

Claims

1. An antibody or an antigen-binding fragment thereof that binds to the immunoglobulin superfamily (IgSF) domain of human triggering expression on myeloid cells 2 (hTREM2) protein and stabilizes the hTREM2 protein of SEQ ID NO:1, 2 or 3, wherein said antibody or antigen-binding fragment thereof comprises:

a) a heavy chain variable region CDR1 comprising, SEQ ID NO: 41 or SEQ ID NO: 44 or SEQ ID NO: 45 or SEQ ID NO: 47; a heavy chain variable region CDR2 comprising, SEQ ID NO: 42 or SEQ ID NO: 46, or SEQ ID NO: 48; a heavy chain variable region CDR3 comprising, SEQ ID NO: 43 or SEQ ID NO: 49; a light chain variable region CDR1 comprising SEQ ID NO: 54 or SEQ ID NO: 57 or SEQ ID NO: 60; a light chain variable region CDR2 comprising, SEQ ID NO: 55 or SEQ ID NO: 58; and a light chain variable region CDR3 comprising SEQ ID NO: 56 or SEQ ID NOs: 59;

b) a heavy chain variable region CDR1 comprising, SEQ ID NO: 4 or SEQ ID NO: 7 or SEQ ID NO: 8 or SEQ ID NO: 10; a heavy chain variable region CDR2 comprising SEQ ID NO: 5 or SEQ ID NO: 9 or SEQ ID NO: 11; a heavy chain variable region CDR3 comprising SEQ ID NO: 6 or SEQ ID NO: 12; a light chain variable region CDR1 comprising SEQ ID NO: 17 or SEQ ID NO: 20 or SEQ ID NO: 23; a light chain variable region CDR2 comprising SEQ ID NO: 18 or SEQ ID NO: 21; and a light chain variable region CDR3 comprising SEQ ID NO: 19 or SEQ ID NO: 22;

c) a heavy chain variable region CDR1 comprising SEQ ID NO: 4 or SEQ ID NO: 7 or SEQ ID NO: 8 or SEQ ID NO: 10; a heavy chain variable region CDR2 comprising SEQ ID NO: 5 or SEQ ID NO: 9 or SEQ ID NO: 11; a heavy chain variable region CDR3 comprising SEQ ID NO: 6 or SEQ ID NO: 12; a light chain variable region CDR1 comprising SEQ ID NO: 17 or SEQ ID NO: 20 or SEQ ID NO: 23; a light chain variable region CDR2 comprising SEQ ID NO: 18 or SEQ ID NO: 21; and a light chain variable region CDR3 comprising SEQ ID NO: 78 or SEQ ID NO: 79; or

d) a heavy chain variable region CDR1 comprising SEQ ID NO: 84 or SEQ ID NO: 87 or SEQ ID NO: 88 or SEQ ID NO: 90; a heavy chain variable region CDR2 comprising, SEQ ID NO: 85 or SEQ ID NO: 89 or SEQ ID NO: 91; a heavy chain variable region CDR3 comprising SEQ ID NO: 86 or SEQ ID NO: 92; a light chain variable region CDR1 comprising SEQ ID NO: 97 or SEQ ID NO: 100 or SEQ ID NO: 103; a light chain variable region CDR2 comprising SEQ ID NO: 98 or SEQ ID NO: 101; and a light chain variable region CDR3 comprising SEQ ID NO: 99 or SEQ ID NO: 102.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof binds one or more residues selected from a group consisting of D39, S40, M41, K42, W44, G45, R46, R47, H67, N68, L69, W70, L71, L72, F74, L75, R77, D87, T88, L89 and G90 of hTREM2.
3. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof binds all the residues S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.
4. The antibody or antigen-binding fragment thereof of claim 3, wherein the antibody or antigen-binding fragment thereof binds all the residues D39, K42, R46 and G90 of hTREM2.
5. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof binds all the residues S40, M41, W44, G45, W70, L71, L72, F74, T88, L89, R47, H67, N68, L69, L75, R77 and D87 of hTREM2.
6. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof activates hTREM2.
7. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof facilitates one or more hTREM2-dependent physiological activities in a TREM2 expressing cell.
8. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof:
 - a) increases phagocytosis in a hTREM2-expressing cell wherein the TREM2 expressing cell is a hM2A macrophage or a human iPS-derived microglia-like cell,
 - b) increases chemotaxis in a hTREM2-expressing cell wherein the TREM2 expressing cell is a hM2a macrophage or a human iPS-derived microglia-like cell,
 - c) increases NFAT-driven reporter gene activity in a human monocytic cell line,
 - d) increases Syk phosphorylation in a hTREM2-expressing cell wherein the TREM2 expressing cell is a hM2A macrophage, or
 - e) increases any combination of two or more of a) to d).

9. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof binds hTREM2 on a cell surface, with a half maximal effective concentration (EC_{50}) of 1 nM or less as measured by FACS analysis on hM2a macrophages.
10. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof binds hTREM2 on a cell surface, with a half maximal effective concentration (EC_{50}) of 0.59 nM or less, as measured by FACS analysis on hM2a macrophages.
11. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof binds hTREM2 with a dissociation constant (K_D) of 150 pM or less, as measured by surface plasmon resonance (SPR).
12. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof binds hTREM2 with a dissociation constant (K_D) of 50 pM or less, as measured by surface plasmon resonance (SPR).
13. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof stabilizes hTREM2 protein on a cell surface of a hTREM2-expressing cell.
14. The antibody or antigen-binding fragment thereof of claim 13, wherein the hTREM2-expressing cell is an M2a macrophage, a dendritic cell, an osteoclast, a microglia, a mast cell, a monocyte, a lung epithelial cell, a Langerhans cell of skin, a Kupffer cell, a neutrophil or a hepatocarcinoma cell.
15. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof reduces shedding of the ectodomain of hTREM2 protein at a concentration of 100 nM or lower in hM2A macrophages.
16. The antibody or antigen-binding fragment thereof of claim 1, wherein TREM2 cell surface expression is increased 3 fold or higher.

17. An antibody or antigen-binding fragment thereof that binds to the IgSF domain of hTREM2 protein, wherein said antibody or antigen-binding fragment thereof comprises:

a) a heavy chain variable region CDR1 comprising SEQ ID NO: 41 or SEQ ID NO: 44 or SEQ ID NO: 45 or SEQ ID NO: 47; a heavy chain variable region CDR2 comprising SEQ ID NO: 42 or SEQ ID NO: 46, or SEQ ID NO: 48; a heavy chain variable region CDR3 comprising SEQ ID NO: 43 or SEQ ID NO: 49; a light chain variable region CDR1 comprising SEQ ID NO: 54 or SEQ ID NO: 57 or SEQ ID NO: 60; a light chain variable region CDR2 comprising SEQ ID NO: 55 or SEQ ID NO: 58; and a light chain variable region CDR3 comprising SEQ ID NO: 56 or SEQ ID NOs: 59;

b) a heavy chain variable region CDR1 comprising SEQ ID NO: 4 or SEQ ID NO: 7 or SEQ ID NO: 8 or SEQ ID NO: 10; a heavy chain variable region CDR2 comprising SEQ ID NO: 5 or SEQ ID NO: 9 or SEQ ID NO: 11; a heavy chain variable region CDR3 comprising SEQ ID NO: 6 or SEQ ID NO: 12; a light chain variable region CDR1 comprising SEQ ID NO: 17 or SEQ ID NO: 20 or SEQ ID NO: 23; a light chain variable region CDR2 comprising SEQ ID NO: 18 or SEQ ID NO: 21; and a light chain variable region CDR3 comprising SEQ ID NO: 19 or SEQ ID NO: 22;

c) a heavy chain variable region CDR1 comprising SEQ ID NO: 4 or SEQ ID NO: 7 or SEQ ID NO: 8 or SEQ ID NO: 10; a heavy chain variable region CDR2 comprising SEQ ID NO: 5 or SEQ ID NO: 9 or SEQ ID NO: 11; a heavy chain variable region CDR3 comprising SEQ ID NO: 6 or SEQ ID NO: 12; a light chain variable region CDR1 comprising SEQ ID NO: 17 or SEQ ID NO: 20 or SEQ ID NO: 23; a light chain variable region CDR2 comprising SEQ ID NO: 18 or SEQ ID NO: 21; and a light chain variable region CDR3 comprising SEQ ID NO: 78 or SEQ ID NO: 79; or

d) a heavy chain variable region CDR1 comprising SEQ ID NO: 84 or SEQ ID NO: 87 or SEQ ID NO: 88 or SEQ ID NO: 90; a heavy chain variable region CDR2 comprising SEQ ID NO: 85 or SEQ ID NO: 89 or SEQ ID NO: 91; a heavy chain variable region CDR3 comprising SEQ ID NO: 86 or SEQ ID NO: 92; a light chain variable region CDR1 comprising SEQ ID NO: 97 or SEQ ID NO: 100 or SEQ ID NO: 103; a light chain variable region CDR2 comprising SEQ ID NO: 98 or SEQ ID NO: 101; and a light chain variable region CDR3 comprising SEQ ID NO: 99 or SEQ ID NO: 102.

18. The antibody or antigen-binding fragment thereof of claim 17 wherein the antibody or antigen-binding fragment thereof comprises

a) a VH polypeptide sequence having at least 95% sequence identity to SEQ ID NO: 13 or to SEQ ID NO: 50, and a VL polypeptide sequence having at least 95% sequence identity to SEQ ID NO: 24 or to SEQ ID NO: 61; or

b) a VH polypeptide sequence having at least 95% sequence identity to SEQ ID NO: 13 or to SEQ ID NO: 93, and a VL polypeptide sequence having at least 95% sequence identity to SEQ ID NO: 80 or to SEQ ID NO: 104.

19. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of claim 17 and a pharmaceutically acceptable carrier.

20. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-17 in the manufacture of a medicament for the treatment of a disease associated with hTREM2 loss of function in a subject in need thereof, wherein a therapeutically effective amount of the medicament is to be administered to the subject.

21. The use of claim 20, wherein the subject comprises cell surface hTREM2 level lower than a reference level, wherein the reference level is the cell surface hTREM2 level in a sample obtained from a healthy subject.

22. The use of claim 20, wherein the disease associated with TREM2 loss of function is a neuroinflammatory or neurodegenerative disease, optionally wherein the neuroinflammatory or neurodegenerative disease is Alzheimer's disease, frontotemporal dementia, Parkinson's disease, amyotrophic lateral sclerosis, Nasu-Hakola disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), anti-NMDA receptor encephalitis, autism, brain lupus (NP-SLE), chemo-induced peripheral neuropathy (CIPN), postherapeutic neuralgia, chronic inflammatory demyelinating polyneuropathy (CIDP), epilepsy, Guillain-Barré Syndrom (GBS), inclusion body myositis, lysosomal storage diseases, sphingomyelinlipidose (Niemann-Pick C), mucopolysaccharidose II/IIIB, metachromatic leukodystrophy, multifocal motor neuropathy, Myasthenia Gravis, Neuro-Behcet's Disease, neuromyelitis optica (NMO), optic neuritis, polymyositis, dermatomyositis, Rasmussen's encephalitis, Rett's Syndrome, stroke, transverse myelitis, traumatic brain injury, spinal cord injury, viral encephalitis, or bacterial meningitis.

23. The use of claim 20, wherein the disease is Alzheimer's disease.

24. The use of claim 20, wherein the disease is Parkinson's disease.
25. The use of claim 20, wherein the disease is multiple sclerosis.
26. The use of claim 20, wherein the disease is amyotrophic lateral sclerosis.
27. The use of claim 20, further comprising at least one additional therapeutic agent to be administered to the subject.
28. An antibody or antigen-binding fragment thereof that binds to the immunoglobulin superfamily (IgSF) domain of human triggering expression on myeloid cells 2 (hTREM2) comprising:
 - a) a heavy chain sequence comprising SEQ ID NO: 15 and a light chain sequence comprising SEQ ID NO: 26;
 - b) a heavy chain sequence comprising SEQ ID NO: 29 and a light chain sequence comprising SEQ ID NO: 26;
 - c) a heavy chain sequence comprising SEQ ID NO: 33 and a light chain sequence comprising SEQ ID NO: 26;
 - d) a heavy chain sequence comprising SEQ ID NO: 35 and a light chain sequence comprising SEQ ID NO: 26;
 - e) a heavy chain sequence comprising SEQ ID NO: 37 and a light chain sequence comprising SEQ ID NO: 26;
 - f) a heavy chain sequence comprising SEQ ID NO: 39 and a light chain sequence comprising SEQ ID NO: 26;
 - g) a heavy chain sequence comprising SEQ ID NO: 52 and a light chain sequence comprising SEQ ID NO: 63;
 - h) a heavy chain sequence comprising SEQ ID NO: 66 and light chain sequence comprising SEQ ID NO: 63;
 - i) a heavy chain sequence comprising SEQ ID NO: 70 and light chain sequence comprising SEQ ID NO: 63;
 - j) a heavy chain sequence comprising SEQ ID NO: 72 and light chain sequence comprising SEQ ID NO: 63;
 - k) a heavy chain sequence comprising SEQ ID NO: 74 and light chain sequence comprising SEQ ID NO: 63;

l) a heavy chain sequence comprising SEQ ID NO: 76 and light chain sequence comprising SEQ ID NO: 63;

m) a heavy chain sequence comprising SEQ ID NO: 15 and light chain sequence comprising SEQ ID NO: 82; or

n) a heavy chain sequence comprising SEQ ID NO: 95 and light chain sequence comprising SEQ ID NO: 106.