[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 one aspect of the present disclosure, there is provided an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody induces one or more TREM2 activities,

and wherein the isolated antibody promotes survival of one or more innate immune cells or increases expression of IL-6.

[0024b] In another aspect of the present disclosure, there is provided an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody inhibits one or more TREM2 activities, and wherein the isolated antibody decreases survival of one or more innate immune cells.

[0024c] In yet another aspect of the present disclosure, there is provided 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.

[0024d] In a further aspect of the present disclosure, there is provided 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;

(b) 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 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.

[0024e] In another aspect of the present disclosure, there is provided 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.

[0024f] In yet another aspect of the present disclosure, there is provided 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.

[0024g] In a further aspect of the present disclosure, there is provided an isolated nucleic acid encoding the antibody as described herein.

[0024h] In another aspect of the present disclosure, there is provided a vector comprising the nucleic acid as described herein.

[0024i] In yet another aspect of the present disclosure, there is provided an isolated host cell comprising the vector as described herein.

[0024j] In a further aspect of the present disclosure, there is provided a method of producing an antibody, comprising culturing the host cell as described herein so that the antibody is produced.

[0024k] In another aspect of the present disclosure, there is provided an isolated antibody produced by the method as described herein.

[0024l] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody as described herein and a pharmaceutically acceptable carrier.

[0024m] In a further aspect of the present disclosure, there is provided a use of an isolated antibody that binds to a TREM2 protein in the manufacture of a medicament for preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, Nasu-Hakola disease, and multiple sclerosis.

[0024n] In another aspect of the present disclosure, there is provided a use of an isolated agonist antibody that binds to a TREM2 protein in the manufacture of a medicament for inducing or promoting innate immune cell survival in an individual.

[0024o] In yet another aspect of the present disclosure, there is provided a use of an isolated antagonist antibody that binds to a TREM2 protein in the manufacture of a medicament for decreasing innate immune cell survival in an individual.

[0025] The present disclosure relates to different classes of anti-TREM2 antibodies. In some embodiments, 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 embodiments, agonist anti-TREM2 antibodies of the present disclosure compete with TREM2 ligands for binding to TREM2 expressed on a cell surface. In some embodiments, 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 embodiments, 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 embodiments, inert or antagonist anti-TREM2 antibodies of the present disclosure block or otherwise inhibit ligand binding to TREM2 expressed on a cell surface.

[0026] The present disclosure also relates 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 embodiments that may be combined with any of the preceding embodiments, the TREM2 protein, the DAP12 protein, or both is a mammalian protein or a human protein. In certain embodiments that may be combined with any of the preceding embodiments, the TREM2 protein, the DAP12 protein, or both is a wild-type protein. In certain embodiments that may be combined with any of the preceding embodiments, the TREM2 protein, the DAP12 protein, or both is a naturally occurring variant. In certain embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the isolated antibody induces or retains TREM2 clustering, DAP12 clustering, or both on a cell surface. In certain embodiments that may be combined with any of the preceding embodiments, the one or more TREM2 activities comprise TREM2 binding to DAP12. In certain embodiments that may be combined with any of the preceding embodiments, the one or more DAP12 activities comprise DAP12 binding to TREM2. In certain embodiments that may be combined with any of the preceding embodiments, the one or more TREM2 activities, DAP12

according to EU or Kabat numbering. In certain embodiments that may be combined with any of the preceding embodiments, the antibody comprises a mouse IgG4 constant region. In certain embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv or scFv fragment.

[0028] The present disclosure relates to an isolated inert antibody that binds to a TREM2 protein. The present disclosure also relates to an isolated antagonist antibody that binds to a TREM2 protein.

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

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] The present disclosure relates 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 embodiments that may be combined with any of the preceding embodiments, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:398. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:399. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:400. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:401. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:402. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:403. In certain embodiments that may be combined with any of the preceding embodiments, 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] The present disclosure also relates 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] The present disclosure also relates 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 embodiments that may be combined with any of the preceding embodiments, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:404. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:405. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:406. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-

L1 comprises the amino acid sequence of SEQ ID NO:407. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:408. In certain embodiments that may be combined with any of the preceding embodiments, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:409. In certain embodiments that may be combined with any of the preceding embodiments, 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] The present disclosure also relates 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) n 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] The present disclosure also relates to an isolated anti-human TREM2 antibody which binds essentially the same TREM2 epitope as the antibody Ab52. The present disclosure also relates to an isolated anti-human TREM2 antibody which binds essentially the same TREM2 epitope as the antibody Ab21.

[0038] In certain embodiments that may be combined with any of the preceding embodiments, the antibody is an agonist antibody, and wherein the antibody induces one or more TREM2 activities, DAP12 activities, or both. In certain embodiments that may be combined with any of the preceding embodiments, the isolated antibody induces or retains TREM2 clustering, DAP12 clustering, or both on a cell surface. In certain embodiments that may be combined with any of the preceding embodiments, 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-a4, IFN-b, IL-6, IL-12 p70, IL-1β, TNF, TNF-α, IL-10, 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; 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

preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv or scFv fragment. In certain embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the Fc region further comprises a S228P amino acid substitution according to EU or Kabat numbering. In certain embodiments that may be combined with any of the preceding embodiments, the antibody is a human antibody, a humanized antibody, a bispecific antibody, a multivalent antibody, or a chimeric antibody. In certain embodiments that may be combined with any of the preceding embodiments, the antibody is a bispecific antibody recognizing a first antigen and a second antigen. In certain embodiments that may be combined with any of the preceding embodiments, the antibody is a monoclonal antibody.

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

present disclosure also relates 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. The present disclosure also relates 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 embodiments, 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 embodiments, the one or more innate immune cells are macrophages. In certain embodiments, the one or more innate immune cells are microglial cells. In certain embodiments, the one or more innate immune cells are M1 microglial cells. In certain embodiments, the one or more innate immune cells are activated M1 microglial cells. In certain embodiments, the one or more innate immune cells are M2 microglial cells. In certain embodiments, the one or more innate immune cells are dendritic cells (DCs). In certain embodiments, the one or more innate immune cells are M1 macrophages. In certain embodiments, the one or more innate immune cells are activated M1 macrophages. In certain embodiments, the one or more innate immune cells are M2 macrophages. In certain embodiments, the one or more innate immune cells are monocytes. In certain embodiments, the one or more innate immune cells are osteoclasts. In certain embodiments, the one or more innate immune cells are Langerhans cells of skin. In certain embodiments, the one or more innate immune cells are Kupffer cells.

[0040] The present disclosure relates 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

[0043] The present disclosure relates 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 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. The present disclosure also relates 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. The present disclosure also relates 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.

[0045] In certain embodiments that may be combined with any of the preceding embodiments, the isolated antibody binds specifically to both human TREM2 and mouse TREM2. In certain embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the isolated antibody has dissociation constant (K_D) for human TREM2 and mouseTREM2 that ranges from less than about 6.70 nM to less than about 0.23 nM. In certain embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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] The present disclosure relates to an isolated nucleic acid encoding the antibody of any one of the preceding embodiments. The present disclosure also relates to a vector comprising the nucleic acid of any one of the preceding embodiments. The present disclosure also relates to a host cell comprising the vector of any one of the preceding embodiments. The present disclosure also relates to an isolated host cell comprising

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

[0047] The present disclosure relates 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 embodiments. The present disclosure also relates to an isolated agonist antibody of any one of the preceding embodiments 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. The present disclosure also relates to use of an isolated agonist antibody of any one of the preceding embodiments 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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] The present disclosure relates 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 embodiments. The present disclosure also relates to an isolated agonist antibody of any one of the preceding embodiments for use in inducing or promoting innate immune cell survival in an individual in need thereof. The present disclosure also relates to use of an isolated agonist antibody of any one of the preceding embodiments in the manufacture of a medicament for inducing or promoting innate immune cell survival in an individual in need thereof. The present disclosure also relates 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. The present disclosure also relates 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. The present disclosure also relates 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] The present disclosure relates 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 embodiments. The present disclosure also relates to an isolated antagonist antibody of any one of the preceding embodiments for use in decreasing innate immune cell survival in an individual in need thereof. The present disclosure also relates to use of an isolated antagonist antibody of any one of the preceding embodiments in the manufacture of a medicament for decreasing innate immune cell survival in an individual in need thereof.

[0050] The present disclosure relates 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, granulomartous 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 embodiments. The present disclosure also relates to an isolated antibody of any one of the preceding embodiments 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, granulomartous 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. The present disclosure also relates to use of an isolated antibody of any one of the preceding embodiments 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, granulomartous 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,

91. The method of claim 90, further comprising recovering the antibody produced by the cell.

92. An isolated antibody produced by the method of claim 90 or claim 44.

93. A pharmaceutical composition comprising the antibody of any one of claims 1-86 and a pharmaceutically acceptable carrier.

94. Use of an isolated antibody that binds to a TREM2 protein in the manufacture of a medicament for preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, Nasu-Hakola disease, and multiple sclerosis.

95. The use of claim 94, wherein the isolated antibody is the isolated antibody of any one of claims 1-86.

96. The use of claim 94 or claim 95, wherein the individual has a heterozygous variant of TREM2, wherein the variant comprises one or more substitutions selected from the group consisting of:

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

viii. a lysine to asparagine amino acid substitution at an amino acid corresponding to amino acid residue Lys186 of SEQ ID NO: 1.

97. The use of claim 94, wherein the individual has a heterozygous variant of TREM2, wherein the variant comprises a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G313 of the nucleic acid sequence encoding SEQ ID NO: 1; a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G267 of the nucleic acid sequence encoding SEQ ID NO: 1; or both.

98. The use of claim 94, wherein the individual has a heterozygous variant of DAP12, wherein the variant comprises one or more variants selected from the group consisting of:

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

99. Use of an isolated agonist antibody that binds to a TREM2 protein in the manufacture of a medicament for inducing or promoting innate immune cell survival in an individual.

100. The use of claim 99, wherein the isolated agonist antibody is the isolated antibody of any one of claims 1, 3, 4-27, 38-66, and 76-86.

101. Use of an isolated antagonist antibody that binds to a TREM2 protein in the manufacture of a medicament for decreasing innate immune cell survival in an individual.

102. The use of claim 101, wherein the isolated antagonist antibody is the isolated antibody of any one of claims 2-15, 28-52, and 67-86.