

Bochner (2008) Ann NY Acad Sci. 1143:61–82). Other Siglecs are activating receptors that contain immunoreceptor tyrosine-based activating motif (ITAM) sequences in their cytoplasmic domains. Those Siglecs act as positive regulators of immune function (Macauley SM. et al., (2014) *Nature Reviews Immunology* 14, 653–666).

[006] The Siglec protein family plays a role in tumor pathogenesis. Many human tumors robustly upregulate sialic acid ligands that bind Siglec-9, which may enable immune evasion and cancer progression (Jandus et al. (2014) J. Clin. Invest. 124:1810-1820). In contrast, tumors lacking sialic acid biosynthesis have reduced growth in mice (Stanczak et al. (2018) J Clin Invest.128:4912-4923). Certain SNPs in Siglec-3, 7, 9 are associated with decreased risk of colorectal and lung cancer (*Id.*).

[007] All references cited herein, including patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[008] The present disclosure is generally directed to Siglec-9 extracellular domain (ECD) fusion proteins and methods of treating cancer and neurodegenerative diseases using Siglec-9 ECD fusion proteins.

[008a] In one aspect, the present disclosure refers to 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. In another aspect, the present disclosure refers to a polypeptide comprising an amino acid sequence selected from any one of SEQ ID NOs: 49-77 and 171-193, lacking its signal peptide. In yet another aspect, the present disclosure refers to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 138. In a further aspect, the present disclosure refers to an isolated polypeptide of SEQ ID NO: 78 joined at its C-terminus to an Fc domain. In a yet further aspect, the present disclosure refers to 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.

[009] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 79-107 and 194-206. In some [embodimentexamples](#), the Siglec-9 IgV domain polypeptide does not comprise the membrane proximal region of Siglec-9, as shown in SEQ ID NO: 147 (MPR).

[010] In some [embodimentexamples](#), the polypeptide further comprises an Fc domain. In some such [embodimentexamples](#), the Fc domain is located at the C-terminus of the polypeptide. In some [embodimentexamples](#), the Fc domain has an IgG1 isotype. In some [embodimentexamples](#), the Fc domain comprises an amino acid sequence selected from SEQ ID NOs: 142-144 and 234-239. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 142 or 143. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 142. In some [embodimentexamples](#), the isolated polypeptide comprises an Fc domain with 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 any combination of a), b), and/or c), relative to the IgG1 polypeptide of SEQ ID No: 142. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 143. In some [embodimentexamples](#), the Fc domain has an IgG4 isotype. In some [embodimentexample](#), the Fc domain comprises an amino acid sequence selected from SEQ ID NOs: 145-146.

[011] In some [embodimentexamples](#), the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 11-39, 148-160, and 168-170. In some [embodimentexample](#), the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 49-77, 171-183, and 191-193. In some

[embodimentexamples](#), the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 49-77 and 171-193, lacking its signal peptide.

[012] In some [embodimentexamples](#), an isolated polypeptide comprising a Siglec-9 IgV domain is provided, which comprises the amino acid sequence of SEQ ID NO: 138. In some [embodimentexamples](#), an isolated polypeptide comprising a Siglec-9 IgV domain is provided, which comprises the amino acid sequence of SEQ ID NO: 138 further comprising an Fc domain, optionally located at the C-terminus of the polypeptide. Optionally, the Fc domain has a human IgG1 isotype. In some cases, the polypeptide further comprises a linker sequence. In some [embodimentexamples](#), the Fc domain comprises an amino acid sequence selected from SEQ ID NOs: 142-144. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 142 or 143. In some [embodimentexamples](#), the polypeptide comprises the amino acid sequence of SEQ ID NO: 139. In some [embodimentexamples](#), the Fc domain has an IgG4 isotype. In some [embodimentexamples](#), the Fc domain comprises an amino acid sequence selected from SEQ ID NOs: 145-146.

[013] In some [embodimentexamples](#), an isolated polypeptide comprising a Siglec-9 IgV domain is provided, which comprises the amino acid sequence of SEQ ID NO: 78 joined at its C-terminus to an Fc domain. In some [embodimentexamples](#), the polypeptide comprises the amino acid sequence of SEQ ID NO: 10. In some [embodimentexamples](#), the polypeptide comprises the amino acid sequence of SEQ ID NO: 227. In some [embodimentexamples](#), the Fc domain has an IgG1 isotype. In some [embodimentexamples](#), the Fc domain comprises an amino acid sequence selected from SEQ ID NOs: 142-144 and 234-239. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 142 or 143. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 142. In some [embodimentexamples](#), the isolated polypeptide comprises an Fc domain with 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 any combination of a), b), and/or c), relative to the IgG1 polypeptide of SEQ ID No: 142. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 143. In some [embodimentexamples](#), the Fc domain has an IgG4 isotype. In some [embodimentexamples](#), the Fc domain comprises an amino acid sequence selected from SEQ ID NOs: 145-146. In some [embodimentexamples](#), an isolated polypeptide comprising a Siglec-9 IgV domain is provided, which comprises an amino acid sequence selected from any one of SEQ ID NOs: 45-48 and 228-233, lacking its associated signal peptide. In some [embodimentexamples](#), the polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 45-48 and 228-233. In some [embodimentexamples](#), the polypeptide comprises the amino acid sequence of SEQ ID NO: 45, lacking its associated signal peptide. In some [embodimentexamples](#), the polypeptide comprises the amino acid sequence of SEQ ID NO: 45. In some [embodimentexamples](#), the polypeptide comprises the amino acid sequence of SEQ ID NO: 48, lacking its associated signal peptide.

[014] In some [embodimentexamples](#), an isolated polypeptide comprising a Siglec-9 IgV domain is provided, which comprises the amino acid sequence of any one of SEQ ID Nos: 207-213 and an Fc domain located at the C-terminus of the polypeptide. In some [embodimentexamples](#), the Fc domain has an IgG1 isotype. In

some [embodimentexamples](#), the Fc domain comprises an amino acid sequence selected from SEQ ID NOs: 142-144 and 234-239. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 142 or 143. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 142. In some [embodimentexamples](#), the isolated polypeptide comprises an Fc domain with 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 any combination of a), b), and/or c), relative to the IgG1 polypeptide of SEQ ID No: 142. In some [embodimentexamples](#), the Fc domain comprises the amino acid sequence of SEQ ID NO: 143. In some [embodimentexamples](#), the Fc domain has an IgG4 isotype. In some [embodimentexamples](#), the Fc domain comprises an amino acid sequence selected from SEQ ID NOs: 145-146. In some [embodimentexamples](#), the polypeptide comprises an amino acid sequence selected from any one of SEQ ID Nos: 161-167. In some [embodimentexamples](#), the polypeptide comprises an amino acid sequence selected from any one of SEQ ID Nos: 184-190, lacking the signal peptide. In some [embodimentexamples](#), the polypeptide comprises an amino acid sequence selected from any one of SEQ ID Nos: 184-190.

[015] In any of the [embodimentexamples](#) of an isolated polypeptide comprising a Siglec-9 IgV domain provided herein, the polypeptide may bind sialic acid on the surface of cells. In some such [embodimentexamples](#), the cells are tumor cells. In some [embodimentexamples](#), the cells express FcR, e.g., FcRγIIA. In some [embodimentexamples](#), the cells are myeloid cells. In some [embodimentexamples](#), the myeloid cells are selected from monocytes, macrophages, dendritic cells, microglia, and myeloid-derived suppressor cells (MDSCs).

[016] In any of the [embodimentexamples](#) of an isolated polypeptide comprising a Siglec-9 IgV domain provided herein, 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;
- 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; or
- j) any one or more of (a) through (i).

In some such [embodimentexamples](#), the MDSCs are human MDSCs and/or the macrophages are human macrophages.

[017] [In one aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleic acid sequence that encodes any one of the isolated polypeptides disclosed herein.](#) In some [embodimentexamples](#), an isolated nucleic acid is provided that comprises a nucleic acid sequence that encodes an isolated polypeptide comprising a Siglec-9 IgV domain provided herein. In some [embodimentexamples](#), the isolated nucleic acid encodes an amino acid sequence selected from any one of SEQ ID NOs: 48-77, 171-193, and 228-233. In some [embodimentexamples](#), 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. [In one aspect, the present disclosure refers to an expression vector comprising any one of the isolated nucleic acids disclosed herein.](#) In some [embodimentexamples](#), an expression vector is provided that comprises the isolated nucleic acid.

[018] [In one aspect, the present disclosure refers to a host cell comprising any one of the isolated nucleic acids or the expression vector disclosed herein.](#) In some [embodimentexamples](#), a host cell is provided, which comprises an isolated nucleic acid or expression vector provided herein. [In one aspect, the present disclosure refers to a host cell that expresses any one of the isolated polypeptides disclosed herein.](#) In some [embodimentexamples](#), a host cell is provided, which expresses an isolated polypeptide comprising a Siglec-9 IgV domain provided herein. [In one aspect, the present disclosure refers to a method of producing a polypeptide comprising culturing the host cell disclosed herein.](#) In some [embodimentexamples](#), a method of producing the polypeptide is provided, comprising culturing the host cell. In some such [embodimentexamples](#), the polypeptide is isolated.

[019] [In one aspect, the present disclosure refers to a pharmaceutical composition comprising any one of the polypeptides disclosed herein and a pharmaceutically acceptable carrier.](#) In various [embodimentexamples](#), a pharmaceutical composition is provided, which comprises an isolated polypeptide comprising a Siglec-9 IgV domain provided herein and a pharmaceutically acceptable carrier. [In one aspect, the present disclosure refers to a pharmaceutical composition comprising \(i\) any one of the polypeptides disclosed herein, or \(ii\) the polypeptide lacking its signal peptide disclosed herein; and a pharmaceutically acceptable carrier.](#) In some [embodimentexamples](#), the pharmaceutical composition may comprise (i) a polypeptide as described herein with its signal peptide, or (ii) a polypeptide lacking its signal peptide; and a pharmaceutically acceptable carrier.

[020] [In one aspect, the present disclosure refers to use of any one of the polypeptides disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating cancer.](#) In some [embodimentexamples](#), a method of treating cancer is provided, comprising administering to a subject with cancer an isolated polypeptide comprising a Siglec-9 IgV domain provided herein or a pharmaceutical composition comprising the polypeptide. In some [embodimentexamples](#), the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), the [use or](#) method further comprises 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. In some [embodimentexamples](#), the [use or](#) method further comprises administering a chemotherapeutic agent.

[021] [In one aspect, the present disclosure refers to use of any one of the polypeptides disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a neurological or neurodegenerative disease.](#) In some [embodimentexamples](#), a method of treating a neurological or neurodegenerative disease is provided, comprising administering to a subject with a neurological or neurodegenerative disease an isolated polypeptide comprising a Siglec-9 IgV domain provided herein or a pharmaceutical composition comprising the polypeptide. In some [embodimentexamples](#), the neurological or neurodegenerative disease is characterized by dysfunctional or deficient microglia. In some [embodimentexamples](#), 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, 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).

[022] In one aspect, the present disclosure refers to use of any one of the polypeptides disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for repolarizing myeloid-derived suppressor cells (MDSCs) to a pro-inflammatory phenotype in a subject. In some [embodimentexamples](#), a method of repolarizing myeloid-derived suppressor cells (MDSCs) to a pro-inflammatory phenotype in a subject is provided, comprising administering to a subject with a neurological or neurodegenerative disease an isolated polypeptide comprising a Siglec-9 IgV domain provided herein or a pharmaceutical composition comprising the polypeptide. In some such [embodimentexamples](#), the subject has cancer. In some [embodimentexamples](#), the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells. In some [embodimentexamples](#), 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. In some cases, the cancer is metastatic. In some [embodimentexamples](#), the subject has a neurological or neurodegenerative disease. In some [embodimentexamples](#), the neurological or neurodegenerative disease is characterized by dysfunctional or deficient microglia. In some [embodimentexamples](#), 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).

[023] In one aspect, the present disclosure refers to use of any one of the polypeptides disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for repolarizing tumor macrophages away from an M2 phenotype in a subject having cancer. In some [embodimentexamples](#), a method of repolarizing tumor macrophages away from an M2 phenotype in a subject having cancer is provided, the method administering to the subject an isolated polypeptide comprising a Siglec-9 IgV domain provided herein or a pharmaceutical composition comprising the polypeptide. In some [embodimentexamples](#), the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells. In some [embodimentexamples](#), 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. In some cases, the cancer is metastatic.

[024] In one aspect, the present disclosure refers to use of any one of the polypeptides disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for activating myeloid cells in a subject. In some [embodimentexamples](#), a method of activating myeloid cells in a subject is provided, the method administering to the subject an isolated polypeptide comprising a Siglec-9 IgV domain provided herein or a pharmaceutical composition comprising the polypeptide. In some cases, the myeloid cells are microglia. In some [embodimentexamples](#), the subject has cancer. In some [embodimentexamples](#), the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells. In some [embodimentexamples](#), 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. In some cases, the cancer is metastatic. In some [embodimentexamples](#), the subject has a neurological or neurodegenerative disease. In some [embodimentexamples](#), the neurological or neurodegenerative disease is characterized by dysfunctional or deficient microglia. In some [embodimentexamples](#), the neurodegenerative disease is selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, and mild cognitive impairment, Parkinson's disease, amyotrophic lateral sclerosis

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 FcγRIIa; 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~~Use of the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63 in the manufacture of a medicament for treating cancer.

65. The ~~method~~use 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~~use of claim 64 or claim 65, wherein the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells.

67. The ~~method~~use 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~~use of any one of claims 64-67, wherein the cancer is metastatic.
69. The ~~method~~use of any one of claims 64-68, ~~further comprising administering wherein the medicament is to be administered with~~ 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~~use of any one of claims 64-69, ~~wherein the medicament is to be administered with~~~~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~~Use of the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63 ~~in the manufacture of a medicament for treating a neurological or neurodegenerative disease.~~
72. The ~~method~~use 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~~use of claim 71 or claim 72, wherein the neurological or neurodegenerative disease is characterized by dysfunctional or deficient microglia.
74. The ~~method~~use 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, 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).
75. ~~A method of repolarizing myeloid-derived suppressor cells (MDSCs) to a pro-inflammatory phenotype in a subject, comprising administering to the subject~~Use of the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63 ~~in the manufacture of a medicament for repolarizing myeloid-derived suppressor cells (MDSCs) to a pro-inflammatory phenotype in a subject.~~
76. The ~~method~~use 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~~use of claim 75 or claim 76, wherein the subject has cancer.
78. The ~~method~~use of claim 77, wherein the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells.
79. The ~~method~~use 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~~use of any one of claims 77-79, wherein the cancer is metastatic.

81. The ~~method~~use of claim 75 or 76, wherein the subject has a neurological or neurodegenerative disease.
82. The ~~method~~use of claim 81, wherein the neurological or neurodegenerative disease is characterized by dysfunctional or deficient microglia.
83. The ~~method~~use 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~~Use of the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63 ~~in the manufacture of a medicament for repolarizing tumor macrophages away from an M2 phenotype in a subject having cancer.~~
85. The ~~method~~use 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~~use of claim 84 or claim 85, wherein the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells.
87. The ~~method~~use 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~~use 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~~Use of the polypeptide of any one of claims 1-53 or the pharmaceutical composition of claim 62 or claim 63 ~~in the manufacture of a medicament for activating myeloid cells in a subject.~~
90. The ~~method~~use 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~~use of claim 89 or 90, wherein the myeloid cells are microglia.
92. The ~~method~~use of any one of claims 89-91, wherein the subject has cancer.
93. The ~~method~~use of claim 92, wherein the cancer is a solid tumor associated with a tumor microenvironment comprising myeloid cells.
94. The ~~method~~use 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~~use of any one of claims 92-94, wherein the cancer is metastatic.
96. The ~~method~~use of claim 89, 90, or 91, wherein the subject has a neurodegenerative disease.
97. The ~~method~~use 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).