levels of Siglec-9 or that disrupt the interactions between Siglec-9 and one or more of its ligands have been reported.

[0016] Accordingly, there is a need for therapeutic antibodies that specifically bind Siglec-9 and reduce Siglec-9 expression on the cell surface, reduce interactions between Siglec-9 and one or more Siglec-9 ligands, and/or reduce one or more Siglec-9 activities in order to treat one or more diseases, disorders, and conditions associated with undesired Siglec-9 activity.

[0017] All references cited herein, including patents, patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[0017a] In one aspect, the present disclosure refers to an isolated anti-Siglec-9 antibody, wherein the anti-Siglec-9 antibody decreases cell surface levels of Siglec-9, as determined by a fluorescence-activated cell sorting (FACS) assay using a threshold value of 21% or higher reduction of Siglec-9 cell surface levels to indicate a decrease, and does not inhibit interaction between Siglec-9 and sialic acid-containing glycoproteins, as determined by a FACS assay using a threshold value of 80% or higher Siglec-9-Fc binding to U937 cells to indicate non-inhibition.

[0017b] Disclosed is an isolated anti-Siglec-9 antibody, wherein the anti-Siglec-9 antibody binds to one or more amino acids within amino acid residues selected from the group consisting of:

i. amino acid residues185-194 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 185-194 of SEQ ID NO: 1;
ii. amino acid residues 86-96 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 86-96 of SEQ ID NO: 1;
iii. amino acid residues 86-96 and 105-116 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 86-96 and 105-116 of SEQ ID NO: 1;
iv. amino acid residues 105-116 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 105-116 of SEQ ID NO: 1; and
v. amino acid residues 107-115 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 107-115 of SEQ ID NO: 1.

[0017c] Disclosed is an isolated anti-Siglec-9 antibody, wherein the anti-Siglec-9 antibody competes with one or more antibodies selected from the group consisting of 2D4, 5B1, 6B2, 6D8, 7H12, and any combination thereof for binding to Siglec-9.

[0017d] Disclosed is an isolated anti-Siglec-9 antibody which binds essentially the same Siglec-9 epitope as a monoclonal antibody selected from the group consisting of: 2D4, 5B1, 6B2, 6D8, and 7H12.

[0017e] In yet another aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleic acid sequence encoding the anti-Siglec-9 antibody disclosed herein.

[0017f] In yet another aspect, the present disclosure refers to a vector comprising the nucleic acid disclosed herein.

[0017g] In yet another aspect, the present disclosure refers to an isolated host cell comprising the vector disclosed herein.

[0017h] In yet another aspect, the present disclosure refers to a method of producing an anti-Siglec-9 antibody, comprising culturing the host cell disclosed herein so that the anti-Siglec-9 antibody is produced.

[0017i] In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the anti-Siglec-9 antibody disclosed herein, and a pharmaceutically acceptable carrier.

[0017j] In yet another aspect, the present disclosure refers to use of a therapeutically effective amount of the anti-Siglec-9 antibody disclosed herein in the manufacture of a medicament for reducing risk of or treating a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, taupathy disease, infections, and cancer.

[0018] The present disclosure is generally directed to Siglec-9 agents, such as anti-Siglec-9 antibodies, and methods of using such Siglec-9 agents. The methods provided herein find use in preventing, reducing risk, or treating an individual having dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, taupathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, solid and blood cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential

CLAIMS

What is claimed is:

1. An isolated anti-Siglec-9 antibody, wherein the anti-Siglec-9 antibody decreases cell surface levels of Siglec-9, as determined by a fluorescence-activated cell sorting (FACS) assay using a threshold value of 21% or higher reduction of Siglec-9 cell surface levels to indicate a decrease, and does not inhibit interaction between Siglec-9 and sialic acid-containing glycoproteins, as determined by a FACS assay using a threshold value of 80% or higher Siglec-9-Fc binding to U937 cells to indicate non-inhibition.

2. The anti-Siglec-9 antibody of claim 1, wherein the antibody decreases cell surface levels of Siglec-9 *in vivo*.

3. The anti-Siglec-9 antibody of any one of claims 1-2, wherein the anti-Siglec-9 antibody inhibits one or more Siglec-9 activities.

4. The anti-Siglec-9 antibody of any one of claims 1-3, wherein the cell surface levels of Siglec-9 are measured on primary cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, and NK cells, or on cell lines.

5. The anti-Siglec-9 antibody of any one of claims 1-4, wherein the anti-Siglec-9 antibody does not reduce TREM2 expression.

6. The anti-Siglec-9 antibody of any one of claims 1-5, wherein the anti-Siglec-9 antibody binds to amino acid residues selected from the group consisting of:

i. amino acid residues 185-194 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 185-194 of SEQ ID NO: 1;

ii. amino acid residues 86-96 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 86-96 of SEQ ID NO: 1;

iii. amino acid residues 86-96 and 105-116 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 86-96 and 105-116 of SEQ ID NO: 1;

iv. amino acid residues 105-116 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 105-116 of SEQ ID NO: 1; and

v. amino acid residues 107-115 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to amino acid residues 107-115 of SEQ ID NO: 1.

7. The anti-Siglec-9 antibody of any one of claims 1-5, wherein the anti-Siglec-9 antibody binds to amino acid residues D189, P190, and R194 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-9 protein corresponding to D189, P190, and R194 of SEQ ID NO: 1.

8. The anti-Siglec-9 antibody of any one of claims 1-7, wherein the anti-Siglec-9 antibody competes with one or more antibodies selected from the group consisting of:

(a) an antibody comprising a light chain variable domain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID: NO 6, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10, an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 14, and a heavy chain variable domain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 19, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 22, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 26;

(b) an antibody comprising a light chain variable domain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID: NO 8, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 12, an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16, and a heavy chain variable domain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 21, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 24, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 28;

(c) an antibody comprising a light chain variable domain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID: NO 9, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 13, an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 17, and a heavy chain variable domain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 21, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 25, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 29;

(d) an antibody comprising a light chain variable domain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID: NO 8, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 12, an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 18, and a heavy chain variable domain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 21, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 24, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 28;

and any combination thereof for binding to Siglec-9.

9. The anti-Siglec-9 antibody of any one of claims 1-8, wherein the anti-Siglec-9 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein:

(a) the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 6 or the amino acid sequence of SEQ ID NO: 6 having one or more conservative amino acid substitutions, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10 or the amino acid sequence of SEQ ID NO: 10 having one or more conservative amino acid substitutions, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 14 or the amino acid sequence of SEQ ID NO: 14 having one or more conservative amino acid substitutions, and the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 19 or the amino acid sequence of SEQ ID NO: 19 having one or more conservative amino acid substitutions, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 22 or the amino acid sequence of SEQ ID NO: 22 having one or more conservative amino acid substitutions, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 26 or the amino acid sequence of SEQ ID NO: 26 having one or more conservative amino acid substitutions; or

(b) the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 8 or the amino acid sequence of SEQ ID NO: 8 having one or more conservative amino acid substitutions, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 12 or the amino acid sequence of SEQ ID NO: 12 having one or more conservative amino acid substitutions, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16 or the amino acid sequence of SEQ ID NO: 16 having one or more conservative amino acid substitutions, and the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 21 or the amino acid sequence of SEQ ID NO: 21 having one or more conservative amino acid substitutions, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 24 or the amino acid sequence of SEQ ID NO: 24 having one or more conservative amino acid substitutions, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 28 or the amino acid sequence of SEQ ID NO: 28 having one or more conservative amino acid substitutions; or

(c) the light chain variable domain comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9 or the amino acid sequence of SEQ ID NO: 9 having one or more conservative amino acid substitutions, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 13 or the amino acid sequence of SEQ ID NO: 13 having one or more conservative amino acid substitutions, and an HVR-L3

comprising the amino acid sequence of SEQ ID NO: 17 or the amino acid sequence of SEQ ID NO: 17 having one or more conservative amino acid substitutions, and the heavy chain variable domain comprises, an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 21 or the amino acid sequence of SEQ ID NO: 21 having one or more conservative amino acid substitutions, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 25 or the amino acid sequence of SEQ ID NO: 25 having one or more conservative amino acid substitutions, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 29 or the amino acid sequence of SEQ ID NO: 29 having one or more conservative amino acid substitutions; or

(d) the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 8 or the amino acid sequence of SEQ ID NO: 8 having one or more conservative amino acid substitutions, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 12 or the amino acid sequence of SEQ ID NO: 12 having one or more conservative amino acid substitutions, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 18 or the amino acid sequence of SEQ ID NO: 18 having one or more conservative amino acid substitutions, and the heavy chain variable domain comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 21 or the amino acid sequence of SEQ ID NO: 21 having one or more conservative amino acid substitutions, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 24 or the amino acid sequence of SEQ ID NO: 24 having one or more conservative amino acid substitutions, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 28 or the amino acid sequence of SEQ ID NO: 28 having one or more conservative amino acid substitutions.

10. The anti-Siglec-9 antibody of any one of claims 1-9, wherein the antibody is of the IgG class the IgM class, or the IgA class.

11. The anti-Siglec-9 antibody of claim 10, wherein the anti-Siglec-9 antibody has an IgG1, IgG2, IgG3, or IgG4 isotype.

12. The anti-Siglec-9 antibody of claim 11, wherein:

(a) the anti-Siglec-9 antibody has a human or mouse IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: N297A, D265A, D270A, L234A, L235A, G237A, P238D, L328E, E233D, G237D, H268D, P271G, A330R, C226S, C229S, E233P, L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, N297Q, P238S, P238A, A327Q, A327G, P329A, K322A, T394D, and any combination thereof, wherein the numbering of the residues is according to EU numbering, or

comprises an amino acid deletion in the Fc region at a position corresponding to glycine 236;

(b) the anti-Siglec-9 antibody has an IgG1 isotype and comprises an IgG2 isotype heavy chain constant domain 1(CH1) and hinge region, optionally wherein the IgG2 isotype CH1 and hinge region comprises the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVERKCCVECPPCP (SEQ ID NO: 171), and optionally wherein the antibody Fc region comprises a S267E amino acid substitution, a L328F amino acid substitution, or both, and/or a N297A or N297Q amino acid substitution, wherein the numbering of the residues is according to EU numbering;

(c) the anti-Siglec-9 antibody has an IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: P238S, V234A, G237A, H268A, H268Q, V309L, A330S, P331S, C214S, C232S, C233S, S267E, L328F, M252Y, S254T, T256E, H268E, N297A, N297Q, A330L, and any combination thereof, wherein the numbering of the residues is according to EU numbering;

(d) the anti-Siglec-9 antibody has a human or mouse IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: L235A, G237A, S228P, L236E, S267E, E318A, L328F, M252Y, S254T, T256E, E233P, F234V, L234A/F234A, S228P, S241P, L248E, T394D, N297A, N297Q, L235E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or

(e) the anti-Siglec-9 antibody has a hybrid IgG2/4 isotype, and optionally wherein the antibody comprises an amino acid sequence comprising amino acids 118 to 260 of human IgG2 and amino acids 261 to 447 of human IgG4, wherein the numbering of the residues is according to EU numbering.

13. The anti-Siglec-9 antibody of any one of claims 1-12, wherein the Siglec-9 protein is a mammalian protein or a human protein.

14. The anti-Siglec-9 antibody of any one of claims 1-13, wherein the anti-Siglec-9 antibody binds Siglec-9 in a pH dependent manner.

15. The anti-Siglec-9 antibody of any one of claims 1-14, wherein the anti-Siglec-9 antibody is an antibody fragment that binds to an epitope comprising amino acid residues on human Siglec-9 or a mammalian Siglec-9 protein.

16. The anti-Siglec-9 antibody of claim 15, wherein the fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv, or scFv fragment.

17. The anti-Siglec-9 antibody of any one of claims 1-16, wherein the anti-Siglec-9 antibody is a murine antibody, a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody.

18. The anti-Siglec-9 antibody of any one of the preceding claims, wherein the anti-Siglec-9 antibody has dissociation constant (K_D) for human Siglec-9 and mammalian Siglec-9 that ranges from about 10 nM to about10 pM, or less than 10 pM, wherein the K_D is determined at a temperature of approximately 25ºC.

19. The anti-Siglec-9 antibody of any one of the preceding claims, wherein the anti-Siglec-9 antibody has dissociation constant (K_D) for human Siglec-9 that ranges from about 9 nM to about 230 pM, or less than 230 pM, wherein the K_D is determined at a temperature of approximately 25ºC.

20. An isolated nucleic acid comprising a nucleic acid sequence encoding the anti-Siglec-9 antibody of any one of the preceding claims.

21. A vector comprising the nucleic acid of claim 20.

22. An isolated host cell comprising the vector of claim 21.

23. A method of producing an anti-Siglec-9 antibody, comprising culturing the host cell of claim 22 so that the anti-Siglec-9 antibody is produced.

24. A pharmaceutical composition comprising the anti-Siglec-9 antibody of any one of claims 1-19, and a pharmaceutically acceptable carrier.

25. Use of a therapeutically effective amount of the anti-Siglec-9 antibody of any one of claims 1-19 in the manufacture of a medicament for reducing risk of or treating a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, taupathy disease, infections, and cancer.