

deficiency of TREM2 being associated with increased pathology (Cheng-Hathaway *et al* (2018) Mol Neurodegener, 13(1):29; Wang *et al* (2015) Cell, 160:1061-1071; Wang *et al* (2016) J Exp Med, 213:667-675; Yuan *et al* (2016) Neuron, 90:724-739; Jay *et al* (2017) J Neurosci, 37:637-647).

[0006] TREM2 is expressed primarily on myeloid lineage cells, including microglia (Colonna and Wang (2016) Nat Rev Neurosci, 17:201-207). Microglia are resident macrophages of the central nervous system that, when activated appropriately, are thought to serve an important protective role in Alzheimer's disease through their housekeeping functions such as facilitating clearance of cellular debris through phagocytosis, as well as secretion of growth factors. It has been shown that TREM2 expression regulates microglial chemotaxis and phagocytosis, and enhances microglial cell survival, proliferation, and differentiation. In addition, it is well known that TREM2 is required to sustain microglial trophic function in the aging brain, and animal studies showed that an overlap exists between aged microglia phenotype and microglial molecular signatures found in models of AD, which include TREM2 pathways (Krasemann *et al* (2017) Immunity, 47(3):566-581). These findings suggest that activation of TREM2 may ameliorate AD pathology and result in improvements in cognitive function through activation of the innate immune system.

[0007] Accordingly, there is a need in the art for novel methods of treating AD and other neurodegenerative diseases through activation of the innate immune system (e.g., microglial activity), for example, using agonistic antibodies that target TREM2.

[0008] All references cited herein, including patents, patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[0009] The present disclosure is generally directed to methods of using compositions that include antibodies, *e.g.*, monoclonal, chimeric, humanized antibodies, antibody fragments, *etc.*, that specifically bind human TREM2.

[0010] In one [aspectexample](#), provided herein is a method of treating and/or delaying the progression of a disease or injury in an individual, comprising administering to the individual an anti-TREM2 antibody at a dose of at least about 15 mg/kg intravenously, wherein the anti-TREM2 antibody is an agonist. In a further [aspectexample](#), provided herein is a method of treating and/or delaying the progression of a disease or injury in an individual, comprising administering to the individual an anti-TREM2 antibody at a dose of at least about 15 mg/kg intravenously, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, and wherein: (i) the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 34), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 35), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 31), the HVR-L1 comprises the amino

acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 41), the HVR-L2 comprises the amino acid sequence KVSNRFS (SEQ ID NO: 33), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 32); or (ii) the HVR-H1 comprises the amino acid sequence YAFSSDWMN (SEQ ID NO: 36), the HVR-H2 comprises the amino acid sequence RIYPGEGDTNYARKFHG (SEQ ID NO: 37), the HVR-H3 comprises the amino acid sequence ARLLRNKPGESYAMDY (SEQ ID NO: 38), the HVR-L1 comprises the amino acid sequence RTSQSLVHSNRYTYLH (SEQ ID NO: 39), the HVR-L2 comprises the amino acid sequence KVSNRVS (SEQ ID NO: 40), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 32).

[0010a] In one aspect, the present disclosure refers to use of an anti-TREM2 antibody in the manufacture of a medicament for treating and/or delaying the progression of a disease or injury in an individual, wherein the medicament is to be administered intravenously at a dose of at least about 15 mg/kg, and wherein the anti-TREM2 antibody is an agonist.

[0010b] In one aspect, the present disclosure refers to use of an anti-TREM2 antibody in the manufacture of a medicament for treating and/or delaying the progression of a disease or injury in an individual, wherein the medicament is to be administered intravenously at a dose of at least about 15 mg/kg, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, and wherein: (i) the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 34), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 35), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 31), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 41), the HVR-L2 comprises the amino acid sequence KVSNRFS (SEQ ID NO: 33), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 32); or (ii) the HVR-H1 comprises the amino acid sequence YAFSSDWMN (SEQ ID NO: 36), the HVR-H2 comprises the amino acid sequence RIYPGEGDTNYARKFHG (SEQ ID NO: 37), the HVR-H3 comprises the amino acid sequence ARLLRNKPGESYAMDY (SEQ ID NO: 38), the HVR-L1 comprises the amino acid sequence RTSQSLVHSNRYTYLH (SEQ ID NO: 39), the HVR-L2 comprises the amino acid sequence KVSNRVS (SEQ ID NO: 40), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 32).

[0011] In some embodimentexamples, the dose is between about 15 mg/kg to about 60 mg/kg. In some embodimentexamples, the dose is about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, or about 60 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of at least about 15 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every week at a dose of at least about 15 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 15 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 20 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 25 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 30 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 35 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 40 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 45 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 50 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 55 mg/kg. In some embodimentexamples, the anti-TREM2 antibody is administered about once every four weeks at a dose of about 60 mg/kg.

[0012] In some embodimentexamples, the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 34), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 35), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 31), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 41), the HVR-L2 comprises the amino acid sequence KVSNRFS (SEQ ID NO: 33), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 32). In some embodimentexamples, the antibody comprises a heavy chain variable region comprising

the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30.

[0013] In some [embodimentexamples](#), the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the HVR-H1 comprises the amino acid sequence YAFSSDWMN (SEQ ID NO: 36), the HVR-H2 comprises the amino acid sequence RIYPGEGDTNYARKFHG (SEQ ID NO: 37), the HVR-H3 comprises the amino acid sequence ARLLRNKPGESYAMDY (SEQ ID NO: 38), the HVR-L1 comprises the amino acid sequence RTSQSLVHSNAYTYLH (SEQ ID NO: 39), the HVR-L2 comprises the amino acid sequence KVSNRVS (SEQ ID NO: 40), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 32). In some [embodimentexamples](#), the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 28 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29.

[0014] In some [embodimentexamples](#), the antibody has a human IgG1 isotype.

[0015] In some [embodimentexamples](#), the antibody has a human IgG1 isotype and comprises amino acid substitutions in the Fc region at the residue positions P331S and E430G, wherein the numbering of the residues is according to EU numbering.

[0016] In some [embodimentexamples](#), the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 43, and a light chain comprising the amino acid sequence of SEQ ID NO: 47; or (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, and a light chain comprising the amino acid sequence of SEQ ID NO: 47.

[0017] In some [embodimentexamples](#), the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 45, and a light chain comprising the amino acid sequence of SEQ ID NO: 48; or (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, and a light chain comprising the amino acid sequence of SEQ ID NO: 48.

[0018] In some [embodimentexamples](#), the disease or injury is selected from dementia, frontotemporal dementia, Alzheimer's disease, Nasu-Hakola disease, cognitive deficit, memory loss, spinal cord injury, traumatic brain injury, a demyelination disorder, multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), or a tauopathy disease.

[0019] In some [embodimentexamples](#), the disease or injury is Alzheimer's disease. In some [embodimentexamples](#), the individual has a Mini-Mental State Examination (MMSE) score of between about 16 points to about 28 points prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the individual has a Clinical Dementia Rating-Global Score (CDR-GS) of 0.5, 1.0, or 2.0 prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the individual has a positive amyloid-PET scan prior to administration of the

anti-TREM2 antibody. In some [embodimentexamples](#), the individual is being administered a cholinesterase inhibitor and/or memantine therapy. In some [embodimentexamples](#), the individual has symptoms of Alzheimer's disease prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the symptoms are mild cognitive impairment and/or mild dementia. In some [embodimentexamples](#), the individual does not have symptoms of Alzheimer's disease prior to administration of the anti-TREM2 antibody.

[0020] In some [embodimentexamples](#), the individual is heterozygous or homozygous for a mutation in TREM2. In some [embodimentexamples](#), the individual comprises an amino acid substitution in a human TREM2 protein at residue position R47H, R62H, or both.

[0021] In some [embodimentexamples](#), the individual has a positive amyloid or tau blood test prior to administration of the anti-TREM2 antibody.

[0022] In some [embodimentexamples](#), administration of the anti-TREM2 antibody results in at least about a 30% decrease in the levels of soluble TREM2 in the cerebrospinal fluid of the individual, compared to the levels of soluble TREM2 in the cerebrospinal fluid of the individual prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), administration of the anti-TREM2 antibody results in at least about a 40% decrease in the levels of soluble TREM2 in the cerebrospinal fluid of the individual, compared to the levels of soluble TREM2 in the cerebrospinal fluid of the individual prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the decrease in the levels of soluble TREM2 in the cerebrospinal fluid of the individual is present at about 2 days after administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the levels of soluble TREM2 in the cerebrospinal fluid of the individual are measured in a sample of cerebrospinal fluid obtained from the individual using an electrochemiluminescent assay.

[0023] In some [embodimentexamples](#), administration of the anti-TREM2 antibody results in at least about a 5% increase in the levels of soluble CSF1R in the cerebrospinal fluid of the individual, compared to the levels of soluble CSF1R in the cerebrospinal fluid of the individual prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the increase in the levels of soluble CSF1R in the cerebrospinal fluid of the individual is present at about 2 days after administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the levels of soluble CSF1R in the cerebrospinal fluid of the individual are measured in a sample of cerebrospinal fluid obtained from the individual using an ELISA assay.

[0024] In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of soluble TREM2 in a sample of blood, plasma, and/or cerebrospinal fluid from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of soluble CSF1R in a sample of blood, plasma, and/or cerebrospinal fluid from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody.

[0025] In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of brain amyloid burden in the brain of the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the levels of brain amyloid burden in the brain of the individual are measured using amyloid-positron emission tomography. In some [embodimentexamples](#), the methods provided herein also comprise measuring tau burden in the brain of the individual, assessed by measuring the levels of tau in the brain of the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the levels of tau in the brain of the individual are measured using tau-positron emission tomography. In some [embodimentexamples](#), the methods provided herein also comprise measuring one or more brain abnormalities in the brain of the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the one or more brain abnormalities are measured using magnetic resonance imaging. In some [embodimentexamples](#), the one or more brain abnormalities is brain volume. In some [embodimentexamples](#), the methods provided herein also comprise measuring brain volume of the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), brain volume is measured using magnetic resonance imaging. In some [embodimentexamples](#), brain volume is measured using volumetric magnetic resonance imaging.

[0026] In some [embodimentexamples](#), the methods provided herein also comprise detecting the presence of an alteration in one or more genes in the individual selected from APOE, TREM2, CD33, TMEM106b, or CLUSTERIN.

[0027] In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of one or more biomarkers of neuroinflammation in a sample of blood, plasma, and/or cerebrospinal fluid from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody.

[0028] In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of one or more biomarkers of neurodegeneration in a sample of blood, plasma, and/or cerebrospinal fluid from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody.

[0029] In some [embodimentexamples](#), the one or more biomarkers of neurodegeneration is neurofilament light.

[0030] In some [embodimentexamples](#), the methods provided herein also comprise measuring the expression levels of TREM2, CSF1R, YKL40, IL-1RA, or osteopontin in a sample of blood, plasma, and/or cerebrospinal fluid from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the expression levels of TREM2, CSF1R, YKL40, IL-1RA, or osteopontin refer to mRNA expression levels. In some [embodimentexamples](#), the expression levels of TREM2, CSF1R, YKL40, IL-1RA, or osteopontin refer to protein expression levels. In some [embodimentexamples](#), the method comprises measuring protein expression levels of sTREM2 or sCSF1R in the sample of blood, plasma, and/or cerebrospinal fluid from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody.

[0031] In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of one or more biomarkers of Alzheimer's disease in a sample of cerebrospinal fluid from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of one or more biomarkers of Alzheimer's disease in a sample of blood from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of one or more biomarkers of Alzheimer's disease in a sample of plasma from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the one or more biomarkers of Alzheimer's disease are selected from A β 42, A β 40, total tau, pTau, neurofilament light, or any combination thereof. In some [embodimentexamples](#), the one or more biomarkers of Alzheimer's disease are A β 40, A β 42, pTau, and/or total tau.

[0032] In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of one or more biomarkers of microglia function in a sample of cerebrospinal fluid from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of one or more biomarkers of microglia function in a sample of blood from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of one or more biomarkers of microglia function in a sample of plasma from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the one or more biomarkers of microglia function are CSF1R, IL1RN, YKL40 and/or osteopontin.

[0033] In some [embodimentexamples](#), the methods provided herein also comprise determining a score of one or more clinical assessments of the individual before and after the individual has received one or more doses of the anti-TREM2 antibody, wherein the one or more clinical assessments are selected from the Mini-Mental State Examination (MMSE) score, the Clinical Dementia Rating-Global Score (CDR-GS), the Clinical Dementia Rating Sum of Boxes (CDR-SB), or the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

[0034] In some [embodimentexamples](#), the methods provided herein also comprise performing tau or amyloid positron emission tomography (PET) imaging assessments in the individual before and after the individual has received one or more doses of the anti-TREM2 antibody.

[0035] In some [embodimentexamples](#), the disease or injury is Alzheimer's disease, and wherein the Alzheimer's disease is early Alzheimer's disease. In some [embodimentexamples](#), the individual has brain amyloidosis prior to administration of the anti-TREM2 antibody, wherein brain amyloidosis is assessed in a sample of cerebrospinal fluid obtained from the individual, or by positron emission tomography (PET). In some [embodimentexamples](#), the individual has a Mini-Mental State Examination (MMSE) score of at least about 22 points

prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the individual has a Clinical Dementia Rating-Global Score (CDR-GS) of between about 0.5 and about 1.0 prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the individual has a Repeatable Battery for the Assessment of Neuropsychological Status on the Delayed Memory Index (RBANS DMI) score of 85 or less prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the individual has a positive amyloid or tau blood test prior to administration of the anti-TREM2 antibody. In some [embodimentexamples](#), the methods provided herein also comprise determining a score of one or more clinical assessments of the individual before and after the individual has received one or more doses of the anti-TREM2 antibody, wherein the one or more clinical assessments are selected from the Clinical Dementia Rating Sum of Boxes (CDR-SB), the Mini-Mental State Examination (MMSE), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Alzheimer's Disease Assessment Scale-Cognitive Subscale-13 (ADAS-Cog13), the Alzheimer's Disease Cooperative Study-Activities of Daily Living adapted to Mild Cognitive Impairment (ADCS-ADL-MCI), and the Alzheimer's Disease Composite Score (ADCOMS). In some [embodimentexamples](#), the methods provided herein also comprise measuring the levels of one or more biomarkers of Alzheimer's disease, including but not limited to any of the biomarkers described herein, before and after the individual has received one or more doses of the anti-TREM2 antibody, wherein the one or more biomarkers of Alzheimer's disease are measured by magnetic resonance imaging (MRI), or in a sample of blood, plasma or cerebrospinal fluid obtained from the individual. In some [embodimentexamples](#), the methods provided herein also comprise performing tau or amyloid positron emission tomography (PET) imaging assessments in the individual before and after the individual has received one or more doses of the anti-TREM2 antibody. In some [embodimentexamples](#), the methods provided herein also comprise performing one or more speech assessments in the individual before and after the individual has received one or more doses of the anti-TREM2 antibody.

[0036] In some [embodimentexamples](#) of the methods provided herein, (a) the dose is about 15 mg/kg and the terminal half-life of the antibody in the plasma of the individual is about 8.63 days; (b) the dose is about 30 mg/kg and the terminal half-life of the antibody in the plasma of the individual is about 7.44 days; (c) the dose is about 45 mg/kg and the terminal half-life of the antibody in the plasma of the individual is about 8.40 days; or (d) the dose is about 60 mg/kg and the terminal half-life of the antibody in the plasma of the individual is about 9.93 days.

[0037] In some [embodimentexamples](#) of the methods provided herein, the method further comprises performing an amyloid or tau blood test on a sample obtained from an individual before and after the individual has received one or more doses of the anti-TREM2 antibody.

[0038] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of soluble TREM2 in a sample of cerebrospinal fluid from the individual before and after the individual has received one or more doses of an

anti-TREM2 antibody. In some **embodimentexamples**, the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of soluble TREM2 in the sample of cerebrospinal fluid. In some **embodimentexamples**, the anti-TREM2 antibody is determined to be active in the individual if the levels of soluble TREM2 in the sample of cerebrospinal fluid are decreased after the individual has received one or more doses of the anti-TREM2 antibody, compared to the levels of soluble TREM2 in the sample of cerebrospinal fluid before the individual received a dose of the anti-TREM2 antibody.

[0038a] In one aspect, the present disclosure refers to a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising: (a) measuring the levels of soluble TREM2 in a sample of cerebrospinal fluid, blood, or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody; (b) measuring the levels of soluble CSF1R in a sample of cerebrospinal fluid, blood, or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody; (c) measuring the levels of YKL40 in a sample of cerebrospinal fluid, blood, or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody; (d) measuring the levels of IL-1RA in a sample of cerebrospinal fluid, blood, or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody; or (e) measuring the levels of osteopontin in a sample of cerebrospinal fluid, blood, or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody.

[0039] In another **aspectexample**, provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of soluble TREM2 in a sample of blood or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some **embodimentexamples**, the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of soluble TREM2 in the sample of blood or plasma. In some **embodimentexamples**, the anti-TREM2 antibody is determined to be active in the individual if the levels of soluble TREM2 in the sample of blood or plasma are decreased after the individual has received one or more doses of the anti-TREM2 antibody, compared to the levels of soluble TREM2 in the sample of blood or plasma before the individual received a dose of the anti-TREM2 antibody.

[0040] In another **aspectexample**, provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of soluble CSF1R in a sample of cerebrospinal fluid, blood, or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some **embodimentexamples**, the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of soluble CSF1R in the sample of cerebrospinal fluid, blood, or plasma. In some **embodimentexamples**, the anti-TREM2 antibody is determined to be active in the individual if the levels of soluble CSF1R in the sample of cerebrospinal fluid, blood, or plasma are increased after the individual has received one or more doses of the anti-TREM2 antibody, compared to the levels of soluble CSF1R in the sample of cerebrospinal fluid, blood, or plasma before the individual received a dose of the anti-TREM2 antibody.

[0041] In another **aspectexample**, provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of YKL40 in a sample of cerebrospinal fluid, blood, or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some **embodimentexamples**, the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of YKL40 in the sample of cerebrospinal fluid, blood, or plasma. In some **embodimentexamples**, the anti-TREM2 antibody is determined to be active in the individual if the levels of YKL40 in the sample of

cerebrospinal fluid, blood, or plasma are increased after the individual has received one or more doses of the anti-TREM2 antibody, compared to the levels of YKL40 in the sample of cerebrospinal fluid, blood, or plasma before the individual received a dose of the anti-TREM2 antibody.

[0042] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of IL-1RA in a sample of cerebrospinal fluid, blood, or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some [embodimentexamples](#), the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of IL-1RA in the sample of cerebrospinal fluid, blood, or plasma. In some [embodimentexamples](#), the anti-TREM2 antibody is determined to be active in the individual if the levels of IL-1RA in the sample of cerebrospinal fluid, blood, or plasma are increased after the individual has received one or more doses of the anti-TREM2 antibody, compared to the levels of IL-1RA in the sample of cerebrospinal fluid, blood, or plasma before the individual received a dose of the anti-TREM2 antibody.

[0043] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of osteopontin in a sample of cerebrospinal fluid, blood, or plasma from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some [embodimentexamples](#), the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of osteopontin in the sample of cerebrospinal fluid, blood, or plasma. In some [embodimentexamples](#), the anti-TREM2 antibody is determined to be active in the individual if the levels of osteopontin in the sample of cerebrospinal fluid, blood, or plasma are increased after the individual has received one or more doses of the anti-TREM2 antibody, compared to the levels of osteopontin in the sample of cerebrospinal fluid, blood, or plasma before the individual received a dose of the anti-TREM2 antibody.

[0044] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of one or more biomarkers of Alzheimer's disease in a sample of cerebrospinal fluid, plasma, or blood from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some [embodimentexamples](#), the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of the one or more biomarkers of Alzheimer's disease in the sample of cerebrospinal fluid, plasma, or blood. In some [embodimentexamples](#), the one or more biomarkers of Alzheimer's disease are selected from A β 42, A β 40, total tau, pTau, neurofilament light, or any combination thereof.

[0045] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of one or more biomarkers of

microglia function in a sample of cerebrospinal fluid, plasma, or blood from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some [embodimentexamples](#), the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of the one or more biomarkers of microglia function in the sample of cerebrospinal fluid, plasma, or blood. In some [embodimentexamples](#), the one or more biomarkers of microglia function are CSF1R, IL1RN, YKL40, and/or osteopontin.

[0046] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of one or more biomarkers of neurodegeneration in a sample of cerebrospinal fluid, plasma, or blood from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some [embodimentexamples](#), the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of the one or more biomarkers of neurodegeneration in the sample of cerebrospinal fluid, plasma, or blood. In some [embodimentexamples](#), the one or more biomarkers of neurodegeneration comprise NfL.

[0047] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the expression levels of TREM2, CSF1R, YKL40, IL-1RA, or osteopontin in a sample of cerebrospinal fluid, plasma, or blood from the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some [embodimentexamples](#), the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the expression levels of TREM2, CSF1R, YKL40, IL-1RA, or osteopontin in the sample of cerebrospinal fluid, plasma, or blood. In some [embodimentexamples](#), the expression levels of TREM2, CSF1R, YKL40, IL-1RA, or osteopontin refer to mRNA expression levels. In some [embodimentexamples](#), the expression levels of TREM2, CSF1R, YKL40, IL-1RA, or osteopontin refer to protein expression levels. In some [embodimentexamples](#), the method comprises measuring the protein expression levels of sTREM2 or sCSF1R in the sample of cerebrospinal fluid, plasma, or blood from the individual before and after the individual has received one or more doses of the anti-TREM2 antibody.

[0048] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring the levels of amyloid burden in the brain of the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some [embodimentexamples](#), the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of amyloid burden in the brain of the individual.

[0049] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring tau burden in the brain of the individual,

assessed by measuring the levels of tau in the brain of the individual, before and after the individual has received one or more doses of an anti-TREM2 antibody. In some [embodimentexamples](#), the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the levels of tau in the brain of the individual.

[0050] In another [aspectexample](#), provided herein is a method of monitoring the treatment of an individual being administered an anti-TREM2 antibody, comprising measuring brain volume of the individual before and after the individual has received one or more doses of an anti-TREM2 antibody. In some [embodimentexamples](#), the method of monitoring treatment provided herein also comprises a step of assessing the activity of the anti-TREM2 antibody in the individual based on the brain volume of the individual.

[0051] In any of the foregoing methods of monitoring treatment, the anti-TREM2 antibody is an agonist.

BRIEF DESCRIPTION OF THE DRAWINGS

[0052] **FIG. 1** shows a diagram of the Phase 1 study described in Example 1 assessing the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AT.1FM when administered as single ascending doses in healthy participants and as multiple doses in participants with mild to moderate AD. SAD = single ascending dose; MD = multiple dose. The arrows indicate administration of AT.1FM at the indicated doses. The ratio of participants administered active drug (AT.1FM) to participants administered placebo is provided for each cohort (active drug:placebo). The asterisk (*) indicates that lumbar punctures are performed to obtain a cerebrospinal fluid (CSF) baseline sample (SAD Cohorts F, G, H, I, K and N; MD Cohorts J, L and M). The plus sign (+) indicates open-label cohorts.

[0053] **FIG. 2** provides safety results for the SAD phase of the Phase 1 study described in Examples 1 and 2. TEAE = treatment emergent adverse event; SAE = serious adverse event; “disc.” = discontinuation. The asterisk (*) indicates a traumatic injury event unrelated to study treatment.

[0054] **FIGS. 3A-3B** show results of experiments that assessed the effect of AT.1FM on the levels of soluble TREM2 (sTREM2) and soluble CSF1R (sCSF1R) in the cerebrospinal fluid (CSF) of participants in the SAD phase of the study described in Examples 1 and 2. **FIG. 3A** shows the percent change in the levels of sTREM2 in CSF two days after administration of the indicated dose of AT.1FM or placebo compared to baseline sTREM2 levels in CSF. **FIG. 3B** shows the percent change in the levels of sCSF1R in CSF two days after administration of the indicated dose of AT.1FM or placebo compared to baseline sCSF1R levels in CSF.

[0055] **FIG. 4** shows the levels of sTREM2 in the CSF of healthy human volunteers administered AT.1FM or placebo. The percent change from baseline (mean $\pm$ standard deviation) of sTREM2 levels in CSF is provided at day 2 (D2) and day 12 (D12) after administration of the indicated dose of AT.1FM or placebo.