

WHAT IS CLAIMED IS:

1. An isolated antibody, or antigen binding portion thereof, which specifically binds a human family with sequence similarity 19, member A5 (FAM19A5) protein ("anti-FAM19A5 antibody"), comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 comprises the amino acid sequences set forth in SEQ ID NOs: 5, 6, and 7, respectively, each of which optionally comprising one, two, three, four, or five mutations, wherein the light chain CDR1, CDR2, and CDR3 comprise the amino acid sequences set forth in SEQ ID NOs: 8, 9, and 10, respectively, wherein at least one of the light chain CDR1, CDR2, and CDR3 comprising one, two, three, four, or five mutations, and wherein the antibody has a reduced immunogenicity in human compared to a reference antibody comprising the VH set forth in SEQ ID NO: 11 and the VL set forth in SEQ ID NO: 12.
2. The antibody of claim 1, wherein the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 7.
3. The antibody of claim 1 or 2, wherein the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 5, with one or two mutations.
4. The antibody of claim 3, wherein the mutations comprise a substitution of Threonine at amino acid 3 of SEQ ID NO: 5 to an acidic amino acid.
5. The antibody of claim 3 or 4, wherein the mutations comprise a substitution of Serine at amino acid 5 of SEQ ID NO: 5 to an acidic amino acid.
6. The antibody of claim 4 or 5, wherein the acidic amino acid comprises Aspartic Acid or Glutamic Acid.
7. The antibody of any one of claims 1 to 6, wherein the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 6, with one, two, three, four, or five mutations.
8. The antibody of claim 7, wherein the mutations comprise a substitution of Arginine at amino acid 16 of SEQ ID NO: 6 to a basic amino acid.
9. The antibody of claim 8, wherein the basic amino acid comprises Lysine.
10. The antibody of claim 8 or 9, wherein the mutations comprise one or more of the following:
 - (a) a substitution of Glycine at amino acid 6 of SEQ ID NO: 6 to an acidic amino acid;
 - (b) a substitution of Serine at amino acid 7 of SEQ ID NO: 6 to an acidic amino acid;
 - (c) a substitution of Serine at amino acid 8 of SEQ ID NO: 6 to an acidic amino acid;
 - (d) a substitution of Threonine at amino acid 9 of SEQ ID NO: 6 to an acidic amino acid; and

(e) a substitution of Arginine at amino acid 16 of SEQ ID NO: 6 to a basic amino acid.

11. The antibody of claim 10, wherein the acidic amino acid comprises Aspartic Acid or Glutamic Acid.

12. The antibody of any one of claims 8 to 11, wherein the basic amino acid comprises Lysine.

13. The antibody of any one of claims 1 to 12, wherein the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 10, with one, two, three, four, or five mutations.

14. The antibody of claim 13, wherein the mutations comprise one or more of the following:

(a) a substitution of Serine at amino acid 6 of SEQ ID NO: 10 to an acidic amino acid or to an aliphatic amino acid;

(b) a substitution of Asparagine at amino acid 7 of SEQ ID NO: 10 to an acidic amino acid or to a hydroxyl or sulfur/selenium-containing amino acid;

(c) a substitution of Glycine at amino acid 8 of SEQ ID NO: 10 to an acidic amino acid or to a hydroxyl or sulfur/selenium-containing amino acid;

(d) a substitution of Glycine at amino acid 9 of SEQ ID NO: 10 to an acidic amino acid or to a hydroxyl or sulfur/selenium-containing amino acid; and

(e) a substitution of Isoleucine at amino acid 10 of SEQ ID NO: 10 to a basic amino acid.

15. The antibody of claim 14, wherein the acidic amino acid comprises Aspartic Acid or Glutamic Acid.

16. The antibody of claim 14 or 15, wherein the hydroxyl or sulfur/selenium-containing amino acid comprises Serine.

17. The antibody of any one of claims 14 to 16, wherein the basic amino acid comprises Histidine.

18. The antibody of any one of claims 1 to 17, wherein the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 8, with one, two, three, or four mutations.

19. The antibody of claim 18, wherein the mutations comprise one or more of the following:

(a) a substitution of Tyrosine at amino acid 6 of SEQ ID NO: 8 to an acidic amino acid;

(b) a substitution of Arginine at amino acid 7 of SEQ ID NO: 8 to an acidic amino acid;

(c) a substitution of Glycine at amino acid 8 of SEQ ID NO: 8 to an acidic amino acid; and

(d) a substitution of Serine at amino acid 9 of SEQ ID NO: 8 to an acidic amino acid.

20. The antibody of claim 19, wherein the acidic amino acid comprises Glutamic Acid or Glutamine.

21. The antibody of any one of claims 1 to 20, wherein the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 9, with one, two, three, or four mutations.

22. The antibody of claim 21, wherein the mutations comprise one or more of the following:

(a) a substitution of Glutamic Acid at amino acid 1 of SEQ ID NO: 9 to an acidic amino acid;

(b) a substitution of Serine at amino acid 2 of SEQ ID NO: 9 to an acidic amino acid;

(c) a substitution of Asparagine at amino acid 3 of SEQ ID NO: 9 to an acidic amino acid, to a basic amino acid, or to an aliphatic amino acid; and

(d) a substitution of Lysine at amino acid 4 of SEQ ID NO: 9 to an acidic amino acid or to an aliphatic amino acid.

23. The antibody of claim 22, wherein the acidic amino acid comprises Glutamine, Asparagine, Aspartic Acid, or Glutamic Acid.

24. The antibody of claim 22 or 23, wherein the basic amino acid comprises Histidine.

25. The antibody of any one of claims 22 to 24, wherein the aliphatic amino acid comprises Leucine.

26. The antibody of claim 22, wherein the mutations comprise a substitution of Serine at amino acid 2 of SEQ ID NO: 9 to an acidic amino acid.

27. The antibody of claim 26, wherein the acidic amino acid comprises Aspartate, Glutamate, Asparagine, Glutamine, or combinations thereof.

28. The antibody of claim 26 or 27, wherein the acidic amino acid is Asparagine.

29. An isolated antibody, or antigen binding portion thereof, which specifically binds to a human FAM19A5 protein, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein: (i) the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 5; (ii) the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 13; (iii) the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 7; (iv) the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 8; (v) the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 20; and (vi) the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 10.

30. An isolated antibody, or antigen binding portion thereof, which specifically binds to a human FAM19A5 protein, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein: (i) the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 14; (ii) the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 15; (iii) the heavy chain CDR3 comprises the amino acid sequence set forth

in SEQ ID NO: 7; (iv) the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 21; (v) the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 22; and (vi) the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 23.

31. An isolated antibody, or antigen binding portion thereof, which specifically binds to a human FAM19A5 protein, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein: (i) the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 14; (ii) the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 15; (iii) the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 7; (iv) the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 21; (v) the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 24; and (vi) the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 23.

32. An isolated antibody, or antigen binding portion thereof, which specifically binds to a human FAM19A5 protein, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein: (i) the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 14; (ii) the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 15; (iii) the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 7; (iv) the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 8; (v) the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 25; and (vi) the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 23.

33. An isolated antibody, or antigen binding portion thereof, which specifically binds to a human FAM19A5 protein, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein: (i) the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 14; (ii) the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 15; (iii) the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 7; (iv) the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 8; (v) the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 24; and (vi) the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 23.

34. An isolated antibody, or antigen binding portion thereof, which specifically binds to a human FAM19A5 protein, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein: (i) the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 14; (ii) the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 15; (iii) the heavy chain CDR3 comprises the amino acid sequence set forth

in SEQ ID NO: 7; (iv) the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 8; (v) the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 26; and (vi) the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 27.

35. An isolated antibody, or antigen binding portion thereof, which specifically binds to a human FAM19A5 protein, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein: (i) the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 14; (ii) the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 15; (iii) the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 7; (iv) the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 8; (v) the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 28; and (vi) the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 29.

36. The antibody of any one of claims 1 to 35, comprising a heavy chain variable region (VH) and a light chain variable region (VL), 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 in SEQ ID NO: 11 and/or 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 in SEQ ID NO: 12.

37. The antibody of any one of claims 1 to 36, wherein the antibody cross-competes with a reference antibody, which comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:

(a) the VH comprises the amino acid sequence set forth in SEQ ID NO: 33, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 38;

(b) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 39;

(c) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 41;

(d) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 40;

(e) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 42;

(f) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 43; or

(g) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 44.

38. The antibody of any one of claims 1 to 37, wherein the antibody binds to the same human FAM19A5 epitope as a reference antibody, which comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:

(a) the VH comprises the amino acid sequence set forth in SEQ ID NO: 33, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 38;

(b) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 39;

(c) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 41;

(d) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 40;

(e) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 42;

(f) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 43; or

(g) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 44.

39. The antibody of claim 38, wherein the human FAM19A5 epitope comprises the amino acid sequence set forth in SEQ ID NO: 90, 91, or 92.

40. An isolated antibody, or antigen binding portion thereof, which specifically binds a human family with sequence similarity 19, member A5 (FAM19A5) protein ("anti-FAM19A5 antibody"), comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3,

wherein the heavy chain CDR1, CDR2, and CDR3 comprises the amino acid sequences set forth in SEQ ID NOs: 16, 17, and 18, respectively, each of which optionally comprising one, two, or three mutations,

wherein the light chain CDR1, CDR2, and CDR3 comprise the amino acid sequences set forth in SEQ ID NOs: 30, 31, and 32, respectively, wherein at least one of the light chain CDR1, CDR2, and CDR3 comprises one, two, or three mutations, and

wherein the antibody has a reduced immunogenicity in human and/or higher binding affinity to human FAM19A5 protein compared to a reference antibody comprising the VH set forth in SEQ ID NO: 35 and the VL set forth in SEQ ID NO: 45.

41. The antibody of claim 40, wherein the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 18, 128, or 129.

42. The antibody of claim 40 or 41, wherein the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 16.

43. The antibody of claim 40 or 41, wherein the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 19.

44. The antibody of any one of claims 40 to 43, wherein the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 17.

45. The antibody of any one of claims 40 to 44, wherein the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 32.

46. The antibody of any one of claims 40 to 45, wherein the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 31.

47. The antibody of any one of claims 40 to 46, wherein the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 30, with one mutation.

48. The antibody of claim 47, wherein the mutation comprises a substitution of Serine at amino acid 4 of SEQ ID NO: 30 to an aliphatic amino acid.

49. The antibody of claim 48, wherein the aliphatic amino acid comprises Valine.

50. The antibody of any one of claims 40 to 49, comprising a heavy chain variable region (VH) and a light chain variable region (VL), 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 in SEQ ID NO: 35 and/or 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 in SEQ ID NO: 45.

51. The antibody of any one of claims 40 to 50, wherein the antibody cross-competes with a reference antibody, which comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the amino acid sequence set forth in SEQ ID NO: 36, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 46.

52. The antibody of any one of claims 40 to 50, wherein the antibody cross-competes with a reference antibody, which comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the amino acid sequence set forth in SEQ ID NO: 37, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 46.

53. The antibody of any one of claims 40 to 50, wherein the antibody cross-competes with a reference antibody, which comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the amino acid sequence set forth in SEQ ID NO: 130, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 46.

54. The antibody of any one of claims 40 to 50, wherein the antibody cross-competes with a reference antibody, which comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the amino acid sequence set forth in SEQ ID NO: 131, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 46.

55. The antibody of any one of claims 1 to 54, wherein the antibody is selected from the group consisting of an IgG1, IgG2, IgG3, IgG4, a variant thereof, and any combination thereof.

56. The antibody of any one of claims 1 to 55, which is a chimeric antibody, a human antibody, or a humanized antibody.

57. The antibody of any one of claims 1 to 56, comprises a Fab, a Fab', a F(ab')₂, a Fv, or a single chain Fv (scFv).

58. The antibody of claim 57, which is a scFv.

59. The antibody of claim 58, wherein the scFv comprises a VH and a VL, wherein:

(a) the VH comprises the amino acid sequence set forth in SEQ ID NO: 33, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 38;

(b) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 39;

(c) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 41;

(d) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 40;

(e) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 42;

(f) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 43;

(g) the VH comprises the amino acid sequence set forth in SEQ ID NO: 34, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 44;

(h) the VH comprises the amino acid sequence set forth in SEQ ID NO: 36, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 46;

(i) the VH comprises the amino acid sequence set forth in SEQ ID NO: 37, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 46;

(j) the VH comprises the amino acid sequence set forth in SEQ ID NO: 130, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 46; or

(k) the VH comprises the amino acid sequence set forth in SEQ ID NO: 131, and the VL comprises the amino acid sequence set forth in SEQ ID NO: 46.

60. The antibody of any one of claims 1 to 59, which exhibits one or more of the following properties:

(a) binds to soluble human FAM19A5 with a KD of 10 nM or less as measured by enzyme-linked immunosorbent assay (ELISA);

(b) binds to membrane bound human FAM19A5 with a KD of 10 nM or less as measured by ELISA;

(c) reduces, reverses, delays, and/or prevents an onset of reactive gliosis;

(d) suppresses an excessive proliferation of reactive astrocytes;

(e) decreases expression of chondroitin sulfate proteoglycans including neurocan and neuronal antigen 2 (NG2);

(f) increases expression of c-fos and pERK in the nucleus of neurons;

(g) promotes survival of neurons;

(h) increases expression of GAP43 in neurons;

(i) promotes regrowth of an axon;

(j) induces normalization of blood vessels, e.g., in a tumor;

(k) suppresses growth of a tumor;

(l) enhances infiltration of immune cells into a tumor;

(m) enhances infiltration of neuronal cells into a tumor;

(n) enhances phagocytic activity of a macrophage or a microglia;

(o) increases a mitochondrial membrane potential of a macrophage or a microglia;

(p) reduces recruitment of myeloid-derive suppressor cells (MDSCs) to a tumor;

(q) reduces necrosis and edema in a tumor;

(r) reduces tissue permeability of a tumor; and

(s) increases a blood flow rate in a tumor.

61. A nucleic acid encoding the antibody of any one of claims 1 to 60.

62. A vector comprising the nucleic acid of claim 61.

63. A cell comprising the vector of claim 62.

64. An immunoconjugate comprising the antibody of any one of claims 1 to 60, linked to an agent.

65. A composition comprising the antibody of any one of claims 1 to 60, the nucleic acid of claim 61, the vector of claim 62, the cell of claim 63, or the immunoconjugate of claim 64, and a carrier.

66. A kit comprising the antibody of any one of claims 1 to 60, the nucleic acid of claim 61, the vector of claim 62, the cell of claim 63, or the immunoconjugate of claim 64, and an instruction for use in therapy.

67. A method of producing an antibody which specifically binds to a human FAM19A5 protein, comprising culturing the cell of claim 63 under suitable conditions and isolating the antibody.

68. Use of an antibody of any one of claims 1 to 60, the nucleic acid of claim 61, the vector of claim 62, the cell of claim 63, or the immunoconjugate of claim 64 in the manufacture of a medicament for ~~A method of treating a disease or condition in a subject in need thereof, comprising administering to the subject an~~ wherein the antibody of any one of claims 1 to 60, the nucleic acid of claim 61, the vector of claim 62, the cell of claim 63, or the immunoconjugate of claim 64 is to be administered to the subject.

69. The ~~method-use~~ use of claim 68, wherein the disease or condition comprises a tumor, a fibrosis, a glaucoma, a mood disorder, a retinopathy, an age-related macular degeneration, or a neuropathic pain.

70. The ~~method-use~~ use of claim 69, wherein the disease or condition is a tumor.

71. The ~~method-use~~ use of claim 69 or 70, wherein the tumor comprises a melanoma, pancreatic cancer, glioma, breast cancer, lymphoma, lung cancer, kidney cancer, prostate cancer, fibrosarcoma, colon adenocarcinoma, liver cancer, or ovarian cancer.

72. The ~~usemethod~~ use of claim 71, wherein the glioma is glioblastoma multiforme (GBM).

73. The ~~usemethod~~ use of any one of claims 68 to 72, wherein the antibody, the nucleic acid, the vector, the cell, or the immunoconjugate induces a normalization of blood vessels.

74. The ~~use~~method of claim 73, wherein the normalization of blood vessels is accompanied by changes in properties of the blood vessels comprising increased connectivity, increased wall thickness, reduced vessel diameter, more regular vessel direction and distribution pattern, increased vessel number, reduction of leakage and permeability, increased pericyte coverage and proximity on the blood vessels, increased oxygenation, or combinations thereof.

75. The ~~use~~method of any one of claims 69 to 74, wherein the antibody, the nucleic acid, the vector, the cell, or the immunoconjugate suppresses growth of the tumor.

76. The ~~use~~method of any one of claims 69 to 75, wherein the antibody, the nucleic acid, the vector, the cell, or the immunoconjugate enhances infiltration of immune cells into the tumor.

77. The ~~use~~method of claim 76, wherein the immune cells comprise macrophages, dendritic cells, T lymphocytes, B lymphocytes, natural killer (NK) cells, or combinations thereof.

78. The ~~use~~method of claim 76 or 77, wherein the immune cells further display hypertrophy.

79. The ~~use~~method of any one of claims 76 to 78, wherein the enhanced infiltration of immune cells into the tumor is accompanied by increased infiltration of neuronal cells into the tumor.

80. The ~~use~~method of claim 79, wherein the neuronal cells comprise astrocytes, glial cells, or combinations thereof.

81. The ~~use~~method of any one of claims 68 to 80, wherein the antibody, the nucleic acid, the vector, the cell, or the immunoconjugate enhances phagocytic activity of a macrophage or a microglia.

82. The ~~use~~method of any one of claims 68 to 81, wherein the antibody, the nucleic acid, the vector, the cell, or the immunoconjugate increases a mitochondrial membrane potential of a macrophage or microglia.

83. The ~~use~~method of any one of claims 69 to 81, wherein the antibody, the nucleic acid, the vector, the cell, or the immunoconjugate reduces recruitment of myeloid-derived suppressor cells (MDSCs) to the tumor.

84. The ~~use~~method of any one of claims 69 to 83, wherein the antibody, the nucleic acid, the vector, the cell, or the immunoconjugate reduces necrosis and edema in the tumor.

85. The ~~use~~method of any one of claims 69 to 84, wherein the antibody, the nucleic acid, the vector, the cell, or the immunoconjugate reduces tissue permeability of the tumor.

86. The ~~use~~method of any one of claims 69 to 85, wherein the antibody, the nucleic acid, the vector, the cell, or the immunoconjugate increases blood flow rate in the tumor.

87. The ~~use~~method of any one of claims 68 to 86, ~~comprising administering~~wherein an additional therapeutic agent is to be administered.

88. The ~~use~~method of claim 87, wherein the additional therapeutic agent comprises a chemotherapy, immunotherapy, radiotherapy, or combinations thereof.

89. A composition comprising the antibody of any one of claims 1 to 60, the nucleic acid of claim 61, the vector of claim 62, the cell of claim 63, or the immunoconjugate of claim 64 for use in therapy.