

WHAT IS CLAIMED IS:

1. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:
 - (a) a variable region comprising:
 - i. a CDR-H1 sequence comprising the sequence of G-F-T-F-T- α_6 -F-Y-M-S (SEQ ID NO:28), wherein α_6 is D or N;
 - ii. 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:29), 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;
 - iii. a CDR-H3 sequence comprising the sequence of γ_1 -R-L- γ_4 -Y-G-F-D-Y (SEQ ID NO:30), wherein γ_1 is A or T; and γ_4 is T or S;
 - iv. 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:31), wherein δ_{10} is N or T;
 - v. a CDR-L2 sequence comprising the sequence WMSTRAS (SEQ ID NO:8); and
 - vi. a CDR-L3 sequence comprising the sequence of Q-Q-F-L-E- ϕ_6 -P-F-T (SEQ ID NO:32), wherein ϕ_6 is Y or F;
 - (b) a first Fc polypeptide that is modified to specifically bind to a transferrin receptor; and
 - (c) a second Fc polypeptide.
2. The antibody of claim 1, wherein the CDR-H1 sequence is selected from SEQ ID NOS:4 or 12.
3. The antibody of claim 1 or 2, wherein the CDR-H2 sequence is selected from SEQ ID NOS:5, 13, or 25.
4. The antibody of any one of claims 1 to 3, wherein the CDR-H3 sequence is selected from SEQ ID NOS:6, 14, or 17.
5. The antibody of any one of claims 1 to 4, wherein the CDR-L1 sequence is selected from SEQ ID NOS:7 or 23.

6. The antibody of any one of claims 1 to 5, wherein the CDR-L3 sequence is selected from SEQ ID NOS:9 or 18.

7. The antibody of any one of claims 1 to 6, wherein the variable region 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.

8. The antibody of any one of claims 1 to 7, wherein the variable region comprises a V_H sequence that has at least 85% sequence identity to any one of SEQ ID NOS:2, 10, 15, 19, 21, 24, and 26.

9. The antibody of claim 8, wherein the V_H sequence has at least 90% sequence identity to SEQ ID NO:15.

10. The antibody of claim 9, wherein the V_H sequence has at least 95% sequence identity to SEQ ID NO:15.

11. The antibody of claim 10, wherein the V_H sequence comprises SEQ ID NO:15.

12. The antibody of claim 8, wherein the V_H sequence has at least 90% sequence identity to SEQ ID NO:24.

13. The antibody of claim 12, wherein the V_H sequence has at least 95% sequence identity to SEQ ID NO:24.

14. The antibody of claim 13, wherein the V_H sequence comprises SEQ ID NO:24.

15. The antibody of any one of claims 1 to 14, wherein the variable region comprises a V_L sequence has at least 85% sequence identity to any one of SEQ ID NOS:3, 11, 16, 20, 22, and 27.

16. The antibody of claim 15, wherein the V_L sequence has at least 90% sequence identity to SEQ ID NO:16.

17. The antibody of claim 16, wherein the V_L sequence has at least 95% sequence identity to SEQ ID NO:16.
18. The antibody of claim 17, wherein the V_L sequence comprises SEQ ID NO:16.
19. The antibody of claim 15, wherein the V_L sequence has at least 90% sequence identity to SEQ ID NO:22.
20. The antibody of claim 19, wherein the V_L sequence has at least 95% sequence identity to SEQ ID NO:22.
21. The antibody of claim 20, wherein the V_L sequence comprises SEQ ID NO:22.
22. The antibody of claim 15, wherein the V_L sequence has at least 90% sequence identity to SEQ ID NO:27.
23. The antibody of claim 22, wherein the V_L sequence has at least 95% sequence identity to SEQ ID NO:27.
24. The antibody of claim 23, wherein the V_L sequence comprises SEQ ID NO:27.
25. The antibody of any one of claims 1 to 7, wherein the variable region 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:21 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:27.

26. The antibody of any one of claims 1 to 25, wherein the first Fc polypeptide comprises: Trp, Leu, or Glu at position 380; Tyr or Phe at position 384; Thr at position 386; Glu at position 387; Trp at position 388; Ser, Ala, or Val at position 389; Ser or Asn at position 390; Thr or Ser at position 413; Glu or Ser at position 415; Glu at position 416; and Phe at position 421, according to EU numbering.

27. The antibody of claim 26, wherein the first Fc polypeptide binds to the apical domain of the transferrin receptor.

28. The antibody of claim 26 or 27, wherein the antibody has improved brain uptake compared to an antibody having a wild-type Fc dimer.

29. The antibody of any one of claims 1 to 28, wherein the first Fc polypeptide has a T366W substitution and the second Fc polypeptide has T366S, L368A, and Y407V substitutions, according to EU numbering.

30. The antibody of any one of claims 1 to 28, wherein the first Fc polypeptide has T366S, L368A, and Y407V substitutions and the second Fc polypeptide has a T366W substitution, according to EU numbering.

31. The antibody of any one of claims 1 to 30, wherein the first Fc polypeptide and/or the second Fc polypeptide comprises a modification that reduces effector function.

32. The antibody of claim 31, wherein the modification that reduces effector function comprises the substitutions of Ala at position 234 and Ala at position 235, according to EU numbering.

33. The antibody of any one of claims 1 to 32, wherein the first Fc polypeptide and/or the second Fc polypeptide comprises amino acid modifications relative to the native Fc sequence that extend serum half-life.

34. The antibody of claim 33, wherein the amino acid modifications comprise substitutions of Leu at position 428 and Ser at position 434, according to EU numbering.

35. The antibody of any one of claims 1 to 34, wherein the first Fc polypeptide comprises the sequence of SEQ ID NO:41 or SEQ ID NO:64, and the second Fc polypeptide comprises the sequence of SEQ ID NO:39 or SEQ ID NO:63.

36. The antibody of claim 35, comprising:

- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:41;
- (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:39; and
- (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

37. The antibody of claim 35, comprising:

- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:64;
- (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:63; and
- (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

38. The antibody of claim 35 or 36, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:42;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:53; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
39. The antibody of claim 35 or 37, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:65;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:73; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
40. The antibody of any one of claims 1 to 34, wherein the first Fc polypeptide comprises the sequence of SEQ ID NO:44 or SEQ ID NO:66, and the second Fc polypeptide comprises the sequence of SEQ ID NO:39 or SEQ ID NO:63.
41. The antibody of claim 40, comprising:
- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:44;
 - (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:39; and
 - (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.
42. The antibody of claim 40, comprising:
- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:66;
 - (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:63; and
 - (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

43. The antibody of claim 40 or 41, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:45;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:53; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
44. The antibody of claim 40 or 42, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:67;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:73; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
45. The antibody of any one of claims 1 to 34, wherein the first Fc polypeptide comprises the sequence of SEQ ID NO:47 or SEQ ID NO:68, and the second Fc polypeptide comprises the sequence of SEQ ID NO:39 or SEQ ID NO:63.
46. The antibody of claim 45, comprising:
- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:47;
 - (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:39; and
 - (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.
47. The antibody of claim 45, comprising:
- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:68;
 - (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:63; and
 - (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

48. The antibody of claim 45 or 46, comprising:

- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:48;
- (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:53; and
- (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.

49. The antibody of claim 45 or 47, comprising:

- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:69;
- (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:73; and
- (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.

50. The antibody of any one of claims 1 to 34, wherein the first Fc polypeptide comprises the sequence of SEQ ID NO:47 or SEQ ID NO:68, and the second Fc polypeptide comprises the sequence of SEQ ID NO:61 or SEQ ID NO:84.

51. The antibody of claim 50, comprising:

- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:47;
- (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:61; and
- (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

52. The antibody of claim 50, comprising:

- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:68;
- (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:84; and
- (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

53. The antibody of claim 50 or 51, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:48;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:52; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
54. The antibody of claim 50 or 52, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:69;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:72; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
55. The antibody of any one of claims 1 to 34, wherein the first Fc polypeptide comprises the sequence of SEQ ID NO:50 or SEQ ID NO:70, and the second Fc polypeptide comprises the sequence of SEQ ID NO:39 or SEQ ID NO:63.
56. The antibody of claim 55, comprising:
- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:50;
 - (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:39; and
 - (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.
57. The antibody of claim 55, comprising:
- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:70;
 - (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:63; and
 - (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

58. The antibody of claim 55 or 56, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:51;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:53; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
59. The antibody of claim 55 or 57, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:71;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:73; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
60. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:
- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:41;
 - (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:39; and
 - (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.
61. The antibody of claim 60, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:42;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:53; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
62. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:

(i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:64;

(ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:63; and

(iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

63. The antibody of claim 62, comprising:

(i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:65;

(ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:73; and

(iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.

64. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:

(i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:44;

(ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:39; and

(iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

65. The antibody of claim 64, comprising:

(i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:45;

(ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:53; and

(iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.

66. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:

(i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:66;

(ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:63; and

(iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

67. The antibody of claim 66, comprising:

(i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:67;

(ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:73; and

(iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.

68. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:

(i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:47;

(ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:39; and

(iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

69. The antibody of claim 68, comprising:

(i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:48;

(ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:53; and

(iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.

70. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:

(i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:68;

(ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:63; and

(iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

71. The antibody of claim 70, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:69;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:73; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
72. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:
- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:47
 - (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:61; and
 - (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.
73. The antibody of claim 72, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:48;
 - (ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:52; and
 - (iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.
74. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:
- (i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:68;
 - (ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:61; and
 - (iii) two light chains each comprising a V_L comprising SEQ ID NO:22.
75. The antibody of claim 74, comprising:
- (i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:69;

(ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:72; and

(iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.

76. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:

(i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:50;

(ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:39; and

(iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

77. The antibody of claim 76, comprising:

(i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:51;

(ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:53; and

(iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.

78. An isolated antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), wherein the antibody comprises:

(i) a first heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the first Fc polypeptide comprising SEQ ID NO:70;

(ii) a second heavy chain (HC) comprising a V_H comprising SEQ ID NO:24 and the second Fc polypeptide comprising SEQ ID NO:63; and

(iii) two light chains each comprising a V_L comprising SEQ ID NO:22.

79. The antibody of claim 78, comprising:

(i) a first heavy chain (HC) that comprises or consists of the amino acid sequence set forth in SEQ ID NO:71;

(ii) a second HC that comprises or consists of the amino acid sequence set forth in SEQ ID NO:73; and

(iii) a first and a second light chain (LC) that each comprises or consists of the amino acid sequence set forth in SEQ ID NO:54.

80. The antibody of any one of claims 1 to 79, wherein the antibody decreases levels of soluble TREM2 protein (sTREM2).

81. The antibody of any one of claims 1 to 80, wherein the antibody enhances TREM2 activity.

82. The antibody of any one of claims 1 to 81, wherein the antibody enhances phagocytosis or enhances the migration, differentiation, function, or survival of myeloid cells, microglia, or macrophages.

83. The antibody of any one of claims 1 to 82, wherein the antibody enhances microglia function without increasing neuroinflammation.

84. The antibody of any one of claims 1 to 83, wherein the antibody enhances Syk phosphorylation.

85. The antibody of claim 84, wherein the antibody enhances Syk phosphorylation in the presence of a TREM2 ligand.

86. The antibody of any one of claims 1 to 85, wherein the antibody exhibits cross-reactivity with a cynomolgus TREM2 protein.

87. A pharmaceutical composition comprising the isolated antibody of any one of claims 1 to 86 and a pharmaceutically acceptable carrier.

88. A kit comprising:
the isolated antibody of any one of claims 1 to 86 or the pharmaceutical composition of claim 87; and
instructions for use thereof.

89. A method of treating a neurodegenerative disease in a subject, comprising administering to the subject the isolated antibody of any one of claims 1 to 86 or the pharmaceutical composition of claim 87.

90. The method of claim 89, 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.

91. A method of decreasing levels of sTREM2 in a subject having a neurodegenerative disease, comprising administering to the subject the isolated antibody of any one of claims 1 to 86 or the pharmaceutical composition of claim 87.

92. A method of enhancing TREM2 activity in a subject having a neurodegenerative disease, comprising administering to the subject the isolated antibody of any one of claims 1 to 86 or the pharmaceutical composition of claim 87.

93. An isolated polynucleotide comprising a nucleotide sequence encoding the antibody of any one of claims 1 to 86.

94. An isolated polynucleotide comprising a nucleotide sequence encoding any one of SEQ ID NOS:42, 45, 48, 51, 53, 54, and 61.

95. An isolated polynucleotide comprising a nucleotide sequence encoding SEQ ID NOS:42, 53, and 54.

96. An isolated polynucleotide comprising a nucleotide sequence encoding SEQ ID NOS:45, 53, and 54.

97. An isolated polynucleotide comprising a nucleotide sequence encoding SEQ ID NOS:48, 53, and 54.

98. An isolated polynucleotide comprising a nucleotide sequence encoding SEQ ID NOS:48, 52, and 54.

99. An isolated polynucleotide comprising a nucleotide sequence encoding SEQ ID NOS:51, 53, and 54.

100. A vector comprising the polynucleotide of any one of claims 93 to 99.

101. A host cell comprising the polynucleotide of any one of claims 93 to 99 or the vector of claim 100.

102. A method of expressing an antibody that specifically binds to a human triggering receptor expressed on myeloid cells 2 (TREM2), comprising: culturing the host cell of claim 101 in under conditions suitable for expression of the antibody.