genes in an individual in need thereof.
42. Use of an isolated antibody of any one of claims 1-36, in the manufacture of a medicament for decreasing innate immune cell survival in an individual in need thereof.
43. Use of an isolated antibody of any one of claims 1-36, in the manufacture of a medicament for preventing, reducing risk of, or treating a disease, disorder or injury.
44. The use of claim 43, wherein the disease, disorder or injury is cancer.
45. An isolated antibody of any one of claims 1-36, for use in therapy.