

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 (e.g. SEQ ID NO:1, 2 or 3).~~
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 one or more residues selected from a group consisting of D39, S40, M41, K42, W44, G45, R46 and R47, one or more residues selected from a group consisting of H67, N68, L69, W70, L71, L72, F74, L75 and R77, and one or more residues selected from a group consisting of D87, T88, L89 and G90 of hTREM2.~~
4. ~~The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds five or more residues selected from a group consisting of D39, S40, M41, K42, W44, G45, R46 and R47, four or more residues selected from a group consisting of H67, N68, L69, W70, L71, L72, F74, L75 and R77, and three or more residues selected from a group consisting of D87, T88, L89 and G90 of hTREM2.~~
5. ~~The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds seven or more residues selected from a group consisting of D39, S40, M41, K42, W44, G45, R46 and R47, four or more residues selected from a group consisting of H67, N68, L69, W70, L71, L72, F74, L75 and R77, and three or more residues selected from a group consisting of D87, T88, L89 and G90 of hTREM2.~~
6. ~~The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds five or more residues selected from a group consisting of D39, S40, M41, K42, W44, G45, R46 and R47, all residues H67, N68, L69,~~

~~W70, L71, L72, F74, L75 and R77, and three or more residues selected from a group consisting of D87, T88, L89 and G90 of hTREM2.~~

~~7. 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 S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.~~

~~8. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds two or more residues selected from a group consisting of S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.~~

~~9. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds three or more residues selected from a group consisting of S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.~~

~~10. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds four or more residues selected from a group consisting of S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.~~

~~11. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds five or more residues selected from a group consisting of S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.~~

~~12. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds six or more residues selected from a group consisting of S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.~~

~~13. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds seven or more residues selected from a group consisting of S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.~~

~~14. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds eight or more residues selected from a group consisting of S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.~~

~~15. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof binds nine or more residues selected from a group consisting of S40, M41, W44, G45, W70, L71, L72, F74, T88 and L89 of hTREM2.~~

~~16. 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.~~

~~17. The antibody or antigen binding fragment thereof of any one of claims 7 to 16, wherein the antibody or antigen binding fragment thereof binds one or more residues selected from a group consisting of D39, K42, R46 and G90 of hTREM2.~~

~~18. The antibody or antigen binding fragment thereof of any one of claims 7 to 16, wherein the antibody or antigen binding fragment thereof binds two or more residues selected from a group consisting of D39, K42, R46 and G90 of hTREM2.~~

~~19. The antibody or antigen binding fragment thereof of any one of claims 7 to 16, wherein the antibody or antigen binding fragment thereof binds three or more residues selected from a group consisting of D39, K42, R46 and G90 of hTREM2.~~

~~20. The antibody or antigen binding fragment thereof of any one of claims 7 to 15, wherein the antibody or antigen binding fragment thereof binds all the residues D39, K42, R46 and G90 of hTREM2.~~

~~21. 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, D39, K42, R46 and G90 of hTREM2.~~

~~22. The antibody or antigen binding fragment thereof of any one of claims 7 to 16, wherein the antibody or antigen binding fragment thereof binds one or more residues selected from a group consisting of R47, H67, N68, L69, L75, R77 and D87 of hTREM2.~~

~~23. The antibody or antigen binding fragment thereof of any one of claims 7 to 16, wherein the antibody or antigen binding fragment thereof binds two or more residues selected from a group consisting of R47, H67, N68, L69, L75, R77 and D87 of hTREM2.~~

~~24. The antibody or antigen binding fragment thereof of any one of claims 7 to 16, wherein the antibody or antigen binding fragment thereof binds three or more residues selected from a group consisting of R47, H67, N68, L69, L75, R77 and D87 of hTREM2.~~

~~25. The antibody or antigen binding fragment thereof of any one of claims 7 to 16, wherein the antibody or antigen binding fragment thereof binds four or more residues selected from a group consisting of R47, H67, N68, L69, L75, R77 and D87 of hTREM2.~~

~~26. The antibody or antigen binding fragment thereof of any one of claims 7 to 16, wherein the antibody or antigen binding fragment thereof binds five or more residues selected from a group consisting of R47, H67, N68, L69, L75, R77 and D87 of hTREM2.~~

~~27. The antibody or antigen binding fragment thereof of any one of claims 7 to 15, wherein the antibody or antigen binding fragment thereof binds six or more residues selected from a group consisting of R47, H67, N68, L69, L75, R77 and D87 of hTREM2.~~

~~28. 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.~~

~~29. The antibody or antigen binding fragment thereof of any one of claims 1 to 28, wherein the antibody or antigen binding fragment thereof activates hTREM2.~~

~~30. The antibody or antigen binding fragment thereof of any one of claims 1 to 29, wherein the antibody or antigen binding fragment thereof facilitates one or more hTREM2-dependent physiological activities in a TREM2-expressing cell.~~

~~31. The antibody or antigen binding fragment thereof of any one of claims 1 to 30, wherein the antibody or antigen binding fragment thereof:~~

- ~~a) increases phagocytosis, e.g., in a hTREM2-expressing cell, e.g., wherein the TREM2-expressing cell is a hM2A macrophage or a human iPS-derived microglia-like cell.~~
- ~~b) increases chemotaxis, e.g., in a hTREM2-expressing cell, e.g., 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, e.g., in a hTREM2-expressing cell, e.g., wherein the TREM2-expressing cell is a hM2A macrophage, or~~
- ~~e) increases any combination of two or more of a) to d).~~

~~32. The antibody or antigen binding fragment thereof of any one of claims 1 to 31, wherein the antibody or antigen binding fragment thereof binds hTREM2 e.g., on a cell surface, with a half maximal effective concentration (EC_{50}) of 1 nM or less, e.g., as measured by FACS analysis on hM2a macrophages.~~

~~33. The antibody or antigen binding fragment thereof of any one of claims 1 to 32, wherein the antibody or antigen binding fragment thereof binds hTREM2, e.g., on a cell surface, with a half maximal effective concentration (EC_{50}) of 0.59 nM or less, e.g., as measured by FACS analysis on hM2a macrophages.~~

~~34. The antibody or antigen binding fragment thereof of any one of claims 1 to 33, wherein the antibody or antigen binding fragment thereof binds hTREM2 with a dissociation constant (K_D) of 150 pM or less, e.g., as measured by surface plasmon resonance (SPR).~~

35. — ~~The antibody or antigen binding fragment thereof of any one of claims 1 to 34, wherein the antibody or antigen binding fragment thereof binds hTREM2 with a dissociation constant (K_D) of 50 pM or less, e.g., as measured by surface plasmon resonance (SPR).~~

36. — ~~The antibody or antigen binding fragment thereof of any one of claims 1 to 35, wherein the antibody or antigen binding fragment thereof stabilizes hTREM2 protein on a cell surface of a hTREM2-expressing cell.~~

37. — ~~The antibody or antigen binding fragment thereof of claim 36, wherein the hTREM2-expressing cell is a macrophage, e.g., 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.~~

38. — ~~The antibody or antigen binding fragment thereof of any one of claims 1 to 37, 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.~~

39. — ~~The antibody or antigen binding fragment thereof of any one of claims 1 to 38, wherein TREM2 cell surface expression is increased 3 fold or higher.~~

40. — ~~The antibody or antigen binding fragment thereof of any one of claims 1 to 39, wherein the IgSF domain of hTREM2 comprises amino acid residues 19 to 132 of any one of SEQ ID NOs 1, 2, and 3.~~

41. — ~~The antibody or antigen binding fragment thereof of any one of claims 1 to 40, wherein said antibody or antigen binding fragment thereof comprises:~~

— ~~a) a heavy chain variable region CDR1 comprising, e.g., consisting of, 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, e.g., consisting of, SEQ ID NO: 42 or SEQ ID NO: 46, or SEQ ID NO:~~

~~48; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 43 or SEQ ID NO: 49; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 54 or SEQ ID NO: 57 or SEQ ID NO: 60; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 55 or SEQ ID NO: 58; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 56 or SEQ ID NOs: 59;~~

~~—— b) a heavy chain variable region CDR1 comprising, e.g., consisting of, 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, e.g., consisting of, SEQ ID NO: 5 or SEQ ID NO: 9 or SEQ ID NO: 11; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6 or SEQ ID NO: 12; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 17 or SEQ ID NO: 20 or SEQ ID NO: 23; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 18 or SEQ ID NO: 21; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 19 or SEQ ID NO: 22;~~

~~e) a heavy chain variable region CDR1 comprising, e.g., consisting of, 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, e.g., consisting of, SEQ ID NO: 5 or SEQ ID NO: 9 or SEQ ID NO: 11; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6 or SEQ ID NO: 12; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 17 or SEQ ID NO: 20 or SEQ ID NO: 23; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 18 or SEQ ID NO: 21; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 78 or SEQ ID NO: 79;~~
~~or~~

~~d) a heavy chain variable region CDR1 comprising, e.g., consisting of, 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, e.g., consisting of, SEQ ID NO: 85 or SEQ ID NO: 89 or SEQ ID NO: 91; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 86 or SEQ ID NO: 92; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 97 or SEQ ID NO: 100 or SEQ ID NO: 103; a light chain variable region~~

CDR2 comprising, e.g., consisting of, SEQ ID NO: 98 or SEQ ID NO: 101; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 99 or SEQ ID NO: 102.

42. — 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, e.g., consisting of, 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, e.g., consisting of, SEQ ID NO: 42 or SEQ ID NO: 46, or SEQ ID NO: 48; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 43 or SEQ ID NO: 49; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 54 or SEQ ID NO: 57 or SEQ ID NO: 60; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 55 or SEQ ID NO: 58; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 56 or SEQ ID NOs: 59;

b) a heavy chain variable region CDR1 comprising, e.g., consisting of, 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, e.g., consisting of, SEQ ID NO: 5 or SEQ ID NO: 9 or SEQ ID NO: 11; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6 or SEQ ID NO: 12; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 17 or SEQ ID NO: 20 or SEQ ID NO: 23; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 18 or SEQ ID NO: 21; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 19 or SEQ ID NO: 22;

c) a heavy chain variable region CDR1 comprising, e.g., consisting of, 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, e.g., consisting of, SEQ ID NO: 5 or SEQ ID NO: 9 or SEQ ID NO: 11; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6 or SEQ ID NO: 12; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 17 or SEQ ID NO: 20 or SEQ ID NO: 23; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 18 or SEQ ID NO: 21; and a light chain

~~variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 78 or SEQ ID NO: 79;
or~~

~~d) a heavy chain variable region CDR1 comprising, e.g., consisting of, 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, e.g., consisting of, SEQ ID NO: 85 or SEQ ID NO: 89 or SEQ ID NO:
91; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 86
or SEQ ID NO: 92; a light chain variable region CDR1 comprising, e.g., consisting of,
SEQ ID NO: 97 or SEQ ID NO: 100 or SEQ ID NO: 103; a light chain variable region
CDR2 comprising, e.g., consisting of, SEQ ID NO: 98 or SEQ ID NO: 101; and a light
chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 99 or SEQ ID
NO: 102.~~

~~43.—The antibody or antigen-binding fragment thereof of any one of claims 1 to 42
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.~~

~~44.—The antibody or antigen-binding fragment thereof of any one of claims 1 to 43
comprising:~~

~~—— a) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO:
7; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 5; a
heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6; a light
chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 17; a light chain
variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 18; and a light chain
variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 19;~~

~~—— b) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 44; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 42; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 43; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 54; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 55; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 56;~~

~~—— c) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 7; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 5; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 17; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 18; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 78; or~~

~~—— d) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 87; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 85; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 86; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 97; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 98; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 99.~~

45. ~~The antibody or antigen binding fragment thereof of any one of claims 1 to 43 comprising:~~

~~—— a) a heavy chain variable region CDR1 of SEQ ID NO: 8; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 9; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 20; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 21; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 22;~~

~~—— b) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 45; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 46; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 43; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 57; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 58; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 59;~~

~~—— c) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 8; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 9; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 20; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 21; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 79; or~~

~~—— d) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 88; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 89; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 86; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 100; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 101; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 102.~~

~~46. — The antibody or antigen binding fragment thereof of any one of claims 1 to 43 comprising:~~

~~—— a) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 10; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 11; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 12; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 23; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 21; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 19;~~

~~—— b) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 47; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 48; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 49; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 60; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 58; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 56;~~

~~—— c) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 10; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 11; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 12; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 23; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 21; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 78; or~~

~~—— d) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 90; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 91; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 92; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 103; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 101; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 99.~~

~~47. The antibody or antigen binding fragment thereof of any one of claims 1 to 43 comprising:~~

~~—— a) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 4; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 5; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 17; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 18; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 19;~~

~~—— b) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 41; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 42; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 43; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 54; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 55; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 56;~~

~~—— c) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 4; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 5; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 6; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 17; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 18; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 78; or~~

~~—— d) a heavy chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 84; a heavy chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 85; a heavy chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 86; a light chain variable region CDR1 comprising, e.g., consisting of, SEQ ID NO: 97; a light chain variable region CDR2 comprising, e.g., consisting of, SEQ ID NO: 98; and a light chain variable region CDR3 comprising, e.g., consisting of, SEQ ID NO: 99.~~

48. ~~The antibody or antigen binding fragment thereof of any one of claims 1-47, wherein the antibody or antigen binding fragment thereof comprises:~~

~~—— a) —— a VH comprising, e.g., consisting of, SEQ ID NO: 13 and a VL comprising, e.g., consisting of, SEQ ID NO: 24; or~~

~~—— b) —— a VH comprising, e.g., consisting of, SEQ ID NO: 50 and a VL comprising, e.g., consisting of, SEQ ID NO: 61; or~~

~~—— c) —— a VH comprising, e.g., consisting of, a sequence having at least 95% homology to SEQ ID NO: 13 and a VL comprising, e.g., consisting of, a sequence having at least 95% homology to SEQ ID NO: 24; or~~

~~—— d) —— a VH comprising, e.g., consisting of, a sequence having at least 95% homology to SEQ ID NO: 50 and a VL comprising, e.g., consisting of, a sequence having at least 95% homology to SEQ ID NO: 61; or~~

~~—— e) —— a VH comprising, e.g. consisting of, a sequence that differs by at least 1, 2, 3, 4, 5, or 6 amino acids from SEQ ID NO: 13 and a VL comprising, e.g. consisting of, a sequence that differs by at least 1, 2, 3, 4, 5, or 6 amino acids from SEQ ID NO: 24; or~~

~~—— f) —— a VH comprising, e.g. consisting of, a sequence that differs by at least 1, 2, 3, 4, 5, or 6 amino acids from SEQ ID NO: 50 and a VL comprising, e.g. consisting of, a sequence that differs by at least 1, 2, 3, 4, 5, or 6 amino acids from SEQ ID NO: 61.~~

~~—— g) —— a VH comprising, e.g., consisting of, SEQ ID NO: 13 and a VL comprising, e.g., consisting of, SEQ ID NO: 80; or~~

~~—— h) —— a VH comprising, e.g., consisting of, SEQ ID NO: 93 and a VL comprising, e.g., consisting of, SEQ ID NO: 104; or~~

~~—— i) —— a VH comprising, e.g., consisting of, a sequence having at least 95% homology to SEQ ID NO: 13 and a VL comprising, e.g., consisting of, a sequence having at least 95% homology to SEQ ID NO: 80; or~~

~~—— j) —— a VH comprising, e.g., consisting of, a sequence having at least 95% homology to SEQ ID NO: 93 and a VL comprising, e.g., consisting of, a sequence having at least 95% homology to SEQ ID NO: 104; or~~

~~—— k) —— a VH comprising, e.g. consisting of, a sequence that differs by at least 1, 2, 3, 4, 5, or 6 amino acids from SEQ ID NO: 13 and a VL comprising, e.g. consisting of, a sequence that differs by at least 1, 2, 3, 4, 5, or 6 amino acids from SEQ ID NO: 80; or~~

~~l) —— a VH comprising, e.g. consisting of, a sequence that differs by at least 1, 2, 3, 4, 5, or 6 amino acids from SEQ ID NO: 93 and a VL comprising, e.g. consisting of, a sequence that differs by at least 1, 2, 3, 4, 5, or 6 amino acids from SEQ ID NO: 104.~~

~~49. —— The antibody or antigen-binding fragment thereof of any one of claims 1-48, wherein the antibody or antigen-binding fragment thereof comprises:~~

~~—— a) a heavy chain amino acid sequence comprising, e.g., consisting of, SEQ ID NO: 15, SEQ ID NO: 29, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, or SEQ ID NO: 39, and a light chain amino acid sequence comprising, e.g., consisting of, SEQ ID NO: 26;~~

- b) a heavy chain amino acid sequence comprising, e.g., consisting of, SEQ ID NO: 52, SEQ ID NO: 66, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, or SEQ ID NO: 76, and a light chain amino acid sequence comprising, e.g., consisting of, SEQ ID NO: 63;
- c) a heavy chain amino acid sequence having at least 95% sequence identity to SEQ ID NO: 15, SEQ ID NO: 29, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, or SEQ ID NO: 39, and a light chain amino acid sequence having at least 95% sequence identity to SEQ ID NO: 26;
- d) a heavy chain amino acid sequence having at least 95% sequence identity to SEQ ID NO: 52, SEQ ID NO: 66, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, or SEQ ID NO: 76, and a light chain amino acid sequence having at least 95% sequence identity to SEQ ID NO: 63;
- e) a heavy chain amino acid sequence comprising, e.g., consisting of, SEQ ID NO: 15, and a light chain amino acid sequence comprising, e.g., consisting of, SEQ ID NO: 82;
- f) a heavy chain amino acid sequence comprising, e.g., consisting of, SEQ ID NO: 95, and a light chain amino acid sequence comprising, e.g., consisting of, SEQ ID NO: 106;
- g) a heavy chain amino acid sequence having at least 95% sequence identity to SEQ ID NO: 15, and a light chain amino acid sequence having at least 95% sequence identity to SEQ ID NO: 82; or
- h) a heavy chain amino acid sequence having at least 95% sequence identity to SEQ ID NO: 95, and a light chain amino acid sequence having at least 95% sequence identity to SEQ ID NO: 106.

50. — 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, e.g., consisting of, SEQ ID NO: 15 and a light chain sequence comprising, e.g., consisting of, SEQ ID NO: 26;
- b) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 29 and a light chain sequence comprising, e.g., consisting of, SEQ ID NO: 26;

- ~~—— c) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 33 and a light chain sequence comprising, e.g., consisting of, SEQ ID NO: 26;~~
- ~~—— d) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 35 and a light chain sequence comprising, e.g., consisting of, SEQ ID NO: 26;~~
- ~~—— e) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 37 and a light chain sequence comprising, e.g., consisting of, SEQ ID NO: 26;~~
- ~~—— f) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 39 and a light chain sequence comprising, e.g., consisting of, SEQ ID NO: 26;~~
- ~~—— g) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 52 and a light chain sequence comprising, e.g., consisting of, SEQ ID NO: 63;~~
- ~~—— h) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 66 and light chain sequence comprising, e.g., consisting of, SEQ ID NO: 63;~~
- ~~—— i) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 70 and light chain sequence comprising, e.g., consisting of, SEQ ID NO: 63;~~
- ~~—— j) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 72 and light chain sequence comprising, e.g., consisting of, SEQ ID NO: 63;~~
- ~~—— k) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 74 and light chain sequence comprising, e.g., consisting of, SEQ ID NO: 63;~~
- ~~—— l) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 76 and light chain sequence comprising, e.g., consisting of, SEQ ID NO: 63;~~
- ~~—— m) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 15 and light chain sequence comprising, e.g., consisting of, SEQ ID NO: 82; or~~
- ~~—— n) a heavy chain sequence comprising, e.g., consisting of, SEQ ID NO: 95 and light chain sequence comprising, e.g., consisting of, SEQ ID NO: 106.~~

51. ~~An antibody or an antigen-binding fragment thereof that competes with any antibody or antigen-binding fragment thereof of any one of claims 1-50 for binding to hTREM2 protein.~~

~~52. — An antibody or an antigen binding fragment thereof that binds to an epitope that overlaps with the epitope of any antibody or antigen binding fragment thereof of any one of claims 1-51.~~

~~53. — The antibody or antigen binding fragment thereof of any one of claims 1-52, wherein the antibody has an IgG1, IgG2, IgG3 or IgG4 isotype.~~

~~54. — The antibody or antigen binding fragment thereof of any one of claims 1-52, wherein the antibody or antigen binding fragment thereof comprises an Fc region selected from an IgG1 Fc region, an IgG2 Fc region, an IgG4 Fc region, or an IgG2/IgG4 hybrid Fc region.~~

~~55. — The antibody or antigen binding fragment thereof of any one of claims 1-49, or 51-54, wherein the antibody or antigen binding fragment thereof comprises a modified Fc region that has reduced antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity compared to the parental antibody.~~

~~56. — The antibody or antigen binding fragment thereof of any one of claims 1-55, wherein the antibody or antigen binding fragment thereof is a human or humanized antibody or fragment thereof.~~

~~57. — The antibody or antigen binding fragment thereof of any one of claims 1-56, wherein the antibody or antigen binding fragment thereof is conjugated to a further moiety.~~

~~58. — The antibody according to any one of claims 1-57, wherein said antibody is of the IgG1 isotype.~~

~~59. — The antibody according to any one of claims 1-56, wherein said antibody is a human or humanized antibody.~~

~~60. The antigen binding fragment of the antibody according to any one of claims 1-57, wherein the antigen binding fragment is selected from a Fab, F(ab')₂, Fv fragments, scFv, minibody, or diabody.~~

~~61. The antibody or antigen binding fragment thereof of any of claims 1-60, wherein said antibody or antigen binding fragment thereof is monoclonal.~~

~~62. The antibody of any one of claims 1-61, wherein the antibody is a multispecific antibody, e.g., a bispecific antibody.~~

~~63. The antibody of claim 62, wherein the multispecific antibody, e.g., the bispecific antibody, specifically binds to hTREM2 and human DAP12 (DNAX activating protein of 12 kDa).~~

~~64. The antibody according to any one of claims 1-63, wherein said antibody has altered effector function through mutation of the Fc region.~~

~~65. A nucleic acid molecule or set of nucleic acid molecules encoding any one of the antibodies or antigen binding fragment thereof according to any one of claims 1 to 64.~~

~~66. The nucleic acid molecule according to claim 65, wherein the nucleic acid is DNA.~~

~~67. The nucleic acid molecule or set of nucleic acid molecules according to claim 65 or 66, comprising one or more of SEQ ID NOs: 14, 28, 51, 65, 16, 30, 34, 36, 38, 40, 53, 67, 71, 73, 75, 77, 25, 31, 62, 68, 27, 32, 64, 69, 13, 93, 15, 95, 80, 104, 82 or 106.~~

~~68. A vector comprising the nucleic acid molecules according to any one of claims 65-67.~~

~~69. The vector of claim 68, wherein the vector is a cloning vector or an expression vector.~~

~~70. — A vector according to claim 68 or 69, wherein said vector comprises one or more of SEQ ID NOs: 14, 28, 51, 65, 16, 30, 34, 36, 38, 40, 53, 67, 71, 73, 75, 77, 25, 31, 62, 68, 27, 32, 64, 69, 13, 93, 15, 95, 80, 104, 82 or 106, or a fragment thereof encoding at least one CDR region.~~

~~71. — A vector according to any one of claims 68-70, wherein the vector is able to replicate in a prokaryotic and/or a eukaryotic cell.~~

~~72. — A vector according to any one of claims 68-71, wherein the vector is selected from a DNA vector, a RNA vector, a plasmid, a cosmid, or a viral vector.~~

~~73. — A vector according to any one of claims 68-72 further comprising a detectable and/or selectable marker.~~

~~74. — A set of two expression vectors according to any one of claims 68-73, one vector encoding a) at least one VH domain comprising SEQ ID NO: 13 or 50, and the other vector encoding at least one VL domain comprising SEQ ID NO: 24 or 61; or
 — b) at least one VH domain comprising SEQ ID NO: 13 or 93, and the other vector encoding at least one VL domain comprising SEQ ID NO: 80 or 104.~~

~~75. — A vector according to any one of claims 68-74, wherein the vector is a viral vector, optionally wherein the viral vectors is a lentivirus, an adenovirus, an adeno-associated virus (AAV), a Herpes Simplex Virus (HSV), a parvovirus, a retrovirus, a vaccinia virus, a Sinbis virus, an influenza virus, a reovirus, a Newcastle disease virus (NDV), a measles virus, a vesicular stomatitis virus (VSV), a poliovirus, a poxvirus, a Seneca Valley virus, a coxsackievirus, an enterovirus, a myxoma virus, or a maraba virus.~~

~~76. — A vector according to claim 75, wherein the vector is an AAV vector.~~

~~77. A vector according to any one of claims 68-76, wherein the vector further comprises a promoter.~~

~~78. A vector according to any one of claims 68-77, wherein the vector comprises an AAV9 capsid and an AAV vector plasmid comprising (1) ITRs derived from AAV2, (2) A CMV enhancer (e.g., comprising SEQ ID NO: 134), (3) a CBA promoter (e.g., comprising SEQ ID NO: 135), (4) an SV40 intron (e.g., comprising SEQ ID NO: 137), (5) a polynucleotide encoding a hTREM2 antibody or antigen-binding fragment thereof (e.g., as described herein), and (6) a BGH poly A signal (e.g., comprising SEQ ID NO: 138).~~

~~79. The vector of claim 78, wherein elements (2) to (6) are disposed on the AAV vector plasmid from 5' to 3'.~~

~~80. The vector of claim 78 or 79, wherein any of the elements (2) to (6) are disposed on the AAV vector plasmid between the 5' ITR and the 3' ITR.~~

~~81. The vector of any one claims 78-80, wherein the AAV vector is a scAAV vector.~~

~~82. A vector according to any one of claims 68-75, wherein the vector is a lentiviral vector.~~

~~83. A cell comprising the nucleic acid molecule or set of nucleic acid molecules according to any one of claims 64-66 or the vector of any one of claims 68-82.~~

~~84. A method of producing a hTREM2 antibody or antigen-binding fragment thereof, the method comprising: (i) culturing the cell of claim 83 and (ii) isolating the hTREM2 antibody or antigen-binding fragment thereof from the culture.~~

~~85. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-64, the nucleic acid molecule or set of nucleic acid~~

molecules of any one of claims 65-67, the vector of any one of claims 68-82, or the cell of claim 83, and a pharmaceutically acceptable carrier.

86.—The antibody or antigen binding fragment thereof of any one of claims 1-64, the nucleic acid molecule or set of nucleic acid molecules of any one of claims 65-67, the vector of any one of claims 68-82, the cell of claim 83, or the pharmaceutical composition of claim 85, for use as a medicament.

87.—The antibody or antigen binding fragment thereof of any one of claims 1-64, the nucleic acid molecule or set of nucleic acid molecules of any one of claims 65-67, the vector of any one of claims 68-82, the cell of claim 83, or the pharmaceutical composition of claim 85, for use in the treatment of a disease associated with hTREM2 loss of function.

88.—Use of the antibody or antigen binding fragment thereof of any one of claims 1-64, the nucleic acid molecule or set of nucleic acid molecules of any one of claims 65-67, the vector of any one of claims 68-82, the cell of claim 83, or the pharmaceutical composition of claim 85, for the manufacture of a medicament for treatment of a disease associated with hTREM2 loss of function.

89.—The antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition of claim 87, or the use according to claim 88, wherein the disease 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), postherpetic neuralgia, chronic inflammatory demyelinating polyneuropathy (CIDP), epilepsy, Guillain-Barré Syndrom (GBS), inclusion body myositis, lysosomal storage diseases, sphingomyelinlipidose (Niemann-Pick C), mucopolysaccharidose II/ HIB, metachromatic leukodystrophy, multifocal motor neuropathy, Myasthenia Gravis, Neuro-Beheet'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.~~

90.—~~The antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition of claim 87, or the use according to claim 88, wherein the disease is Alzheimer's disease.~~

91.—~~The antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition of claim 87, or the use according to claim 88, wherein the disease is Parkinson's disease.~~

92.—~~The antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition of claim 87, or the use according to claim 88, wherein the disease is multiple sclerosis.~~

93.—~~The antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition of claim 87, or the use according to claim 88, wherein the disease is frontotemporal dementia.~~

94.—~~The antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition of claim 87, or the use according to claim 88, wherein the antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition is administered to the subject through an oral, intravenous, intracranial, intrathecal, subcutaneous, or intranasal route.~~

95.—~~The antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition of claim 87, or the use according to claim 88, wherein the antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or~~

the pharmaceutical composition is administered to the subject in combination with at least one additional therapeutic agent or procedure.

96. — ~~The antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition of claim 87, or the use according to claim 88, wherein the antibody or antigen binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition is administered to the subject in combination with at least one additional therapeutic agent, wherein said agent comprises one or more of BACE inhibitors, anti Tau antibodies, Tau antisense oligonucleotides, anti amyloid beta antibodies, fingolimod, BG12 or dimethyl fumarate, interferon beta or tysabri.~~

97. — ~~A method of treating a disease associated with hTREM2 loss of function in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the antibody or antigen binding fragment thereof of any one of claims 1-64, the nucleic acid molecule or set of nucleic acid molecules of any one of claims 65-67, the vector of any one of claims 68-82, the cell of claim 83, or the pharmaceutical composition of claim 85.~~

98. — ~~The method of claim 97, wherein the method comprises:~~

- ~~—— a) assaying the cell surface hTREM2 level in a sample obtained from a subject;~~
- ~~—— b) selecting a subject whose cell surface hTREM2 level is lower than a reference level, wherein the reference level is the cell surface hTREM2 level in a sample obtained from a healthy subject; and~~
- ~~—— c) administering to the selected subject a therapeutically effective amount of the antibody or antigen binding fragment thereof of any one of claims 1 to 64, the nucleic acid molecule or set of nucleic acid molecules of any one of claims 65-67, the vector of any one of claims 68-82, the cell of claim 83, or the pharmaceutical composition of claim 85.~~

99. — ~~The method of claim 98, wherein the sample comprises cerebrospinal fluid.~~

100. ~~The method of claim 98 or 99, wherein the cell surface TREM2 level in said sample is determined by an assay selected from flow cytometry, immunohistochemistry, Western blotting, immunofluorescent assay, radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), homogeneous time-resolved fluorescence (HTRF), or positron emission tomography (PET).~~

101. ~~The method of any one of claims 97-100, 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), postherpetic neuralgia, chronic inflammatory demyelinating polyneuropathy (CIDP), epilepsy, Guillain-Barré Syndrom (GBS), inclusion body myositis, lysosomal storage diseases, sphingomyelinlipidose (Niemann-Pick C), mucopolysaccharidose II/III B, 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.~~

102. ~~The method of any one of claims 97-101, wherein the disease is Alzheimer's disease.~~

103. ~~The method of any one of claims 97-101, wherein the disease is Parkinson's disease.~~

104. ~~The method of any one of claims 97-101, wherein the disease is multiple sclerosis.~~

105. ~~The method of any one of claims 97-101, wherein the disease is frontotemporal dementia.~~

106.— ~~The method of any one of claims 97-105, wherein said antibody or antigen-binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition is administered to the subject through an oral, intravenous, intracranial, intrathecal, subcutaneous, or intranasal route.~~

107.— ~~A method of stabilizing hTREM2 protein in a subject, the method comprising administering to the subject the antibody or antigen-binding fragment thereof of any one of claims 1-64, the nucleic acid molecule or set of nucleic acid molecules of any one of claims 65-67, the vector of any one of claims 68-82, the cell of claim 83, or the pharmaceutical composition of claim 85, in an amount effective to stabilize hTREM2.~~

108.— ~~The method of any one of claims 97-107, the method further comprising administering at least one additional therapeutic agent to the subject or performing at least one additional therapeutic procedure.~~

109.— ~~The method of claim 108, wherein said additional therapeutic agent comprises one or more of BACE inhibitors, anti-Tau antibodies, Tau antisense oligonucleotides, anti-amyloid beta antibodies, fingolimod, BG12 or dimethyl fumarate, interferon beta or tysabri.~~

110.— ~~The method of claim 108 or 109, wherein the antibody or antigen-binding fragment thereof of any one of claims 1-64, the nucleic acid molecule or set of nucleic acid molecules of any one of claims 65-67, the vector of any one of claims 68-82, the cell of claim 83, or the pharmaceutical composition of claim 85 is administered concurrently with, prior to, or subsequent to, the additional therapeutic agent.~~

111.— ~~The method of any one of claims 97-110, wherein administering the antibody or antigen-binding fragment thereof, the nucleic acid molecule or set of nucleic acid molecules, the vector, the cell, or the pharmaceutical composition has one or more of the following effects a-d:~~

— a) Increasing TREM2-dependent cellular activities like phagocytosis and chemotaxis;

- ~~b) Triggering TREM2 dependent gene transcription,~~
- ~~c) Increasing TREM2 dependent intracellular signaling pathways via Syk phosphorylation,~~
- ~~d) Increasing clearance of cellular debris.~~

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 (EC₅₀) 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 (EC₅₀) 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), posttherapeutic 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.