

What is claimed:

1. An isolated antibody which specifically binds to a triggering receptor expressed on myeloid cells-1 (TREM-1), comprising a heavy chain variable region (VH), a light chain variable region (VL), and an IgG1 heavy chain constant region, wherein the IgG1 heavy chain constant region comprises one or more amino acid substitutions compared to a wild-type IgG1 heavy chain constant region (SEQ ID NO: 9).

2. An isolated antibody which cross-competes with mAb 0318 for binding to blocking TREM-1, comprising a heavy chain variable region (VH), a light chain variable region (VL), and an IgG1 heavy chain constant region, wherein the IgG1 heavy chain constant region comprises one or more amino acid substitutions compared to a wild-type IgG1 heavy chain constant region (SEQ ID NO: 9).

3. The antibody of claim 1 or 2, wherein the antibody binds to the same TREM-1 epitope as mAb 0318.

4. The antibody of claim 1 or 2, wherein the antibody specifically binds to a TREM-1 epitope comprising one or more amino acid residues selected from the group consisting of the D38, V39, K40, C41, D42, Y43, T44, L45, E46, K47, F48, A49, S50, S51, Q52, K53, A54, W55, Q56, Y90, H91, D92, H93, G94, L95, and L96 of SEQ ID NO: 1.

5. The antibody of claim 1 or 2, wherein the antibody specifically binds to a TREM-1 epitope comprising amino acids D38 to L45, E46 to Q56, and/or Y90 to L96 of SEQ ID NO: 1.

6. The antibody of any one of claims 1 to 5, wherein the IgG1 heavy chain constant region comprises one or more amino acid substitutions selected from the group consisting of K214R, L234A, L235E, G237A, D356E, and L358M, per EU numbering.

7. The antibody of any one of claims 1 to 5, wherein the IgG1 heavy chain constant region comprises one or more amino acid substitutions selected from the group consisting of K214R, L234A, L235E, G237A, A330S, P331S, D356E, and L358M, per EU numbering.

8. The antibody of any one of claims 1 to 5, wherein the IgG1 heavy chain constant region comprises one or more amino acid substitutions selected from the group consisting of K214R, C226S, C229S, and P238S, per EU numbering.

9. The isolated antibody of any one of claims 1 to 5, wherein the IgG1 heavy chain constant region comprises one or more amino acid substitutions selected from the group consisting of S131C, K133R, G137E, G138S, Q196K, I199T, N203D, K214R, C226S, C229S, and P238S, per EU numbering.

10. The antibody of any one of claims 1 to 9, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR3 comprises DMGIRRQFAY (SEQ ID NO: 26) or DMGIRRQFAY (SEQ ID NO: 26) except one or two substitutions.

11. The antibody of claim 10, wherein the heavy chain CDR3 comprises DQGIRRQFAY (SEQ ID NO: 72).

12. The antibody of any one of claims 1 to 11, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR2 comprises RIRTKSSNYATYYAASVKG (SEQ ID NO: 25) or RIRTKSSNYATYYAASVKG (SEQ ID NO: 25) except one or two substitutions.

13. The antibody of any one of claims 1 to 12, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1 comprises TYAMH (SEQ ID NO: 24) or TYAMH (SEQ ID NO: 24) except one or two substitutions.

14. The antibody of any one of claims 1 to 13, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the light chain CDR1 comprises RASQSVDTFDYSFLH (SEQ ID NO: 27) or RASQSVDTFDYSFLH (SEQ ID NO: 27) except one or two substitutions.

15. The antibody of any one of claims 1 to 14, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the light chain CDR2 comprises RASNLES (SEQ ID NO: 28) or RASNLES (SEQ ID NO: 28) except one or two substitutions.

16. The antibody of any one of claims 1 to 15, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the light chain CDR3 comprises QQSNQDPYT (SEQ ID NO: 29) or QQSNQDPYT (SEQ ID NO: 29) except one or two substitutions.

17. The antibody of any one of claims 1 to 16, wherein the VH comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as SEQ ID NO: 14.

18. The antibody of any one of claims 1 to 17, wherein the VL comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as SEQ ID NO: 15.

19. The antibody of any one of claims 1 to 18, comprising a heavy chain variable region and a light chain variable region, wherein the VH comprises SEQ ID NO: 14 and the VL comprises SEQ ID NO: 15.

20. The antibody of claim 19, comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, or SEQ ID NO: 53.

21. The antibody of claim 20, comprising a heavy chain and a light chain, wherein the light chain comprises SEQ ID NO: 54.

22. An isolated antibody which specifically binds to TREM-1, comprising a heavy chain CDR1, CDR2, CDR3; a light chain CDR1, CDR2, CDR3; and an IgG1 heavy chain constant region,

wherein the heavy chain CDR1, CDR2, and CDR3 comprises TYAMH (SEQ ID NO: 24), RIRTKSSNYATYYAASVKG (SEQ ID NO: 25), and DMGIRRQFAY (SEQ ID NO: 26), respectively;

wherein the light chain CDR1, CDR2, and CDR3 comprises RASQSVDTFDYSFLH (SEQ ID NO: 27), RASNLES (SEQ ID NO: 28), and QQSNQDPYT (SEQ ID NO: 29), respectively; and

wherein the IgG1 heavy chain constant region comprises one or more amino acid substitutions selected from the group consisting of L234A, L235E, and G237A, per EU numbering.

23. An isolated antibody which specifically binds to TREM-1, comprising a heavy chain CDR1, CDR2, CDR3; a light chain CDR1, CDR2, CDR3; and an IgG1 heavy chain constant region,

wherein the heavy chain CDR1, CDR2, and CDR3 comprises TYAMH (SEQ ID NO: 24), RIRTKSSNYATYYAASVKG (SEQ ID NO: 25), and DMGIRRQFAY (SEQ ID NO: 26), respectively;

wherein the light chain CDR1, CDR2, and CDR3 comprises RASQSVDTFDYSFLH (SEQ ID NO: 27), RASNLES (SEQ ID NO: 28), and QQSNQDPYT (SEQ ID NO: 29), respectively; and

wherein the IgG1 heavy chain constant region comprises amino acid substitutions selected from the group consisting of L234A, L235E, G237A, A330S, and P331S, per EU numbering.

24. An isolated antibody which specifically binds to TREM-1, comprising a heavy chain CDR1, CDR2, CDR3; a light chain CDR1, CDR2, CDR3; and an IgG1 heavy chain constant region,

wherein the heavy chain CDR1, CDR2, and CDR3 comprises TYAMH (SEQ ID NO: 24), RIRTKSSNYATYYAASVKG (SEQ ID NO: 25), and DMGIRRQFAY (SEQ ID NO: 26), respectively;

wherein the light chain CDR1, CDR2, and CDR3 comprises RASQSVDTFDYSFLH (SEQ ID NO: 27), RASNLES (SEQ ID NO: 28), and QQSNQDPYT (SEQ ID NO: 29), respectively; and

wherein the IgG1 heavy chain constant region comprises one or more amino acid substitutions selected from the group consisting of K214R, C226S, C229S, and P238S, per EU numbering.

25. An isolated antibody which specifically binds to TREM-1, comprising a heavy chain CDR1, CDR2, CDR3; a light chain CDR1, CDR2, CDR3; and an IgG1 heavy chain constant region,

wherein the heavy chain CDR1, CDR2, and CDR3 comprises TYAMH (SEQ ID NO: 24), RIRTKSSNYATYYAASVKG (SEQ ID NO: 25), and DMGIRRQFAY (SEQ ID NO: 26), respectively;

wherein the light chain CDR1, CDR2, and CDR3 comprises RASQSVDTFDYSFLH (SEQ ID NO: 27), RASNLES (SEQ ID NO: 28), and QQSNQDPYT (SEQ ID NO: 29), respectively; and

wherein the IgG1 heavy chain constant region comprises one or more amino acid substitutions selected from the group consisting of S131C, K133R, G137E, G138S, Q196K, I199T, N203D, K214R, C226S, C229S, and P238S, per EU numbering.

26. The antibody of any one of claims 1 to 25, wherein TREM-1 comprises an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 7.

27. The antibody of any one of claims 1 to 26, which has a decreased binding affinity to Fc γ RI (CD64), Fc γ RIIA (CD32), Fc γ RIIB (CD32), Fc γ RIIIA (CD16a), Fc γ RIIIB (CD16b), or any combination thereof compared to an antibody comprising a heavy chain consisting of the amino acid sequence as set forth in SEQ ID NO: 76 and a light chain consisting of the amino acid sequence as set forth in SEQ ID NO: 54.

28. The antibody of any one of claims 1 to 26, which has a decreased binding affinity to Fc γ RI (CD64) by at least two fold, at least three fold, at least four fold, at least five fold, at least six fold, at least seven fold, at least eight fold, at least nine fold, or at least 10 fold compared to an antibody comprising a heavy chain consisting of the amino acid sequence as set forth in SEQ ID NO: 76 and a light chain consisting of the amino acid sequence as set forth in SEQ ID NO: 54.

29. The antibody of any one of claims 1 to 28, which is less immunogenic compared to an antibody comprising a heavy chain consisting of the amino acid sequence as set forth in SEQ ID NO: 76 and a light chain consisting of the amino acid sequence as set forth in SEQ ID NO: 54.

30. The antibody of any one of claims 1 to 29, which does not agonize TREM-1 signaling upon binding to TREM-1 and in the absence of a stimulator.

31. The antibody of any one of claims 1 to 30, which does not induce expression of an inflammatory cytokine in immature dendritic cells (iDCs) when the cells are incubated in the presence of the antibody and in the absence of a stimulator compared to an antibody comprising a heavy chain consisting of the amino acid sequence as set forth in SEQ ID NO: 76 and a light chain consisting of the amino acid sequence as set forth in SEQ ID NO: 54.

32. The antibody of any one of claims 1 to 31, which blocks the production of an inflammatory cytokine in a cell when the cells are activated in the presence of both the antibody and a stimulator.

33. The antibody of any one of claims 30 to 31, wherein the stimulator is a TREM-1 ligand.

34. The antibody of claim 31 or 32, wherein the inflammatory cytokine is selected from a group consisting of IL-6, TNF- α , IL-8, IL-1 β , IL-12, chitinase-3-like protein 1 (CHI3L1), and combinations thereof.

35. The antibody of any one of claims 1 to 34, which binds human FcRn, cynomolgus FcRn, and/or mouse FcRn in a pH dependent manner.

36. The antibody of any one of claims 1 to 35, which is more thermally stable compared to a reference antibody comprising a heavy chain consisting of the amino acid sequence as set forth in SEQ ID NO: 76 and a light chain consisting of the amino acid sequence as set forth in SEQ ID NO: 54, as measured by a Capillary Differential scanning calorimeter (CAP-DSC).

37. The antibody of any one of claims 1 to 36, wherein about 10% to 20%, about 20% to 30% (e.g., 24%), or about 30% to 40% of the antibody is reversible when it is heated to 77 °C.

38. The antibody of claim 36 or 37, which has a higher melting temperature (T_m) compared to an antibody comprising a heavy chain consisting of the amino acid sequence as set forth in SEQ ID NO: 76 and a light chain consisting of the amino acid sequence as set forth in SEQ ID NO: 54.

39. The antibody of any one of claims 1 to 38, which has a viscosity of less than 5 cP, less than 4 cP, less than 3 cP, less than 2.5 cP, less than 2.4 cP, less than 2.3 cP, less than 2.2 cP, less than 2.1 cP, less than 2 cP, less than 1.9 cP, less than 1.8 cP, less than 1.7 cP, less than 1.6 cP, less than 1.5 cP, less than 1.4 cP, less than 1.3 cP, less than 1.2 cP, less than 1.1 cP, less than 1.0 cP, less than 0.9 cP, less than 0.8 cP, less than 0.7 cP, less than 0.6 cP, less than 0.5 cP, less than 0.4 cP, less than 0.3 cP, less than 0.2 cP, or less than 0.1 cP at a concentration of 80 mg/mL.

40. The antibody of any one of claims 1 to 38, which has a viscosity of less than 10 cP (e.g., 9 cP) at a concentration of 130 mg/mL.

41. The antibody of any one of claims 1 to 40, which binds to human TREM-1 with a K_D of less than 4 nM (e.g., 3.4 nM) as measured by Biacore.

42. The antibody of any one of claims 1 to 41, which binds to cynomolgus TREM-1 with a K_D of less than 1 nM (e.g., 0.91 nM), as measured by Biacore.

43. The antibody of any one of claims 1 to 42, which is monomeric as observed by size-exclusion high-performance liquid chromatography (SE-HPLC).

44. The antibody of any one of claims 1 to 43, which exhibits minimal risk for fragmentation as observed by two-dimensional liquid chromatography-tandem mass spectrometry (2D-LC/MS) or intact mass analysis using liquid chromatography-tandem mass spectrometry (LC/MS).

45. The antibody of any one of claims 1 to 44, which has an isoelectric point of 8 to 9 (e.g., 8.75).

46. The antibody of any one of claims 1 to 45, which is stable in a formulation comprising histidine, sucrose, arginine, and NaCl.

47. The antibody of claim 46, which is stable for at least 2 months in a formulation comprising 20 mM histidine, 150 mM sucrose, 25 mM arginine, and 50 mM NaCl.

48. The antibody of claim 46 or 47, wherein the formulation is at a pH of 6.0 and/or wherein the formulation is stored at 4°C, 25°C, or 40°C.

49. A bispecific molecule comprising the antibody of any one of claims 1 to 48, linked to a molecule having a second binding specificity.

50. A nucleic acid encoding the antibody of any one of claims 1 to 48.

51. A vector comprising the nucleic acid of claim 50.
52. A cell comprising the vector of claim 51.
53. An immunoconjugate comprising the antibody of any one of claims 1 to 48, linked to an agent.
54. A composition comprising the antibody of any one of claims 1 to 48, the bispecific molecule of claim 49, the nucleic acid of claim 50, the vector of claim 51, the cell of claim 52, or the immunoconjugate of claim 53, and a carrier.
55. A kit comprising the antibody of any one of claims 1 to 48, the bispecific molecule of claim 49, the nucleic acid of claim 50, the vector of claim 51, the cell of claim 52, or the immunoconjugate of claim 53, and an instruction for use.
56. A method of inhibiting TREM-1 activity in a subject in need thereof, comprising administering the antibody of any one of claims 1 to 48, the bispecific molecule of claim 49, the nucleic acid of claim 50, the vector of claim 51, the cell of claim 52, or the immunoconjugate of claim 53 to the subject.
57. A method of treating an inflammatory disease or an autoimmune disease in a subject in need thereof, comprising administering the antibody of any one of claims 1 to 48, the bispecific molecule of claim 49, the nucleic acid of claim 50, the vector of claim 51, the cell of claim 52, or the immunoconjugate of claim 53 to the subject.
58. The method of claim 57, wherein the inflammatory disease or the autoimmune disease is selected from the group consisting of an inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), irritable bowel syndrome, rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, systemic lupus erythematosus (SLE), lupus nephritis, vasculitis, sepsis, systemic inflammatory response syndrome (SIRS), type I diabetes, Grave's disease, multiple sclerosis (MS), autoimmune myocarditis, Kawasaki disease, coronary artery disease, chronic obstructive pulmonary disease, interstitial lung disease, autoimmune thyroiditis, scleroderma, systemic sclerosis, osteoarthritis, atopic dermatitis, vitiligo, graft versus host disease, Sjogren's syndrome, autoimmune nephritis, Goodpasture's syndrome, chronic inflammatory demyelinating polyneuropathy, allergy, asthma, other autoimmune diseases that are a result of either acute or chronic inflammation, and any combinations thereof.
59. The method of any one of claims 56 to 58, further comprising administering one or more additional therapeutics.

60. The method of claim 59, wherein the additional therapeutics is an anti-IP-10 antibody or an anti-TNF- α antibody.