

Claims

1. An isolated antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising an amino acid sequence of SEQ ID NO:308; an HVR-H2 comprising an amino acid sequence of SEQ ID NO:309; and an HVR-H3 comprising an amino acid sequence of SEQ ID NO:310; and the light chain variable region comprises: an HVR-L1 comprising an amino acid sequence of SEQ ID NO:314; an HVR-L2 comprising an amino acid sequence of SEQ ID NO:315; and an HVR-L3 comprising an amino acid sequence of SEQ ID NO:316.

2. The antibody of claim 1, wherein the antibody comprises a heavy chain variable region, wherein the heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 304.

3. The antibody of claim 1, wherein the antibody comprises a light chain variable region, wherein the light chain variable region comprises an amino acid sequence of SEQ ID NO:305.

4. The antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence of SEQ ID NO:304, and the light chain variable region comprises an amino acid sequence of SEQ ID NO:305.

5. The antibody of claim 1, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 320-327 and the light chain comprises an amino acid sequence of SEQ ID NO:363.

6. The antibody of claim 5, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NOs: 324 or 325 and the light chain comprises an amino acid sequence of SEQ ID NO:363.

7. The antibody of claim 5, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 327 and the light chain comprises an amino acid sequence of SEQ ID NO:363.

8. The antibody of claim 5, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 323 and the light chain comprises an amino acid sequence of SEQ ID NO:363.

9. An isolated antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:94; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:96; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:102; and the light chain variable region comprises: an

HVR-L1 comprising the amino acid sequence of SEQ ID NO:104; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:105; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:107.

10. The antibody of claim 9, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:14, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:22.

11. The antibody of claim 9, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 355-362 and the light chain comprises an amino acid sequence of SEQ ID NO:365.

12. The antibody of claim 11, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 360 and the light chain comprises an amino acid sequence of SEQ ID NO:365.

13. The antibody of claim 11, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 362 and the light chain comprises an amino acid sequence of SEQ ID NO:365.

14. The antibody of claim 11, wherein the antibody comprises a heavy chain and a light chain wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 358 and the light chain comprises an amino acid sequence of SEQ ID NO:365.

15. An isolated antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising an amino acid sequence selected from the groups consisting of SEQ ID NOs:94, 108, 116, 146, 147, 308, and 311; an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:95, 96, 97, 98, 99, 110, 111, 117, 118, 119, 120, 121, 122, 149, 150, 151, 152, 153, 309, and 312; and an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:100, 101, 102, 112, 123, 124, 125, 126, 127, 128, 129, 154, 310, and 313; and the light chain variable region comprises: an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:104, 103, 113, 130, 131, 132, 133, 134, 135, 136, 137, 138, 156, 157, 158, 314, and 317; an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:105, 106, 114, 139, 140, 141, 142, 143, 159, 160, 161, 315, and 318; and an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:107, 115, 144, 145, 163, 316, and 319.

16. The antibody of claim 1, 9, or 15, wherein the antibody is humanized.

17. The antibody of any one of claims 1-16, wherein the antibody (a) decreases cell surface levels of MS4A4A or decreases intracellular levels of MS4A4A, (b) increases soluble

TREM2 levels, increases membrane TREM2 levels, or increases soluble TREM2 and increases membrane TREM2 levels in myeloid cells, and/or (c) reduces expression of M2 cell surface markers on myeloid cells.

18. The antibody of any one of claims 1-17, wherein the antibody increases mRNA and/or protein expression of gelsolin and/or osteopontin on myeloid cells.

19. The antibody of any one of claims 1-18, wherein the antibody is a monoclonal antibody.

20. The antibody of any one of claims 1-19, wherein the antibody further binds to cynomolgus monkey MS4A4A of SEQ ID NO:3.

21. The antibody of any one of claims 1-4, 9, 10, and 15-20, wherein the antibody is of the IgG class and has an IgG1, IgG2, or IgG4 isotype.

22. The antibody of claim 21, wherein the antibody has an IgG 1 isotype and comprises a modified Fc comprising the N325S and L328F mutations according to EU numbering.

23. The antibody of any one of claims 1-4, 9, 10, and 15-22, wherein the antibody is an antibody fragment.

24. The antibody of claim 23, wherein the antibody fragment is a Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment.

25. The antibody of any one of claims 1-24, wherein the antibody is a bispecific antibody recognizing a first antigen and a second antigen.

26. The antibody of claim 25, wherein the first antigen is MS4A4A and the second antigen is an antigen facilitating transport across the blood-brain-barrier.

27. The antibody of claim 25, wherein the first antigen is MS4A4A, and the second antigen is

(a) an antigen facilitating transport across the blood-brain-barrier selected from the group consisting of transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopeptide, and ANG1005;

(b) a disease-causing agent selected from the group consisting of disease-causing peptides or proteins or, disease-causing nucleic acids, wherein the disease-causing nucleic acids are antisense GGCCC (G₂C₄) repeat-expansion RNA, the disease-causing proteins are selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrP^{Sc}, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin

8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides;

(c) ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA-4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG-3, and phosphatidylserine; or

(d) a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells.

28. A pharmaceutical composition comprising the antibody of any one of claims 1-27 and a pharmaceutically acceptable carrier.

29. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of claims 1-27.

30. An isolated host cell comprising the nucleic acid of claim 29.

31. A method of producing an antibody that binds to human MS4A4A, comprising culturing the cell of claim 30 so that the antibody is produced.

32. The antibody of any one of claims 1-27 or the pharmaceutical composition of claim 28 for use in treating an individual having a disease, disorder, or injury selected from the group consisting of Alzheimer's disease and late onset Alzheimer's disease.

33. The antibody of any one of claims 1-27 or the pharmaceutical composition of claim 28 for use in treating an individual having a CSF1R-deficient disease or disorder, wherein the CSF1R-deficient disease or disorder is adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) or hereditary diffuse leukoencephalopathy with spheroids (HDLS).