

What is claimed is:

1. An isolated polypeptide comprising a Siglec-9 IgV domain comprising an amino acid sequence selected from any one of SEQ ID NOs: 109-137 and 214-226.
2. The isolated polypeptide of claim 1, wherein the polypeptide comprises a Siglec-9 extracellular domain (ECD) comprising the Siglec-9 IgV domain, a C2 type 1 (C2T1) domain, and a C2 type 2 (C2T2) domain.
3. The isolated polypeptide of claim 1 or claim 2, wherein the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 79-107 and 194-206.
4. The isolated polypeptide of any one of claims 1-3, wherein the polypeptide further comprises an Fc domain.
5. The isolated polypeptide of claim 4, wherein the Fc domain is located at the C-terminus of the polypeptide.
6. The isolated polypeptide of claim 4 or claim 5, wherein the Fc domain has a human IgG1 isotype.
7. The isolated polypeptide of claim 6, wherein the Fc domain has a human IgG1 isotype that has:
 - a) reduced binding to FcγRIII;
 - b) reduced antibody-dependent cellular cytotoxicity (ADCC) and/or reduced complement binding activity;
 - c) increased binding to FcγRIIa; or
 - d) any combination of a), b), and/or c),relative to the IgG1 polypeptide of SEQ ID No: 142.
8. The isolated polypeptide of claim 6 or 7, wherein the Fc domain comprises an amino acid sequence selected from any one of SEQ ID NOs: 142-144 and 234-239.
9. The isolated polypeptide of claim 8, wherein the Fc domain comprises the amino acid sequence of SEQ ID NO: 142 or 143.
10. The isolated polypeptide of claim 6 or 7, wherein the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 11-39, 148-160, and 168-170.
11. The isolated polypeptide of claim 10, wherein the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 49-77, 171-183, and 191-193.
12. A polypeptide comprising an amino acid sequence selected from any one of SEQ ID NOs: 49-77 and 171-193, lacking its signal peptide.
13. The isolated polypeptide of claim 4 or claim 5, wherein the Fc domain has a human IgG4 isotype.
14. The isolated polypeptide of claim 13, wherein the Fc domain comprises the amino acid sequence of SEQ ID NO: 145 or 146.
15. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 138.
16. The isolated polypeptide of claim 15, wherein the polypeptide further comprises an Fc domain.

17. The isolated polypeptide of claim 16, wherein the Fc domain is located at the C-terminus of the polypeptide.
18. The isolated polypeptide of claim 17, wherein the Fc domain has a human IgG1 isotype.
19. The isolated polypeptide of claim 18, comprising a linker sequence.
20. The isolated polypeptide of claim 18 or 19, wherein the Fc domain comprises an amino acid sequence selected from any one of SEQ ID NOs: 142-144.
21. The isolated polypeptide of claim 20, wherein the Fc domain comprises the amino acid sequence of SEQ ID NO: 142 or 143.
22. The isolated polypeptide of claim 19, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 139.
23. The isolated polypeptide of claim 17, wherein the Fc domain has a human IgG4 isotype.
24. The isolated polypeptide of claim 23, wherein the Fc domain comprises the amino acid sequence of SEQ ID NO: 145 or 146.
25. An isolated polypeptide of SEQ ID NO: 78 joined at its C-terminus to an Fc domain.
26. The isolated polypeptide of claim 25, wherein the Fc domain has a human IgG1 or IgG4 isotype.
27. The isolated polypeptide of claim 26, wherein the Fc domain has a human IgG1 isotype that has:
 - a) reduced binding to FcγRIII;
 - b) reduced antibody-dependent cellular cytotoxicity (ADCC) and/or reduced complement binding activity;
 - c) increased binding to FcγRIIIa; or
 - d) any combination of a), b), and/or c),relative to the IgG1 polypeptide of SEQ ID No: 142.
28. The isolated polypeptide of claim 26 or 27, wherein the Fc domain has a human IgG1 isotype and comprises an amino acid sequence selected from any one of SEQ ID NOs: 142-144 and 234-239.
29. The isolated polypeptide of claim 26, wherein the Fc domain comprises the amino acid sequence of SEQ ID NO: 142.
30. The isolated polypeptide of claim 26, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:10.
31. The isolated polypeptide of claim 26 or 27, wherein the Fc domain comprises the amino acid sequence of SEQ ID NO: 143.
32. The isolated polypeptide of claim 26, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 227.
33. The isolated polypeptide of claim 26, wherein the Fc domain has a human IgG4 isotype and comprises the amino acid sequence of SEQ ID NO: 145 or 146.
34. The isolated polypeptide of claim 25, wherein the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 45-48 and 228-233, lacking its associated signal peptide.
35. The isolated polypeptide of claim 34, wherein the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 45-48 and 228-233.

36. The isolated polypeptide of claim 34, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 45, lacking its associated signal peptide.
37. The isolated polypeptide of claim 36, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 45.
38. The isolated polypeptide of claim 34, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 48, lacking its associated signal peptide.
39. An isolated polypeptide comprising an amino acid sequence selected from any one of SEQ ID NOs: 207-213 and an Fc domain located at the C-terminus of the polypeptide.
40. The isolated polypeptide of claim 39, wherein the Fc domain has a human IgG1 or IgG4 isotype.
41. The isolated polypeptide of claim 40, wherein the Fc domain has a human IgG1 isotype that has:
- a) reduced binding to FcγRIII;
 - b) reduced antibody-dependent cellular cytotoxicity (ADCC) and/or reduced complement binding activity;
 - c) increased binding to FcγRIIa; or
 - d) any combination of a), b), and/or c),
- relative to the IgG1 polypeptide of SEQ ID No: 142.
42. The isolated polypeptide of claim 40 or 41, wherein the Fc domain has a human IgG1 isotype and comprises an amino acid sequence selected from any one of SEQ ID NOs: 142-144 and 234-239.
43. The isolated polypeptide of claim 39, comprising an amino acid sequence selected from any one of SEQ ID NOs: 161-167.
44. The isolated polypeptide of claim 40, comprising an amino acid sequence selected from any one of SEQ ID NOs: 184-190, lacking its associated signal peptide.
45. The isolated polypeptide of claim 44, comprising an amino acid sequence selected from any one of SEQ ID NOs: 184-190.
46. The isolated polypeptide of claim 40, wherein the Fc domain has a human IgG4 isotype and comprises the amino acid sequence of SEQ ID NO: 145 or 146.
47. The isolated polypeptide of any one of claims 1-46, wherein the polypeptide binds sialic acid on the surface of cells.
48. The isolated polypeptide of claim 47, wherein the cells are tumor cells.
49. The isolated polypeptide of claim 47, wherein the cells express FcR.
50. The isolated polypeptide of claim 47, wherein the cells are myeloid cells.
51. The isolated polypeptide of claim 50, wherein the myeloid cells are selected from monocytes, macrophages, dendritic cells, microglia, and myeloid-derived suppressor cells (MDSCs).
52. The isolated polypeptide of any one of claims 1-51, wherein the polypeptide
- a) blocks cell binding of any one or more Siglec family members selected from Siglec-3, Siglec-5, Siglec-7, Siglec-9, Siglec-10, and Siglec-15;
 - b) relieves MDSC-mediated suppression of T-cells, optionally as determined by measuring an increase in IFNγ expression or an increase in T-cell proliferation;

- c) repolarizes MDSCs to a pro-inflammatory phenotype;
 - d) increases expression of CD86 on MDSCs, increases expression of CD11b on MDSCs, and/or decreases expression of CD163 on MDSCs;
 - e) repolarizes tumor macrophages away from an M2 phenotype;
 - f) reduces CD163+ and/or CD206+ macrophages;
 - g) induces expression of one or more chemokines selected from CCL3, CCL4, CCL5, CCL17, CXCL1, CXCL9, and IL-8 in MDSCs;
 - h) reduces myeloid cell recruitment into the tumor microenvironment; or
 - i) binds to MDSCs with an affinity of less than 100 nM, less than 50 nM, less than 25 nM, less than 20 nM, less than 10 nM, less than 5 nM, less than 2 nM, 1-50 nM, 1-25 nM, 1-20 nM, 1-10 nM, 1-5 nM, or 1-2 nM;
 - j) any one or more of (a) through (i).
53. The isolated polypeptide of claim 52, wherein the MDSCs are human MDSCs and/or the macrophages are human macrophages.
54. An isolated nucleic acid comprising a nucleic acid sequence that encodes the isolated polypeptide of any one of claims 1-53.
55. The isolated nucleic acid of claim 54, wherein the isolated nucleic acid encodes an amino acid sequence selected from any one of SEQ ID NOs: 45-77, 171-193, and 228-233.
56. The isolated nucleic acid of claim 54, wherein the isolated nucleic acid encodes a polypeptide comprising an amino acid sequence selected from any one of SEQ ID NOs: 10-39, 148-170, and 227.
57. An expression vector comprising the isolated nucleic acid of any one of claims 54-56.
58. A host cell comprising the isolated nucleic acid of any one of claims 54-56 or the expression vector of claim 57.
59. A host cell that expresses the isolated polypeptide of any one of claims 1 to 53.
60. A method of producing a polypeptide comprising culturing the host cell of claim 58 or claim 59.
61. The method of claim 60, comprising isolating the polypeptide.
62. A pharmaceutical composition comprising the polypeptide of any one of claims 1-53 and a pharmaceutically acceptable carrier.
63. A pharmaceutical composition comprising (i) the polypeptide of any one of claims 7, 10, 12, 27, 31, 32, 34, 36, 38, 41, 43 and 44, or (ii) the polypeptide of claim 22 lacking its signal peptide; and a pharmaceutically acceptable carrier.
64. A method of treating cancer comprising administering to a subject with cancer the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63.
65. The method of claim 64, comprising administering the polypeptide of any one of claims 7, 10, 12, 27, 31, 32, 34, 36, 38, 41, 43 and 44.
66. The method of claim 64 or claim 65, wherein the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells.

67. The method of any one of claims 64-66, wherein the cancer is selected from renal cell carcinoma, sarcoma, pancreatic cancer, glioblastoma, ovarian cancer, colorectal cancer, lung cancer, melanoma, bladder cancer, head and neck cancer, breast cancer and uterine cancer.
68. The method of any one of claims 64-67, wherein the cancer is metastatic.
69. The method of any one of claims 64-68, further comprising administering an antagonist of PD-1 or PD-L1, optionally wherein the antagonist of PD-1 or PD-L1 is an antibody that binds to PD-1 or PD-L1, respectively.
70. The method of any one of claims 64-69, further comprising administering a chemotherapeutic agent.
71. A method of treating a neurological or neurodegenerative disease, comprising administering to a subject with a neurological or neurodegenerative disease the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63.
72. The method of claim 71, comprising administering the polypeptide of any one of claims 7, 10, 12, 27, 31, 32, 34, 36, 38, 41, 43 and 44.
73. The method of claim 71 or claim 72, wherein the neurological or neurodegenerative disease is characterized by dysfunctional or deficient microglia.
74. The method of any one of claims 71-73, wherein the neurological or neurodegenerative disease is selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, and mild cognitive impairment, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, Tauopathy disease, multiple sclerosis, immune-mediated neuropathies (such as neuropathic pain), Nasu-Hakola disease, pediatric-onset leukoencephalopathy and adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP).
75. A method of repolarizing myeloid-derived suppressor cells (MDSCs) to a pro-inflammatory phenotype in a subject, comprising administering to the subject the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63.
76. The method of claim 75, comprising administering the polypeptide of any one of claims 7, 10, 12, 27, 31, 32, 34, 36, 38, 41, 43 and 44.
77. The method of claim 75 or claim 76, wherein the subject has cancer.
78. The method of claim 77, wherein the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells.
79. The method of claim 77 or claim 78, wherein the cancer is selected from renal cell carcinoma, sarcoma, pancreatic cancer, glioblastoma, ovarian cancer, colorectal cancer, lung cancer, melanoma, bladder cancer, head and neck cancer, breast cancer and uterine cancer.
80. The method of any one of claims 77-79, wherein the cancer is metastatic.
81. The method of claim 75 or 76, wherein the subject has a neurological or neurodegenerative disease.
82. The method of claim 81, wherein the neurological or neurodegenerative disease is characterized by dysfunctional or deficient microglia.

83. The method of claim 81 or 82, wherein the neurodegenerative disease is selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, and mild cognitive impairment, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, Taupathy disease, multiple sclerosis, immune-mediated neuropathies (such as neuropathic pain), Nasu-Hakola disease, pediatric-onset leukoencephalopathy and adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP).
84. A method of repolarizing tumor macrophages away from an M2 phenotype in a subject having cancer, the method comprising administering to the subject the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63.
85. The method of claim 81, comprising administering the polypeptide of any one of claims 7, 10, 12, 27, 31, 32, 34, 36, 38, 41, 43 and 44.
86. The method of claim 84 or claim 85, wherein the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells.
87. The method of any one of claims 84-86, wherein the cancer is selected from renal cell carcinoma, sarcoma, pancreatic cancer, glioblastoma, ovarian cancer, colorectal cancer, lung cancer, melanoma, bladder cancer, head and neck cancer, breast cancer and uterine cancer.
88. The method of any one of claims 84-87, wherein the cancer is metastatic.
89. A method of activating myeloid cells in a subject, the method comprising administering to the subject the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63.
90. The method of claim 89, comprising administering the polypeptide of any one of claims 7, 10, 12, 27, 31, 32, 34, 36, 38, 41, 43 and 44.
91. The method of claim 89 or 90, wherein the myeloid cells are microglia.
92. The method of any one of claims 89-91, wherein the subject has cancer.
93. The method of claim 92, wherein the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells.
94. The method of claim 92 or 93, wherein the cancer is selected from renal cell carcinoma, sarcoma, pancreatic cancer, glioblastoma, ovarian cancer, colorectal cancer, lung cancer, melanoma, bladder cancer, head and neck cancer, breast cancer and uterine cancer.
95. The method of any one of claims 92-94, wherein the cancer is metastatic.
96. The method of claim 89, 90, or 91, wherein the subject has a neurodegenerative disease.
97. The method of claim 96, wherein the neurodegenerative disease is selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, and mild cognitive impairment, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, Taupathy disease, multiple sclerosis, immune-mediated neuropathies (such as neuropathic pain), Nasu-Hakola disease, pediatric-onset leukoencephalopathy and adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP).