promotes survival of macrophages, as determined by an *in vitro* cell culture viability assay using macrophages isolated from mouse bone marrow.

[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 the isolated antibody disclosed herein for use in a method of preventing, reducing risk, or treating an individual having dementia, frontotemporal dementia, Alzheimer's disease, or multiple sclerosis.

[0024g] In a further aspect of the present disclosure, there is provided the isolated antibody disclosed herein for use in a method of inducing or promoting macrophage survival in an individual in need thereof.

[0025] The present disclosure relates to different classes of anti-TREM2 antibodies. In some embodiments, anti-TREM2 antibodies are agonist antibodies that bind to

CLAIMS

What is claimed is:

1. An isolated human or humanized antibody that binds to a TREM2 protein and, when cross-linked or plate-bound, promotes survival of macrophages, as determined by an *in vitro* cell culture viability assay using macrophages isolated from mouse bone marrow.

2. The isolated antibody of claim 1, wherein the antibody competes for binding of TREM2 with one or more TREM2 ligands.

3. The isolated antibody of claim 2, 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.

4. The isolated antibody of any one of claims 1 to 3, wherein the antibody:

i. increases expression of CD83 and CD86; and/or

ii. induces Syk phosphorylation; and/or

iii. increases expression of IL-6; and/or

iv. increases expression of MCP-1.

5. The isolated antibody of any one of claims 1 to 4, wherein the isolated 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 0.65 nM to 5.75 nM.

6. The isolated antibody of any one of claims 1 to 5, 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 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;

ii. 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; and

iii. 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.

7. The isolated antibody of claim 6, wherein 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.

8. The isolated antibody of any one of claims 1 to 6, wherein when the antibody is not cross-linked or plate-bound, the antibody does not inhibit survival of macrophages.

9. The isolated antibody of any one of claims 1 to 7, wherein when the antibody is not cross-linked or plate-bound, the antibody inhibits survival of macrophages.

10. The isolated antibody of any one of claims 1 to 6 and 8, wherein 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 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.

11. The isolated antibody of any one of claims 1 to 6 and 8, wherein the isolated 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:

i. 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; or

ii. 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.

12. The isolated antibody of any one of claims 1 to 5, wherein 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: 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.

13. The isolated antibody of any one of claims 1 to 5, wherein the isolated 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:

i. 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; or

ii. 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.

14. The isolated antibody of any one of claims 1 to 7 and 9, wherein the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein:

i. 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

ii. 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: 34, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 101, 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: 215.

15. The isolated antibody of any one of claims 1 to 7 and 9, wherein the isolated 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:

i. 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;

ii. 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: 34, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 101, 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: 215;

iii. 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

iv. the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 355, and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 356.

16. The isolated antibody of any one of claims 1 to 6 and 9, wherein 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 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 to 6 and 9, wherein the isolated 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:

i. 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; or

ii. 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 to 17, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

19. The isolated antibody of claim 18, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.

20. The isolated antibody of claim 19, wherein:

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 the EU numbering system;

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 the EU numbering system;

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 the EU numbering system, 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 the EU numbering system;

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 YTCNVDHKPS 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 the EU numbering system;

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 the EU numbering system, optionally wherein the Fc region further comprises a S228P amino acid substitution according to the EU numbering system; 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 the EU numbering system;

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 the EU numbering system.

21. The isolated antibody of any one of claims 1 to 20, wherein 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.

22. The isolated antibody of any one of claims 1 to 21, wherein the isolated antibody is a bispecific antibody, a multivalent antibody, or a chimeric antibody.

23. The isolated antibody of any one of claims 1 to 22, wherein the antibody is a monoclonal antibody.

24. The isolated antibody of any one of claims 1 to 21, wherein the isolated 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.

25. The isolated antibody of any one of claims 1 to 22, wherein the isolated 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 DAP12 or 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: transferrin receptor, insulin receptor, insulin like growth factor receptor, LRP-1, and LRP1.

26. The isolated antibody of any one of claims 1 to 21, wherein the isolated 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.

27. The isolated antibody of any one of claims 1 to 26, wherein the isolated antibody binds specifically to both human TREM2 and mouse TREM2.

28. An isolated nucleic acid encoding the antibody of any one of the preceding claims.

29. A vector comprising the nucleic acid of claim 28.

30. An isolated host cell comprising the vector of claim 29.

31. A pharmaceutical composition comprising the antibody of any one of claims 1 to 27 and a pharmaceutically acceptable carrier.

32. The isolated antibody of any one of claims 1 to 27 for use in a method of preventing, reducing risk, or treating an individual having dementia, frontotemporal dementia, Alzheimer's disease, or multiple sclerosis.

33. The antibody for the use of claim 32, wherein the individual has Alzheimer's disease.

34. The antibody for the use of claim 32 or 33, 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.

35. The antibody for the use of claim 32 or 33, 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.

36. The antibody for the use of claim 32 or 33, 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.

37. The isolated antibody of any one of claims 1 to 27 for use in a method of inducing or promoting macrophage survival in an individual in need thereof.