

WHAT IS CLAIMED IS:

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to a human TREM2, wherein the antibody or antigen-binding fragment thereof comprises:
 - (a) a CDR-H1 sequence comprising the sequence of G-F-T-F-T- α_6 -F-Y-M-S (SEQ ID NO:48), wherein α_6 is D or N;
 - (b) a CDR-H2 sequence comprising the sequence of V-I-R-N- β_5 - β_6 -N- β_8 -Y-T- β_{11} - β_{12} -Y-N-P-S-V-K-G (SEQ ID NO:49), wherein β_5 is K or R; β_6 is A or P; β_8 is G or A; β_{11} is A or T; and β_{12} is G or D;
 - (c) a CDR-H3 sequence comprising the sequence of γ_1 -R-L- γ_4 -Y-G-F-D-Y (SEQ ID NO:50), wherein γ_1 is A or T; and γ_4 is T or S;
 - (d) a CDR-L1 sequence comprising the sequence of Q-S-S-K-S-L-L-H-S- δ_{10} -G-K-T-Y-L-N (SEQ ID NO:51), wherein δ_{10} is N or T;
 - (e) a CDR-L2 sequence comprising the sequence of WMSTRAS (SEQ ID NO:8); and
 - (f) a CDR-L3 sequence comprising the sequence of Q-Q-F-L-E- ϕ_6 -P-F-T (SEQ ID NO:52), wherein ϕ_6 is Y or F.
2. The isolated antibody or antigen-binding fragment of claim 1, wherein:
 - (a) the CDR-H1 sequence is selected from any one of SEQ ID NOS:4 and 12;
 - (b) the CDR-H2 sequence is selected from any one of SEQ ID NOS:5, 13, and 25;
 - (c) the CDR-H3 sequence is selected from any one of SEQ ID NOS:6, 14, and 17;
 - (d) the CDR-L1 sequence is selected from any one of SEQ ID NOS:7 and 23; and/or
 - (e) the CDR-L3 sequence is selected from any one of SEQ ID NOS:9 and 18.

3. The isolated antibody or antigen-binding fragment of claim 1 or 2, wherein the antibody or antigen-binding fragment comprises:

(a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:18; or

(b) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:23, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:18; or

(c) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:18; or

(d) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:23, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:18; or

(e) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:6, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:9; or

(f) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:12, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:13, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:9; or

(g) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:9.

4. The isolated antibody or antigen-binding fragment of any one of claims 1 to 3, comprising a V_H sequence that has at least 85% sequence identity to any one of SEQ ID NOS:2, 10, 15, 19, 21, 24, 26, and 79.

5. The isolated antibody or antigen-binding fragment of claim 4, wherein:

- (a) the V_H sequence has at least 90% sequence identity to SEQ ID NO:15;
- (b) the V_H sequence has at least 95% sequence identity to SEQ ID NO:15;

or

- (c) the V_H sequence comprises SEQ ID NO:15.

6. The isolated antibody or antigen-binding fragment of claim 4, wherein:

- (a) the V_H sequence has at least 90% sequence identity to SEQ ID NO:24;
- (b) the V_H sequence has at least 95% sequence identity to SEQ ID NO:24;

or

- (c) the V_H sequence comprises SEQ ID NO:24.

7. The isolated antibody or antigen-binding fragment of claim 4, wherein:

- (a) the V_H sequence has at least 90% sequence identity to SEQ ID NO:79;
- (b) the V_H sequence has at least 95% sequence identity to SEQ ID NO:79;

or

- (c) the V_H sequence comprises SEQ ID NO:79.

8. The isolated antibody or antigen-binding fragment of any one of claims 1 to 7, comprising a V_L sequence that has at least 85% sequence identity to any one of SEQ ID NOS:3, 11, 16, 20, 22, and 68.

9. The isolated antibody or antigen-binding fragment of claim 8, wherein:

(a) the V_L sequence has at least 90% sequence identity to SEQ ID NO:16;

(b) the V_L sequence has at least 95% sequence identity to SEQ ID NO:16;

or

(c) the V_L sequence comprises SEQ ID NO:16.

10. The isolated antibody or antigen-binding fragment of claim 8, wherein:

(a) the V_L sequence has at least 90% sequence identity to SEQ ID NO:22;

(b) the V_L sequence has at least 95% sequence identity to SEQ ID NO:22;

or

(c) the V_L sequence comprises SEQ ID NO:22.

11. The isolated antibody or antigen-binding fragment of claim 8, wherein:

(a) the V_L sequence has at least 90% sequence identity to SEQ ID NO:68;

(b) the V_L sequence has at least 95% sequence identity to SEQ ID NO:68;

or

(c) the V_L sequence comprises SEQ ID NO:68.

12. The isolated antibody or antigen-binding fragment of any one of claims 1 to 11, wherein the antibody or antigen-binding fragment comprises:

(a) a V_H sequence comprising SEQ ID NO:15 and a V_L sequence comprising SEQ ID NO:16; or

(b) a V_H sequence comprising SEQ ID NO:19 and a V_L sequence comprising SEQ ID NO:20; or

- (c) a V_H sequence comprising SEQ ID NO:21 and a V_L sequence comprising SEQ ID NO:20; or
- (d) a V_H sequence comprising SEQ ID NO:19 and a V_L sequence comprising SEQ ID NO:22; or
- (e) a V_H sequence comprising SEQ ID NO:79 and a V_L sequence comprising SEQ ID NO:22; or
- (f) a V_H sequence comprising SEQ ID NO:24 and a V_L sequence comprising SEQ ID NO:20; or
- (g) a V_H sequence comprising SEQ ID NO:26 and a V_L sequence comprising SEQ ID NO:20; or
- (h) a V_H sequence comprising SEQ ID NO:24 and a V_L sequence comprising SEQ ID NO:22; or
- (i) a V_H sequence comprising SEQ ID NO:26 and a V_L sequence comprising SEQ ID NO:22; or
- (j) a V_H sequence comprising SEQ ID NO:2 and a V_L sequence comprising SEQ ID NO:3; or
- (k) a V_H sequence comprising SEQ ID NO:10 and a V_L sequence comprising SEQ ID NO:11; or
- (l) a V_H sequence comprising SEQ ID NO:24 and a V_L sequence comprising SEQ ID NO:68.

13. An isolated antibody or antigen-binding fragment thereof that specifically binds to a human TREM2, wherein the antibody or antigen-binding fragment thereof comprises:

- (a) a CDR-H1 sequence comprising the sequence of GFSIEDFYIH (SEQ ID NO:29);
- (b) a CDR-H2 sequence comprising the sequence of W-I-D-P-E- β_6 -G- β_8 -S-K-Y-A-P-K-F-Q-G (SEQ ID NO:47), wherein β_6 is N or Q and β_8 is D or E;
- (c) a CDR-H3 sequence comprising the sequence of HADHGNYGSTMDY (SEQ ID NO:31);
- (d) a CDR-L1 sequence comprising the sequence of HASQHINVWLS (SEQ ID NO:32);
- (e) a CDR-L2 sequence comprising the sequence of KASNLHT (SEQ ID NO:33); and

(f) a CDR-L3 sequence comprising the sequence of QQGQTYPRT (SEQ ID NO:34).

14. The isolated antibody or antigen-binding fragment of claim 13, wherein the CDR-H2 sequence is selected from SEQ ID NOS:30, 39, 41, and 43.

15. The isolated antibody or antigen-binding fragment of claim 13 or 14, wherein the antibody or antigen-binding fragment comprises:

(a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:29, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:30, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:31, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:32, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:33, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:34; or

(b) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:29, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:39, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:31, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:32, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:33, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:34; or

(c) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:29, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:41, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:31, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:32, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:33, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:34; or

(d) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:29, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:43, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:31, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:32, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:33, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:34.

16. The isolated antibody or antigen-binding fragment of any one of claims 13 to 15, comprising a V_H sequence that has at least 85% sequence identity to any one of SEQ ID NOS:27, 35, 37, 38, 40, 42, 44, 45, and 46.

17. The isolated antibody or antigen-binding fragment of claim 16, wherein:

(a) the V_H sequence has at least 90% sequence identity to SEQ ID NO:27;

(b) the V_H sequence has at least 95% sequence identity to SEQ ID NO:27;

or

(c) the V_H sequence comprises SEQ ID NO:27.

18. The isolated antibody or antigen-binding fragment of any one of claims 13 to 17, comprising a V_L sequence that has at least 85% sequence identity to SEQ ID NO:28 or SEQ ID NO:36.

19. The isolated antibody or antigen-binding fragment of claim 18, wherein:

(a) the V_L sequence has at least 90% sequence identity to SEQ ID NO:28;

(b) the V_L sequence has at least 95% sequence identity to SEQ ID NO:28;

or

(c) the V_L sequence comprises SEQ ID NO:28.

20. The isolated antibody or antigen binding fragment of claim 18, wherein the antibody or antigen-binding fragment comprises:

(a) a V_H sequence comprising SEQ ID NO:27 and a V_L sequence comprising SEQ ID NO:28; or

(b) a V_H sequence comprising SEQ ID NO:35 and a V_L sequence comprising SEQ ID NO:36; or

(c) a V_H sequence comprising SEQ ID NO:37 and a V_L sequence comprising SEQ ID NO:36; or

(d) a V_H sequence comprising SEQ ID NO:38 and a V_L sequence comprising SEQ ID NO:36; or

(e) a V_H sequence comprising SEQ ID NO:40 and a V_L sequence comprising SEQ ID NO:36; or

(f) a V_H sequence comprising SEQ ID NO:42 and a V_L sequence comprising SEQ ID NO:36; or

(g) a V_H sequence comprising SEQ ID NO:44 and a V_L sequence comprising SEQ ID NO:36; or

(h) a V_H sequence comprising SEQ ID NO:45 and a V_L sequence comprising SEQ ID NO:36; or

(i) a V_H sequence comprising SEQ ID NO:46 and a V_L sequence comprising SEQ ID NO:36.

21. An isolated antibody or antigen-binding fragment thereof that specifically binds to a human TREM2, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a CDR-H1 sequence comprising the amino acid sequence of any one of SEQ ID NOS:4, 12, and 29;

(b) a CDR-H2 sequence comprising the amino acid sequence of any one of SEQ ID NOS:5, 13, 25, 30, 39, 41, and 43;

(c) a CDR-H3 sequence comprising the amino acid sequence of any one of SEQ ID NOS:6, 14, 17, and 31;

(d) a CDR-L1 sequence comprising the amino acid sequence of any one of SEQ ID NOS:7, 23, and 32;

(e) a CDR-L2 sequence comprising the amino acid sequence of any one of SEQ ID NOS:8 and 33; and

(f) a CDR-L3 sequence comprising the amino acid sequence of any one of SEQ ID NOS:9, 18, and 34.

22. The isolated antibody or antigen-binding fragment of claim 21, wherein the antibody or antigen-binding fragment comprises:

(a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:6, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:9; or

(b) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:18; or

(c) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of

amino acid sequence of SEQ ID NO:31, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:32, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:33, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:34; or

(k) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:9.

23. The isolated antibody or antigen-binding fragment of claim 21 or 22, comprising:

(a) a heavy chain variable region that has at least 85% sequence identity to any one of SEQ ID NOS:2, 10, 15, 19, 21, 24, 26, 27, 35, 37, 38, 40, 42, 44, 45, 46, and 79; and/or

(b) a light chain variable region that has at least 85% sequence identity to any one of SEQ ID NOS:3, 11, 16, 20, 22, 28, and 36.

24. The isolated antibody or antigen-binding fragment of any one of claims 21 to 23, wherein the antibody or antigen-binding fragment comprises:

(a) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:2 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:3; or

(b) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:10 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:11; or

(c) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:15 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:16; or

(d) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:19 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:20; or

(e) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:21 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:20; or

(f) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:19 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:22; or

(g) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:79 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:22; or

- (h) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:24 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:20; or
- (i) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:26 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:20; or
- (j) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:24 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:22; or
- (k) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:26 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:22; or
- (l) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:27 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:28; or
- (m) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:35 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:36; or
- (n) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:37 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:36; or
- (o) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:38 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:36; or
- (p) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:40 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:36; or
- (q) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:42 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:36; or
- (r) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:44 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:36; or
- (s) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:45 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:36; or
- (t) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:46 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:36; or
- (u) a V_H sequence that has at least 85% sequence identity to SEQ ID NO:24 and a V_L sequence that has at least 85% sequence identity to SEQ ID NO:68.

25. An isolated antibody or antigen-binding fragment thereof that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody or antigen-binding fragment thereof recognizes an epitope that is the same or substantially the same as the epitope recognized by an antibody clone selected from the group consisting of: Clone CL0020306, Clone CL0020188, Clone CL0020188-1, Clone CL0020188-2, Clone

CL0020188-3, Clone CL0020188-4, Clone CL0020188-5, Clone CL0020188-6, Clone CL0020188-7, Clone CL0020188-8, Clone CL0020307, Clone CL0020123, Clone CL0020123-1, Clone CL0020123-2, Clone CL0020123-3, Clone CL0020123-4, Clone CL0020123-5, Clone CL0020123-6, Clone CL0020123-7, and Clone CL0020123-8.

26. The isolated antibody or antigen-binding fragment of claim 25, wherein the antibody or antigen-binding fragment recognizes an epitope that is the same or substantially the same as the epitope recognized by an antibody clone selected from the group consisting of: Clone CL0020123, Clone CL0020123-1, Clone CL0020123-2, Clone CL0020123-3, Clone CL0020123-4, Clone CL0020123-5, Clone CL0020123-6, Clone CL0020123-7, and Clone CL0020123-8; optionally

wherein the antibody or antigen-binding fragment recognizes one or more of the following in SEQ ID NO:1: (i) amino acid residues 55-63 (GEKGPCQRV (SEQ ID NO:70)), (ii) amino acids 96-107 (TLRNLPQHDAGL (SEQ ID NO:71)), and (iii) amino acid residues 126-129 (VEVL (SEQ ID NO:72)).

27. The isolated antibody or antigen-binding fragment of claim 25, wherein the antibody or antigen-binding fragment recognizes an epitope that is the same or substantially the same as the epitope recognized by an antibody clone selected from the group consisting of: Clone CL0020188, Clone CL0020188-1, Clone CL0020188-2, Clone CL0020188-3, Clone CL0020188-4, Clone CL0020188-5, Clone CL0020188-6, Clone CL0020188-7, Clone CL0020188-8, Clone CL0020307, and Clone CL0020306; optionally

wherein the antibody or antigen-binding fragment recognizes amino acid residues 143-149 (FPGESSES (SEQ ID NO:69)) in SEQ ID NO:1.

28. An isolated antibody or antigen-binding fragment thereof that specifically binds to a human TREM2, wherein:

(a) the antibody or antigen-binding fragment thereof recognizes an epitope comprising or consisting of one or more of the following in SEQ ID NO:1: (i) amino acid residues 55-63 (GEKGPCQRV (SEQ ID NO:70)), (ii) amino acids 96-107 (TLRNLPQHDAGL (SEQ ID NO:71)), and (iii) amino acid residues 126-129 (VEVL (SEQ ID NO:72)); or

(b) the antibody or antigen-binding fragment thereof recognizes an epitope comprising or consisting of amino acid residues 143-149 (FPGESSES (SEQ ID NO:69)) in SEQ ID NO:1.

29. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 28, wherein:

(a) the antibody or antigen-binding fragment thereof decreases levels of soluble TREM2 protein (sTREM2);

(b) the antibody or antigen-binding fragment thereof enhances TREM2 activity; optionally wherein:

(i) the antibody or antigen-binding fragment thereof enhances phagocytosis or enhances the migration, differentiation, function, or survival of myeloid cells, microglia, or macrophages; optionally

wherein the antibody or antigen-binding fragment thereof enhances microglia function without increasing neuroinflammation; or

(ii) the antibody or antigen-binding fragment thereof enhances Syk phosphorylation; optionally

wherein the antibody or antigen-binding fragment thereof enhances Syk phosphorylation in the presence of a TREM2 ligand; and/or

(c) the antibody or antigen-binding fragment thereof exhibits cross-reactivity with a cynomolgus TREM2 protein.

30. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 29, wherein:

(a) the antibody is a monoclonal antibody;

(b) the antibody is a chimeric antibody;

(c) the antibody is a humanized antibody;

(d) the antibody is a fully human antibody; or

(e) the antigen-binding fragment is a Fab, a F(ab')₂, a scFv, or a bivalent scFv.

31. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 30 and a pharmaceutically acceptable carrier.

32. An antibody or antigen-binding fragment thereof that competes with the isolated antibody of any one of claims 1 to 30 for binding to the human TREM2 protein.

33. A kit comprising:

the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 30 or the pharmaceutical composition of claim 31; and
instructions for use thereof.

34. Use of the isolated antibody or antigen-binding fragment of any one of claims 1 to 30 or 32, or the composition of claim 31, in the manufacture of a medicament for treating a neurodegenerative disease in a subject; optionally

wherein the neurodegenerative disease is selected from the group consisting of: Alzheimer's disease, primary age-related tauopathy, progressive supranuclear palsy (PSP), frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, argyrophilic grain dementia, amyotrophic lateral sclerosis, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (ALS-PDC), corticobasal degeneration, chronic traumatic encephalopathy, Creutzfeldt-Jakob disease, dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, familial British dementia, familial Danish dementia, Gerstmann-Straussler-Scheinker disease, globular glial tauopathy, Guadeloupean parkinsonism with dementia, Guadeloupean PSP, Hallevorden-Spatz disease, hereditary diffuse leukoencephalopathy with spheroids (HDLS), Huntington's disease, inclusion-body myositis, multiple system atrophy, myotonic dystrophy, Nasu-Hakola disease, neurofibrillary tangle-predominant dementia, Niemann-Pick disease type C, pallido-ponto-nigral degeneration, Parkinson's disease, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, subacute sclerosing panencephalitis, and tangle only dementia.

35. Use of the isolated antibody or antigen-binding fragment of any one of claims 1 to 30 or 32, or the composition of claim 31, in the manufacture of a medicament for decreasing levels of sTREM2 or enhancing TREM2 activity in a subject having a neurodegenerative disease.

WHAT IS CLAIMED IS:

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to a human TREM2, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a CDR-H1 sequence comprising the sequence of G-F-T-F-T-D-F-Y-M-S (SEQ ID NO:4);

(b) a CDR-H2 sequence comprising the sequence of V-I-R-N- β_5 - β_6 -N- β_8 -Y-T- β_{11} - β_{12} -Y-N-P-S-V-K-G (SEQ ID NO:49), wherein β_5 is K; β_6 is A; β_8 is G or A; β_{11} is A; and β_{12} is G;

(c) a CDR-H3 sequence comprising the sequence of A-R-L-T-Y-G-F-D-Y (SEQ ID NO:17);

(d) a CDR-L1 sequence comprising the sequence of Q-S-S-K-S-L-L-H-S- δ_{10} -G-K-T-Y-L-N (SEQ ID NO:51), wherein δ_{10} is N or T;

(e) a CDR-L2 sequence comprising the sequence of W-M-S-T-R-A-S (SEQ ID NO:8); and

(f) a CDR-L3 sequence comprising the sequence of Q-Q-F-L-E-Y-P-F-T (SEQ ID NO:18).

2. The isolated antibody or antigen-binding fragment of claim 1, wherein:

(a) the CDR-H2 sequence is selected from any one of SEQ ID NOS:5 and 25; and/or

(b) the CDR-L1 sequence is selected from any one of SEQ ID NOS:7 and 23.

3. The isolated antibody or antigen-binding fragment of claim 1 or 2, wherein the antibody or antigen-binding fragment comprises:

(a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:18; or

(b) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of

SEQ ID NO:23, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:18; or

(c) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:18; or

(d) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17, a CDR-L1 comprising the amino acid sequence of SEQ ID NO:23, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:18.

4. The isolated antibody or antigen-binding fragment of any one of claims 1 to 3, comprising a V_H sequence that has at least 85% sequence identity to any one of SEQ ID NOS:15, 19, 21, 24, 26, and 79.

5. The isolated antibody or antigen-binding fragment of claim 4, wherein:

(a) the V_H sequence has at least 90% sequence identity to SEQ ID NO:15;

(b) the V_H sequence has at least 95% sequence identity to SEQ ID NO:15;

or

(c) the V_H sequence comprises SEQ ID NO:15.

6. The isolated antibody or antigen-binding fragment of claim 4, wherein:

(a) the V_H sequence has at least 90% sequence identity to SEQ ID NO:24;

(b) the V_H sequence has at least 95% sequence identity to SEQ ID NO:24;

or

(c) the V_H sequence comprises SEQ ID NO:24.

7. The isolated antibody or antigen-binding fragment of claim 4, wherein:

(a) the V_H sequence has at least 90% sequence identity to SEQ ID NO:79;

(b) the V_H sequence has at least 95% sequence identity to SEQ ID NO:79;

or

(c) the V_H sequence comprises SEQ ID NO:79.

8. The isolated antibody or antigen-binding fragment of any one of claims 1 to 7, comprising a V_L sequence that has at least 85% sequence identity to any one of SEQ ID NOS:16, 20, and 22.

9. The isolated antibody or antigen-binding fragment of claim 8, wherein:

(a) the V_L sequence has at least 90% sequence identity to SEQ ID NO:16;

(b) the V_L sequence has at least 95% sequence identity to SEQ ID NO:16;

or

(c) the V_L sequence comprises SEQ ID NO:16.

10. The isolated antibody or antigen-binding fragment of claim 8, wherein:

(a) the V_L sequence has at least 90% sequence identity to SEQ ID NO:22;

(b) the V_L sequence has at least 95% sequence identity to SEQ ID NO:22;

or

(c) the V_L sequence comprises SEQ ID NO:22.

11. The isolated antibody or antigen-binding fragment of claim 8, wherein:

(a) the V_L sequence has at least 90% sequence identity to SEQ ID NO:20;

(b) the V_L sequence has at least 95% sequence identity to SEQ ID NO:20;

or

(c) the V_L sequence comprises SEQ ID NO:20.

12. The isolated antibody or antigen-binding fragment of any one of claims 1 to 11, wherein the antibody or antigen-binding fragment comprises:

(a) a V_H sequence comprising SEQ ID NO:15 and a V_L sequence comprising SEQ ID NO:16; or

(b) a V_H sequence comprising SEQ ID NO:19 and a V_L sequence comprising SEQ ID NO:20; or

(c) a V_H sequence comprising SEQ ID NO:21 and a V_L sequence comprising SEQ ID NO:20; or

(d) a V_H sequence comprising SEQ ID NO:19 and a V_L sequence comprising SEQ ID NO:22; or

(e) a V_H sequence comprising SEQ ID NO:79 and a V_L sequence comprising SEQ ID NO:22; or

(f) a V_H sequence comprising SEQ ID NO:24 and a V_L sequence comprising SEQ ID NO:20; or

(g) a V_H sequence comprising SEQ ID NO:26 and a V_L sequence comprising SEQ ID NO:20; or

(h) a V_H sequence comprising SEQ ID NO:24 and a V_L sequence comprising SEQ ID NO:22; or

(i) a V_H sequence comprising SEQ ID NO:26 and a V_L sequence comprising SEQ ID NO:22.

13. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 12, wherein:

(a) the antibody or antigen-binding fragment thereof decreases levels of soluble TREM2 protein (sTREM2);

(b) the antibody or antigen-binding fragment thereof enhances TREM2 activity; and/or

(c) the antibody or antigen-binding fragment thereof exhibits cross-reactivity with a cynomolgus TREM2 protein.

14. The isolated antibody or antigen-binding fragment thereof of claim 13(b), wherein:

(i) the antibody or antigen-binding fragment thereof enhances phagocytosis or enhances the migration, differentiation, function, or survival of myeloid cells, microglia, or macrophages; or

(ii) the antibody or antigen-binding fragment thereof enhances Syk phosphorylation.

15. The isolated antibody or antigen-binding fragment thereof of claim 14(i), wherein the antibody or antigen-binding fragment thereof enhances microglia function without increasing neuroinflammation.

16. The isolated antibody or antigen-binding fragment thereof of claim 14(ii), wherein the antibody or antigen-binding fragment thereof enhances Syk phosphorylation in the presence of a TREM2 ligand.

17. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 16, wherein:

- (a) the antibody is a monoclonal antibody;
- (b) the antibody is a chimeric antibody;
- (c) the antibody is a humanized antibody;
- (d) the antibody is a fully human antibody; or
- (e) the antigen-binding fragment is a Fab, a F(ab')₂, a scFv, or a bivalent scFv.

18. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 17 and a pharmaceutically acceptable carrier.

19. A kit comprising:

the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 17 or the pharmaceutical composition of claim 18; and
instructions for use thereof.

20. Use of the isolated antibody or antigen-binding fragment of any one of claims 1 to 17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for treating a neurodegenerative disease in a subject.

21. The use of claim 20, wherein the neurodegenerative disease is selected from the group consisting of: Alzheimer's disease, primary age-related tauopathy, progressive supranuclear palsy (PSP), frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, argyrophilic grain dementia, amyotrophic lateral sclerosis, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (ALS-PDC), corticobasal degeneration, chronic traumatic encephalopathy, Creutzfeldt-Jakob disease, dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, familial British dementia, familial Danish dementia, Gerstmann-Straussler-Scheinker disease, globular glial tauopathy, Guadeloupean parkinsonism with dementia, Guadeloupean PSP, Hallevorden-Spatz disease, hereditary diffuse leukoencephalopathy with spheroids (HDLS), Huntington's disease, inclusion-body myositis, multiple system atrophy, myotonic dystrophy, Nasu-Hakola disease,

neurofibrillary tangle-predominant dementia, Niemann-Pick disease type C, pallido-ponto-nigral degeneration, Parkinson's disease, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, subacute sclerosing panencephalitis, and tangle only dementia.

22. The use of claim 20 or 21, wherein the isolated antibody or antigen-binding fragment or the pharmaceutical composition decreases levels of sTREM2 or enhances TREM2 activity in the subject.