(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 March 2017 (09.03.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/040301 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61P 35/00* (2006.01)
A61P 25/00 (2006.01) *A61K 39/00* (2006.01)

(21) International Application Number:
PCT/US2016/049032

(22) International Filing Date:
26 August 2016 (26.08.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/211,656 28 August 2015 (28.08.2015) US
62/265,742 10 December 2015 (10.12.2015) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

[Continued on next page]

(54) Title: ANTI-SIGLEC-7 ANTIBODIES AND METHODS OF USE THEREOF

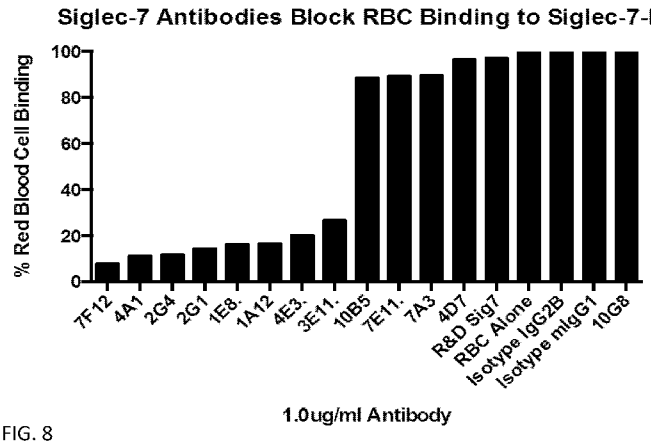


FIG. 8

(57) Abstract: The present disclosure is generally directed to compositions that include antibodies, e.g., monoclonal, chimeric, humanized antibodies, antibody fragments, etc., that specifically bind on or more epitopes within a Siglec-7 protein, e.g., human Siglec-7 or a mammalian Siglec-7, and use of such compositions in preventing, reducing risk, or treating an individual in need thereof.

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— *with sequence listing part of description (Rule 5.2(a))*

ANTI-SIGLEC-7 ANTIBODIES AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/211,656, filed August 28, 2015, and U.S. Provisional Application No. 62/265,742, filed December 10, 2015, each of which is hereby incorporated by reference in its entirety.

SUBMISSION OF SEQUENCE LISTING ON ASCII TEXT FILE

[0002] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 735022000840SEQLISTING.TXT, date recorded: August 26, 2016, size: 405 KB).

FIELD OF THE INVENTION

[0003] This present disclosure relates to anti-Siglec-7 antibodies and therapeutic uses of such antibodies.

BACKGROUND OF THE INVENTION

[0004] Sialic acid-binding Ig-like lectin-7 (Siglec-7), is a type 1, immunoglobulin-like, transmembrane protein expressed on immune and hematopoietic cells, including immature and mature myeloid cells, such as monocytes, macrophages, dendritic cells, neutrophils, mast cells, and microglial cells, as well as lymphoid cells, such as natural killer cells, and subsets of T cells (Crocker et al. (2007) Nat Rev Immunol. 7:255–266; Angata and Varki (2000) Glycobiology 10:4: 431-438, Nicoll et al (1999) JBC 274:48: 34089-34095; Falco et al. (1999) J. Exp. Med. 190: 793-802). Siglec-7 is a member of the Siglec family of lectins that bind sialic acid residues of glycoproteins and glycolipids. One potential binding target for Siglec proteins are gangliosides; that is, glycolipids that consist of a ceramide linked to a sialylated glycan. Most gangliosides share a common lacto-ceramide core and one or more sialic acid residues. Diversity in the Siglec ligands is generated by the addition of other neutral sugars and sialic acid in different linkages, and modification of sialic acid itself.

[0005] Fourteen Siglec proteins have been identified in humans and nine in mice that are comprised of 2-17 extracellular Ig domains including an amino-terminal V-set domain that contains the sialic acid-binding site. The sialic acid-binding region is located on the V-set Ig-like domain, which contains a two aromatic residues and one arginine motif highly conserved in all Siglecs (Crocker et al. (2007) Nat Rev Immunol. 7:255–266; McMillan and Crocker (2008) Carbohydr Res. 343:2050–2056; Von Gunten and Bochner (2008) Ann NY Acad Sci. 1143:61–82; May et al. (1998) Mol Cell. 1:719–728; Crocker et al. (1999) Biochem J. 341:355–361; and Crocker and Varki (2001) Trends Immunol. 2:337–342). The binding sites to sialylated ligands have been mapped by crystal

structures with and without ligand bound (Alphey et al., (2003) J. Biol. Chem. 278:5: 3372-3377; Attrill et al., (2006) J. Biol. Chem.281 32774-32783; and Varki et al., Glycobiology, 16 pp. 1R–27R). Since cell membranes are rich in sialic acids, ligand binding by Siglecs can occur in cis and in trans, both affecting their functional properties. Each Siglec has a distinct preference for binding the diverse types of sialylated glycans that are found on the surface of mammalian cells (Crocker et al. (2007) Nat Rev Immunol. 7:255–266; and Crocker et al. (2007) Nat Rev Immunol. 7:255–266). Most Siglec proteins, including Siglec-7, contain one or more immunoreceptor tyrosine-based inhibitory motif (ITIM) sequences in their cytoplasmic tails, which enable them as inhibitory receptors and negative regulators of immune functions through recruitment of the tyrosine phosphatases SHP1 and SHP2 (Crocker et al. (2007) Nat Rev Immunol. 7:255–266; McMillan and Crocker (2008) Carbohydr Res. 343:2050–2056; and Von Gunten and Bochner (2008) Ann NY Acad Sci. 1143:61–82). Certain Siglecs contain immunoreceptor tyrosine-based activating motif (ITAM) sequences in their cytoplasmic tails, which enable them to act as activating receptors and positive regulators of immune function through predicted recruitment of spleen tyrosine kinase (Syk) (Macauley SM. et al., (2014) *Nature Reviews Immunology* 14, 653–666). The Siglec protein family is associated with multiple human disease including, autoimmunity, susceptibility to infection, multiple types of cancer including lymphoma, leukemia and acute myeloid leukemia, systemic lupus erythematosus, rheumatoid arthritis, neurodegenerative disorders, asthma, allergy, sepsis, chronic obstructive pulmonary disease, graft-versus-host disease, eosinophilia, and osteoporosis (Macauley SM. et al., (2014) *Nature Reviews Immunology* 14, 653–666).

[0006] Siglec-7 was cloned in 1999 (Falco et al. (1999) J. Exp. Med. 190: 793-802; Nicoll et al (1999) JBC 274:48: 34089-34095; Angata and Varki (2000) Glycobiology 10:4: 431-438), and selective expression was detected on granulocytes, monocytes, resting and activated natural killer cells and a subset of resting $CD8^+$ T cells in human peripheral blood (Nicoll et al (1999) JBC 274:48: 34089-34095; Falco et al. (1999) J. Exp. Med. 190: 793-802).

[0007] Siglec-7 contains an extracellular N-terminal Ig-like (immunoglobulin-like) V-type domain, two Ig-like C2-set domains as well as one consensus ITIM motif and a non-conforming membrane-distal ITIM-like motif in its cytoplasmic domain. Siglec-7 was shown to bind red blood cells in a sialic acid dependent manner due to loss of binding upon sialidase treatment. The binding is thought to be mediated by α2-3 or α2-6 sialic acid linkages (Nicoll et al (1999) JBC 274:48: 34089-34095; Angata and Varki (2000) Glycobiology 10:4: 431-438). Further investigation revealed that Siglec-7 more potently binds α2-8 disialyl residues with 10nM affinity and demonstrates higher affinity for branched α2-6 sialyl residues compared to terminal α2-3 or α2-6 sialic acids (Yamaji (2002) J. Biol. Chem. 277:8 6324-6332). *In vivo* Siglec-7 ligands are expressed on b-series gangliosides such as GD2, GD3, and GT1b, which can be found on cells of the central nervous

system, melanoma cells, and subsets of T cells (Urmacher et al. (1989) Am. J. Dermatopathol. 11: 577-581, Kniep et al. (1993) Blood 82: 1776-1786). High resolution crystal structure of the N-terminal V-set Ig-like domain of Siglec-7 suggests that ligand binding specificity of Siglec family members resides in the variable C-C' loop (Alphey et al. (2003) J. Biol. Chem 278:5 3372-3377).

[0008] Siglec-7 undergoes phosphorylation of Tyr-437, and Tyr-460 by tyrosine kinases, likely c-Src or Lck (Avril et al., (2004) J. Imm. 173: 6841-6849). Following phosphorylation predominantly on the proximal Tyr-437, but also on distal Tyr-460 of its ITIM domains, Siglec-7 binds SHP-2/PTPN11 and SHP-1/PTPN6 (Avril et al., (2004) J. Imm. 173: 6841-6849). Phosphatase activity is associated with decreased intracellular calcium mobilization, and decreased tyrosine phosphorylation on multiple proteins (Ulyanova, T., et al., (1999) *Eur J Immunol* 29, 3440-3449; Paul, S.P., et al., (2000). *Blood* 96, 483-490) as well as with blockade of signal transduction and immune response, in part, through dephosphorylation of signaling molecules on adjacent activating receptors, including those that contain ITAM motifs, pattern recognition receptors, Toll-like receptors and damage-associated molecular pattern (DAMP) receptors.

[0009] Some, but not all, Siglec ligands induce receptor downregulation (Macauley SM. et al., (2014) *Nature Reviews Immunology* 14, 653–666). Ligand-induced receptor degradation has been reported for tyrosine kinase receptors (Monsonego-Oran et al., (2002) Febs letters 528, 83-89; and Fasen et al., (2008) Cell & Molecular Biology 9. 251-266), as well as steroid receptors (Callige et al., (2005) Mol. Cell. Biol. 25. 4349-4358; and Pollenz et al., (2006) Chemico-Biological Interactions. 164. 49-59). Suppressor of cytokine signaling 3 (SOCS3) has been shown to compete with SHP-1/2 and binds Siglec-7 upon ITIM phosphorylation in the presence of Siglec-7 crosslinking (Orr et al. (2007) J. Biol. Chem. 282: 3418-3422). SOCS3 binding results in ECS E3 ligase targeting of Siglec-7 for proteasomeal degradation (Willams and Palmer (2012) Biochem. Soc. Trans. 40: 215–218; Orr et al. (2007) J. Biol. Chem. 282: 3418-3422).

[0010] Activation of Siglec-7 signaling has also been shown to be associated with an increase in production of proinflammatory cytokines IL-6, IL-1alpha, MIP-1beta, IL-8 and TNFalpha, as well as upregulation of adhesion molecules ICAM-1 and CD49e selectively in human monocytes (Varchetta et al. (2012) PLOS One 7: 9: e45821). These activities of Siglec-7 appear to be mediated through the phosphorylation of ERK (Varchetta et al. (2012) PLOS One 7: 9: e45821). It has been proposed that the association between ITIM-containing Siglec receptors and activating receptors may be mediated by extracellular ligands that bind and bridge these receptors (Macauley SM. et al., (2014) *Nature Reviews Immunology* 14, 653–666).

[0011] Multiple studies indicate an inhibitory role for Siglec-7 in function of natural killer cells, regulation of T cell receptor signaling, and attenuation of signaling in DCs (Crocker et al., (2012) Ann. N Y Acad. Sci. 1253, 102–111; Pillai et al., (2012) Annu. Rev. Immunol. 30, 357–392; von

Gunten and Bochner (2008) Ann. N Y Acad. Sci. 1143, 61–82; Ikehara et al. (2004) J. Biol. Chem. 279:41 43117-43125; Nicoll et al. (2003) Eur. J. Imm. 33:6:1642-1648; Hudak et al. (2013) Nat. Chem. Biol.; Bax et al. (2007) J. Imm 179: 12: 8216-8224; Lock et al. (2004) Immunobiology 209: 1-2:199-207). Functional studies in natural killer cells have demonstrated that tumor cells expressing Siglec-7 binding sialic acid ligands inhibit NK cell activation and tumor cell killing. Many human tumors robustly upregulate sialic acid ligands, which enables immune evasion and cancer progression (Jandus et al. (2014) J. Clinic. Invest. 124:4: 1810-1820). Moreover, Hudak et al. performed glycocalyx engineering and showed that cells coated with synthetic sialoside glycopolymers were protected from NK cytotoxicity. It is proposed that sialic acid upregulation on tumors facilitates a state of "super self" that strongly inhibits natural killer cell immunosurveillance (Macauley and Paulson (2014) Nat. Chem. Biol. 10:1: 7-8).

[0012] There is no apparent mouse homolog of Siglec-7; however mouse Siglec-E is 53% similar, therefore the closest related Siglec. In mice, genetic inactivation of Siglec-E does not lead to obvious developmental, histological, or behavioral abnormalities; and Siglec-E-deficient mice breed normally, indicating that Siglec-E is not an essential gene and that its function may be limited to innate immunity (McMillan et al. (2013) Blood 121:11: 2084-2094). Upon challenge of Siglec-E deficient mice with aerosol LPS, increased neutrophil recruitment in the lung was demonstrated, which could be reversed by blockade of the β2-integrin CD11b. The Siglec-E deficient neutrophils were shown to have increased phosphorylation of Syk and p38 MAPK in a CD11b-dependent manner. This data suggests that Siglec-E functions to suppress neutrophil recruitment in a model of acute lung inflammation (McMillan et al. (2013) Blood 121:11: 2084-2094).

[0013] In oncology, Siglec-7 has been suggested as a therapeutic target for chronic and acute myeloid leukemic as crosslinking Siglec-7 inhibited cellular proliferation (Vitale et al. (1999) PNAS 96: 15091-15096; Vitale et al. (2001) PNAS 98:10: 5764-5769). Siglec-7 activity has also been shown to inhibit cytokine-induced cellular proliferation (Orr et al. (2007) J. Biol. Chem. 282: 3418-3422).

[0014] Antibodies to Siglec-7 have been described in, for example, WO2011038301, Jandus et al. (2014) J. Clinical Invest. 124:4: 1810-1820, Varchetta et al. (2012) PLOS One 7: 9: e45821et al. (2012). Falco et al. (1999) J. Exp. Med. 190: 793-802, Nicoll et al (1999) JBC 274:48: 34089-34095, Nicoll et al. (2003) Eur. J. Imm. 33: 1642–1648. However, these antibodies do not display the functional characteristics required for a therapeutic antibody.

[0015] Accordingly, there is a need for therapeutic antibodies that specifically bind Siglec-7 and reduce Siglec-7 expression on the cell surface, reduce interactions between Siglec-7 and one or more Siglec-7 ligands, and/or reduce one or more Siglec-7 activities in order to treat one or more diseases, disorders, and conditions associated with undesired Siglec-7 activity.

[0016] All references cited herein, including patents, patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

[0017] The present disclosure is generally directed to Siglec-7 agents, such as anti-Siglec-7 antibodies, and methods of using such Siglec-7 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7 and/or Siglec-7 ligands, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza. The methods provided herein also find use in inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof. The methods provided herein find further use in decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, neutrophils, natural killer (NK) cells, myeloid-derived suppressor cells, tumor-associated macrophages, neutrophils, NK cells, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cell in an individual in need thereof.

[0018] Certain aspects of the present disclosure are based, at least in part, on the identification of anti-Siglec-7 antibodies that are capable of decreasing cell surface levels of Siglec-7 on human primary immune cells and Siglec-7-expressing cell lines and/or that are capable of inhibiting the binding of Siglec-7 ligands to Siglec-7 (*see, e.g.*, **Examples 3-5**).

[0019] Accordingly, certain aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody decreases cellular levels of Siglec-7. In some embodiments, the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 without inhibiting interaction between Siglec-7 and one or more Siglec-7 ligands. In some embodiments, the antibody further inhibits interaction between Siglec-7 and one or more Siglec-7 ligands.

[0020] Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 and inhibits interaction between Siglec-7 and one or more Siglec-7 ligands.

[0021] In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody decreases cell surface levels of Siglec-7, decreases intracellular levels of Siglec-7, decreases total levels of Siglec-7, or any combination thereof. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody induces Siglec-7 degradation, Siglec-7 cleavage, Siglec-7 internalization, Siglec-7 shedding, downregulation of Siglec-7 expression, or any combination thereof. In some embodiments that may be combined with any of the preceding embodiments, antibody decreases cellular levels of Siglec-7 *in vivo*. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody inhibits cell surface clustering of Siglec-7. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody inhibits one or more Siglec-7 activities. In some embodiments that may be combined with any of the preceding embodiments, the one or more Siglec-7 activities are selected from: (a) Siglec-7 binding to one or more Siglec-7 ligands, optionally wherein the one or more Siglec-7 ligands are selected from sialic acid-containing glycoproteins, sialic acid-containing glycolipids, and any combination thereof; (b) Siglec-7 binding to SHP1 or SHP2; (c) phosphorylation of Tyr-437, Tyr-460, or both, induced by one or more SRC family tyrosine kinases, optionally, wherein the one or more SRC family tyrosine kinases are selected from Syk, LCK, FYM, and ZAP-70; (d) modulated expression of one or more pro-inflammatory cytokines, optionally wherein the one or more pro-inflammatory cytokines are selected from a group consisting IFN-a4, IFN-beta, IL-1β, IL-1alpha, TNF-α, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-33, MCP-1, and MIP-1-beta; (e) modulated expression of one or more pro-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; (f) modulated

expression of one or more anti-inflammatory cytokines, optionally wherein the one or more anti-inflammatory cytokines are selected from IL-4, IL-10, IL-13, IL-35, IL-16, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, or IL-6; (g) modulated expression of one or more anti-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; (h) modulate expression of one or more proteins selected from the group consisting of C1qa, C1qB, C1qC, C1s, C1R, C4, C2, C3, ITGB2, HMOX1, LAT2, CASP1, CSTA, VSIG4, MS4A4A, C3AR1, GPX1, TyroBP, ALOX5AP, ITGAM, SLC7A7, CD4, ITGAX, and PYCARD; (i) inhibition of extracellular signal-regulated kinase (ERK) phosphorylation; (j) decreasing tyrosine phosphorylation on one or more cellular proteins, optionally, wherein the one or more cellular proteins comprise ZAP-70 and the tyrosine phosphorylation occurs on Tyr-319 of ZAP-70; (k) modulated expression of C-C chemokine receptor 7 (CCR7); (l) inhibition of microglial cell chemotaxis toward CCL19-expressing and CCL21-expressing cells; (m) decreasing T cell proliferation induced by one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, M1 microglia, activated M1 microglia, M2 microglia, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, and M2 NK cells; (n) inhibition of osteoclast production, decreased rate of osteoclastogenesis, or both; (o) decreasing survival of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; (p) decreasing proliferation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; (q) inhibiting migration of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; (r) inhibiting one or more functions of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1

NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; (s) inhibiting maturation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; (t) inhibition of one or more types of clearance selected from apoptotic neuron clearance, nerve tissue debris clearance, dysfunctional synapse clearance, non-nerve tissue debris clearance, bacteria clearance, other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, and tumor cell clearance; optionally wherein the disease-causing protein is selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides and the tumor cell is from a cancer selected from 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, and thyroid cancer; (u) inhibition of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, dysfunctional synapses, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, disease-causing nucleic acids, or tumor cells; optionally wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin,

immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and the tumor cells are from a cancer selected from 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, or thyroid cancer; (v) binding to Siglec-7 ligand on tumor cells; (w) binding to Siglec-7 ligand on cells selected from neutrophils, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, and NK cells; (x) inhibition of tumor cell killing by one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; (y) inhibiting anti-tumor cell proliferation activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; (z) inhibition of anti-tumor cell metastasis activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; (aa) inhibition of one or more ITAM motif containing receptors, optionally wherein the one or more ITAM motif containing receptors are selected from TREM1, TREM2, Sirp beta, FcgR, DAP10, and DAP12; (bb) inhibition of signaling by one or more pattern recognition receptors (PRRs), optionally wherein the one or more PRRs are selected from receptors that identify pathogen-associated molecular patterns (PAMPs), receptors that identify damage-associated molecular patterns (DAMPs), and any combination thereof; (cc) inhibition of one or more receptors comprising the motif $D/Ex_{0-2}YxxL/IX_{6-8}YxxL/I$ (SEQ ID NO: 537); (dd) inhibition of signaling by one or more Toll-like receptors; (ee) inhibition of the JAK-STAT signaling pathway; (ff) inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB); (gg) de-phosphorylation of an ITAM motif containing receptor; (hh) modulated expression of one or more inflammatory receptors, optionally wherein the one or more inflammatory receptors comprise CD86 and the one or more inflammatory receptors are expressed on one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; (ii) increasing expression of one or more Siglec-7-dependent genes; (jj) normalization of disrupted Siglec-7-dependent gene expression; (kk) decreasing expression of one or more ITAM-dependent genes, optionally wherein the one more ITAM-dependent genes are activated by nuclear factor of activated T cells (NFAT) transcription factors; (ll) promoting differentiation of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages,

tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells; (mm) promoting or rescuing functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells; (nn) increasing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells into tumors; (oo) increasing the number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; (pp) enhancing tumor-promoting activity of myeloid-derived suppressor cells; (qq) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; (rr) increasing tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes; (ss) enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); (tt) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (uu) decreasing infiltration of tumor-specific NK cells with tumor killing potential; (vv) decreasing the tumor killing potential of NK cells; (ww) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (xx) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (yy) increasing tumor volume; (zz) increasing tumor growth rate; (aaa) increasing metastasis; (bbb) increasing rate of tumor recurrence; (ccc) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more target proteins selected from PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines; (ddd) inhibition of PLCγ/PKC/calcium mobilization; and (eee) inhibition of PI3K/Akt, Ras/MAPK signaling. In some embodiments that may be combined with any of the preceding embodiments, the one or more Siglec-7 activities are selected from: (a) Siglec-7 binding to one or more Siglec-7 ligands, optionally wherein the one or more Siglec-7 ligands are selected from the group consisting of sialic acid-containing glycoproteins, sialic acid-containing glycolipids, and any combination thereof; (b) decreasing proliferation of one or more cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; (c) inhibiting

migration of one or more cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; (d) inhibiting one or more functions of one or more cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; (e) inhibition of one or more types of clearance selected from the group consisting of apoptotic neuron clearance, nerve tissue debris clearance, dysfunctional synapse clearance, non-nerve tissue debris clearance, bacteria clearance, other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, and tumor cell clearance; optionally wherein the disease-causing protein is selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides and the tumor cell is from a cancer selected from the group consisting of 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, and thyroid cancer; (f) inhibition of tumor cell killing by one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; (g) inhibiting anti-tumor cell proliferation activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; (h) modulated expression of one or more inflammatory receptors, optionally wherein the one or more inflammatory receptors comprise CD86 and the one or more inflammatory receptors are expressed on one or more of microglia, macrophages, neutrophils, NK

cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; (i) promoting or rescuing functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells; (j) increasing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells into tumors; (k) increasing the number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; (l) enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); (m) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (n) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (o) increasing tumor volume; (p) increasing tumor growth rate; and (q) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more target proteins selected from the group consisting of PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody exhibits one or more activities selected from the group consisting of: (a) increasing the number of tumor infiltrating $CD3^+$ T cells; (b) inhibiting Siglec-7 binding to one or more Siglec-7 ligands; (c) decreasing cellular levels of Siglec-7 in peripheral immune cells; (d) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in blood; (e) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in the tumor; (f) reducing PD-L1 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (g) reducing PD-L2 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (h) reducing CD11b levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (i) reducing B7-H3 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (j) reducing CD200R levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (k)

reducing CD163 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (l) reducing CD206 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (m) decreasing tumor growth rate of solid tumors; (n) reducing tumor volume; (o) increasing efficacy of one or more PD-1 inhibitors; (p) increasing efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, optionally wherein the one or more checkpoint inhibitor therapies and/or immune-modulating therapies target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, LAG3, or any combination thereof; (q) inhibiting differentiation, survival, and/or one or more functions of non-tumorigenic myeloid-derived suppressor cells (MDSC); (r) inducing cell death of one or more myeloid-derived suppressor cells (MDSC); and (s) increasing proliferation of T cells in the presence of non-tumorigenic myeloid-derived suppressor cells (MDSC). In some embodiments that may be combined with any of the preceding embodiments, the one or more Siglec-7 ligands are selected from Siglec-7 ligands expressed on red blood cells, Siglec-7 ligands expressed on bacterial cells, Siglec-7 ligands expressed on apoptotic cells, Siglec-7 ligands expressed on nerve cells, Siglec-7 ligands expressed on glial cells, Siglec-7 ligands expressed on microglia, Siglec-7 ligands expressed on astrocytes, Siglec-7 ligands expressed on tumor cells, Siglec-7 ligands expressed on viruses, Siglec-7 ligands expressed on dendritic cells, Siglec-7 ligands bound to beta amyloid plaques, Siglec-7 ligands bound to Tau tangles, Siglec-7 ligands on disease-causing proteins, Siglec-7 ligands on disease-causing peptides, Siglec-7 ligands expressed on macrophages, Siglec-7 ligands expressed on neutrophils, Siglec-7 ligands expressed on monocytes, Siglec-7 ligands expressed on natural killer cells, Siglec-7 ligands expressed on T cells, Siglec-7 ligands expressed on T helper cells, Siglec-7 ligands expressed on cytotoxic T cells, Siglec-7 ligands expressed on B cells, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor dendritic cells, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor macrophages, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor neutrophils, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor NK cells, Siglec-7 ligands expressed on myeloid-derived suppressor cells, Siglec-7 ligands expressed on regulatory T cells, secreted mucins, sialic acid, sialic acid-containing glycolipids, sialic acid-containing glycoproteins, alpha-2,8-disialyl containing glycolipids, branched alpha-2,6-linked sialic acid-containing glycoproteins, terminal alpha-2,6-linked sialic acid-containing glycolipids, terminal alpha-2,3-linked sialic acid-containing glycoproteins, and disialogangliosides. In some embodiments that may be combined with any of the preceding embodiments, the cellular levels of Siglec-7 are measured on primary cells selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, and NK cells, or on cell lines, and wherein the cellular levels of Siglec-7 are measured utilizing an *in vitro* cell assay. In some embodiments that

may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody does not reduce TREM2 expression. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody does not reduce cell surface levels of TREM2, does not reduce intracellular levels of TREM2, does not reduce total levels of TREM2, or any combination thereof. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody does not reduce cellular levels of TREM2 *in vivo*. In some embodiments that may be combined with any of the preceding embodiments, the cellular levels of TREM2 are measured on primary cells selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, and NK cells, or on cell lines, and wherein the cellular levels of TREM2 are measured utilizing an *in vitro* cell assay.

[0022] In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds a discontinuous Siglec-7 epitope. In some embodiments that may be combined with any of the preceding embodiments, the discontinuous Siglec-7 epitope comprises two or more peptides, three or more peptides, four or more peptides, five or more peptides, six or more peptides, seven or more peptide, eight or more peptides, nine or more peptides, or 10 or more peptides. In some embodiments that may be combined with any of the preceding embodiments, each of the peptides comprise five or more, six or more, seven or more, eight or more, nine or more, 10 or more, 11 or more, 12 or more, 13 or more 14 or more, 15 or more, 16 or more, 17 or more, 18 or more, 19 or more, or 20 or more amino acid residues of the amino acid sequence of SEQ ID NO: 1; or five or more, six or more, seven or more, eight or more, nine or more, 10 or more, 11 or more, 12 or more, 13 or more 14 or more, 15 or more, 16 or more, 17 or more, 18 or more, 19 or more, or 20 or more amino acid residues on a mammalian Siglec-7 protein corresponding to the amino acid sequence of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to a conformational epitope of Siglec-7. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 39-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of SEQ ID NO: 1; or within amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 39-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. amino acid residues 60-69 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 of SEQ ID NO: 1; ii. amino acid residues 60-69 and 84-95 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 and 84-95 of SEQ ID NO: 1;

iii. amino acid residues 60-69 and 117-127 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1; iv. amino acid residues 68-78 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 68-78 of SEQ ID NO: 1; v. amino acid residues 84-95 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 84-95 of SEQ ID NO: 1; vi. amino acid residues 111-122 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 111-122 of SEQ ID NO: 1; vii. amino acid residues 111-122 and 282-291 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 111-122 and 282-291 of SEQ ID NO: 1; viii. amino acid residues 113-123 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 113-123 of SEQ ID NO: 1; ix. amino acid residues 113-125 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 113-125 of SEQ ID NO: 1; x. amino acid residues 117-127 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 117-127 of SEQ ID NO: 1; and xi. amino acid residues 282-291 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 282-291 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 60-69 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 60-69 and 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 and 84-95 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 60-69 and 117-127 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 68-78 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 68-78 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 84-95 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the

anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 111-122 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 111-122 and 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122 and 282-291 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 113-123 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-123 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 113-125 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-125 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 117-127 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 117-127 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 282-29 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acid residues selected from the group consisting of M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian Siglec-7 protein corresponding to an amino acid residue selected from the group consisting of M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody competes with one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof for binding to Siglec-7. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain, the heavy chain variable domain, or both comprise at least one, two, three, four, five, or six HVRs selected from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 of a monoclonal antibody selected from: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1,

and 10G8. In some embodiments that may be combined with any of the preceding embodiments: (a) the HVR-L1 comprises an amino acid sequence selected from SEQ ID NOs: 7-19 and 476; (b) the HVR-L2 comprises an amino acid sequence selected from SEQ ID NOs: 20-32 and 477; (c) the HVR-L3 comprises an amino acid sequence selected from SEQ ID NOs: 33-45 and 478; (d) the HVR-H1 comprises an amino acid sequence selected from SEQ ID NOs: 46-58 and 479; (e) the HVR-H2 comprises an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482; or (f) the HVR-H3 comprises an amino acid sequence selected from SEQ ID NOs: 72-84 and 483. In some embodiments that may be combined with any of the preceding embodiments: (a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 7, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 59, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 72; (b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 60, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 73; (c) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 62, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 75; (d) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 37, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 50, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 63, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 76; (e) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 12, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 25, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 38, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 64, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 77; (f) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 13, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 39, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 52, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 65, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 78; (g) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-

L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79; (h) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 480, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74; (i) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 481 and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79; (j) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 41, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 67, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 80; (k) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 42, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 68, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 81; (l) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 82; (m) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83; (n) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 476, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 477, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 478, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83; (o) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino

acid sequence of SEQ ID NO: 479, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 482, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 483; or (p) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 84. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 7, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 59, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 72. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 60, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 73. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 62, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 75. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 37, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 50, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 63, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 76. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 12, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 25, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 38, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 64, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 77. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 13, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 39, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:

52, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 65, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 78. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 480, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 481, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 41, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 67, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 80. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 42, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 68, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 81. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 82. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:

57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 476, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 477, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 478, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 479, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 482, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 483. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 84. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 7-19 and 476, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 7-19 and 476; (b) an HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 20-32 and 477, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 20-32 and 477; and (c) an HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 33-45 and 478, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 33-45 and 478; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 46-58 and 479, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 46-58 and 479; (b) an HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482; and (c) an HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 72-84 and 483, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 72-84 and 483. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7

antibody comprises a light chain variable domain comprising an amino acid sequence selected from SEQ ID NOs: 189-318, 449-461, and 484-489; and/or a heavy chain variable domain comprising an amino acid sequence selected from SEQ ID NOs: 319-448, 462-474, and 490-496. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody comprises a light chain variable domain of a monoclonal antibody selected from: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8; and/or a heavy chain variable domain of a monoclonal antibody selected from: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8.

[0023] Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 39-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of SEQ ID NO: 1; or within amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 39-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. amino acid residues 60-69 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 of SEQ ID NO: 1; ii. amino acid residues 60-69 and 84-95 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 and 84-95 of SEQ ID NO: 1; iii. amino acid residues 60-69 and 117-127 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1; iv. amino acid residues 68-78 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 68-78 of SEQ ID NO: 1; v. amino acid residues 84-95 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 84-95 of SEQ ID NO: 1; vi. amino acid residues 111-122 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 111-122 of SEQ ID NO: 1; vii. amino acid residues 111-122 and 282-291 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 111-122 and 282-291 of SEQ ID NO: 1; viii. amino acid residues 113-123 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 113-123 of SEQ ID NO: 1; ix. amino acid residues 113-125 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 113-125 of SEQ ID NO: 1; x. amino acid residues 117-127 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 117-127 of SEQ ID

NO: 1; and xi. amino acid residues 282-291 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 282-291 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 60-69 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 60-69 and 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 and 84-95 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 60-69 and 117-127 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 68-78 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 68-78 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 84-95 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 111-122 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 111-122 and 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122 and 282-291 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 113-123 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-123 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 113-125 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-125 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the

anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 117-127 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 117-127 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 282-29 of SEQ ID NO: 1. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody binds to one or more amino acid residues selected from the group consisting of M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian Siglec-7 protein corresponding to an amino acid residue selected from the group consisting of M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1.

[0024] Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain, the heavy chain variable domain, or both comprise at least one, two, three, four, five, or six HVRs selected from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 of a monoclonal antibody selected from: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8.

[0025] In some embodiments that may be combined with any of the preceding embodiments: (a) the HVR-L1 comprises an amino acid sequence selected from SEQ ID NOs: 7-19 and 476; (b) the HVR-L2 comprises an amino acid sequence selected from SEQ ID NOs: 20-32 and 477; (c) the HVR-L3 comprises an amino acid sequence selected from SEQ ID NOs: 33-45 and 478; (d) the HVR-H1 comprises an amino acid sequence selected from SEQ ID NOs: 46-58 and 479; (e) the HVR-H2 comprises an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482; or (f) the HVR-H3 comprises an amino acid sequence selected from SEQ ID NOs: 72-84 and 483. In some embodiments that may be combined with any of the preceding embodiments: (a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 7, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 59, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 72; (b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 60, and the HVR-H3 comprises the

amino acid sequence of SEQ ID NO: 73; (c) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 22, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 48, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 61, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74; (d) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 62, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 75; (e) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 37, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 50, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 63, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 76; (f) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 12, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 25, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 38, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 64, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 77; (g) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 13, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 39, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 52, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 65, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 78; (h) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79; (i) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 480, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74; (j) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 481 and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79; (k) the HVR-L1 comprises the amino acid sequence of

SEQ ID NO: 15, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 41, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 67, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 80; (l) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 42, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 68, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 81; (m) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 82; (n) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83; (o) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 476, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 477, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 478, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83; (p) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 479, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 482, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 483; or (q) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 84. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 7, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 59, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 72. In some embodiments that may be combined with any

of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 60, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 73. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 22, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 48, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 61, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 62, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 75. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 37, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 50, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 63, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 76. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 12, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 25, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 38, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 64, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 77. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 13, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 39, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 52, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 65, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 78. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79. In some embodiments that may be combined with any

of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 480, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74. In some embodiments that may be combined with any of the preceding embodiments, he HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 481 and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 41, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 67, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 80. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 42, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 68, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 81. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 82. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 476, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 477, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 478, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83. In some embodiments that may be combined

with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 479, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 482, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 483. In some embodiments that may be combined with any of the preceding embodiments, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 84. In some embodiments, the light chain variable domain comprises: (a) an HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 7-19 and 476, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 7-19 and 476; (b) an HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 20-32 and 477, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 20-32 and 477; and (c) an HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 33-45 and 478, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 33-45 and 478; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 46-58 and 479, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 46-58 and 479; (b) an HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482; and (c) an HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 72-84 and 483, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 72-84 and 483.

[0026] Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 7, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 59, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 72. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain

variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 60, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 73. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the amino acid sequence of SEQ ID NO: 9, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 22, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 48, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 61, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 62, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 75. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 37, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 50, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 63, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 76. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 12, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 25, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 38, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 64, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 77. Other aspects

of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 13, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 39, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 52, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 65, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 78. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 480, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 481 and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid

sequence of SEQ ID NO: 41, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 67, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 80. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 42, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 68, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 81. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 82. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 476, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 477, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 478, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable

domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 479, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 482, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 483. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an HVR-L1, anHVR-L2, and an HVR-L3, and a heavy chain variable domain comprising an HVR-H1, anHVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 84. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an amino acid sequence selected from SEQ ID NOs: 189-318, 449-461, and 484-489; and/or a heavy chain variable domain comprising an amino acid sequence selected from SEQ ID NOs: 319-448, 462-474, and 490-496. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain of a monoclonal antibody selected from: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8; and/or a heavy chain variable domain of a monoclonal antibody selected from: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody competes with one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof for binding to Siglec-7. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody which binds essentially the same Siglec-7 epitope as a monoclonal antibody selected from: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8. Other aspects of the present disclosure relate to an isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 7-19 and 476, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 7-19 and 476; (b) an HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 20-32 and 477, or an amino acid sequence with at least about

90% homology to an amino acid sequence selected from SEQ ID NOs: 20-32 and 477; and (c) an HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 33-45 and 478, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 33-45 and 478; and/or wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 46-58 and 479, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 46-58 and 479; (b) an HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482; and (c) an HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 72-84 and 483, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 72-84 and 483.

[0027] In some embodiments that may be combined with any of the preceding embodiments, the antibody is of the IgG class the IgM class, or the IgA class. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody has an IgG1, IgG2, IgG3, or IgG4 isotype. In some embodiments that may be combined with any of the preceding embodiments, the antibody binds an inhibitory Fc receptor. In some embodiments that may be combined with any of the preceding embodiments, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In some embodiments that may be combined with any of the preceding embodiments: (a) the anti-Siglec-7 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: 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 or Kabat numbering, or comprises an amino acid deletion in the Fc region at a position corresponding to glycine 236; (b) the anti-Siglec-7 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: 475), 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-7 antibody has an IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from: 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 or Kabat numbering; (d) the anti-Siglec-7 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: 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 or Kabat numbering; or (e) the anti-Siglec-7 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 or, Kabat numbering. In some embodiments that may be combined with any of the preceding embodiments: (a) the anti-Siglec-7 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: N297A, N297Q, D270A, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; (b) the anti-Siglec-7 antibody has an IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from: P238S , V234A, G237A, H268A, H268Q, H268E, V309L, N297A, N297Q, A330S, P331S, C232S, C233S, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; or (c) the anti-Siglec-7 antibody has an IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from: E233P, F234V, L234A/F234A, L235A, G237A, E318A, S228P, L236E, S241P, L248E, T394D, M252Y, S254T, T256E, N297A, N297Q, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In some embodiments that may be combined with any of the preceding embodiments: (a) the Fc region further comprises one or more additional amino acid substitutions at a position selected from A330L, L234F; L235E, P331S, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; (b) the Fc region further comprises one or more additional amino acid substitutions at a position selected from M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; or (c) the Fc region further comprises a S228P amino acid substitution according to EU or Kabat numbering. In some embodiments that may be combined with any of the preceding embodiments, the antibody has an IgG4 isotype. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody comprises an S228P amino acid substitution at residue position 228, an F234A amino acid substitution at residue position 234, and an L235A amino acid substitution at residue position 235, wherein the numbering of the residue position is according to EU numbering.

In some embodiments that may be combined with any of the preceding embodiments, the antibody has an IgG4 isotype and comprises an S228P amino acid substitution at residue position 228, an F234A amino acid substitution at residue position 234, and an L235A amino acid substitution at residue position 235, wherein the numbering of the residue position is according to EU numbering. In some embodiments that may be combined with any of the preceding embodiments, the Siglec-7 protein is a mammalian protein or a human protein. In some embodiments that may be combined with any of the preceding embodiments, the Siglec-7 protein is a wild-type protein. In some embodiments that may be combined with any of the preceding embodiments, the Siglec-7 protein is a naturally occurring variant. In some embodiments that may be combined with any of the preceding embodiments, the Siglec-7 protein is expressed on one or more cells selected from human dendritic cells, human macrophages, human neutrophils, human NK cells, human monocytes, human osteoclasts, human T cells, human T helper cell, human cytotoxic T cells, human granulocytes, and human microglia. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds specifically to a mammalian Siglec-7 protein, human Siglec-7 protein, or both. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds Siglec-7 in a pH dependent manner. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds Siglec-7 at a pH that ranges from 5.5 to 8.0. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody dissociates from Siglec-7 at a pH of less than 5.0. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody is an antibody fragment that binds to an epitope comprising amino acid residues on human Siglec-7 or a mammalian Siglec-7 protein. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody is an antibody fragment that binds to one or more human proteins selected from human Siglec-7, a naturally occurring variant of human Siglec-7, and a disease variant of human Siglec-7. In some embodiments that may be combined with any of the preceding embodiments, the antibody fragment is cross-linked to a second antibody fragment that binds to one or more human proteins selected from human Siglec-7, a naturally occurring variant of human Siglec-7, and a disease variant of human Siglec-7. In some embodiments that may be combined with any of the preceding embodiments, the fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv, or scFv fragment. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody is a murine antibody. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody is a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody is a bispecific antibody

recognizing a first antigen and a second antigen. In some embodiments that may be combined with any of the preceding embodiments, the first antigen is Siglec-7 and the second antigen is: (a) an antigen facilitating transport across the blood-brain-barrier; (b) an antigen facilitating transport across the blood-brain-barrier selected from transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopep peptide, and ANG1005; (c) a disease-causing agent selected from disease-causing peptides or proteins or, disease-causing nucleic acids, wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides; (d) ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27 , GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, and phosphatidylserine; and (e) a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody is a conjugated antibody. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody is conjugated to a detectable marker, a toxin, or a therapeutic agent. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody is conjugated to a toxin selected from ricin, ricin A-chain, doxorubicin, daunorubicin, a maytansinoid, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin, diphtheria toxin, *Pseudomonas* exotoxin (PE) A, PE40, abrin, abrin A chain, modeccin A chain, alpha-sarcin, gelonin, mitogellin, retstrictocin, phenomycin, enomycin, curicin, crotin, calicheamicin, *Saponaria officinalis* inhibitor, glucocorticoid, auristatin, auromycin, yttrium, bismuth, combrestatin, duocarmycins, dolastatin, cc1065, and a cisplatin. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody is used in combination with one or

more antibodies that specifically bind a disease-causing agent selected from disease-causing peptides, disease-causing proteins, amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and any combination thereof; or with one or more antibodies that bind an immunomodulatory protein selected from: PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27 , GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, TREM1, TREM2, CD33, Siglec-5, Siglec-9, Siglec-11, phosphatidylserine, disease-causing nucleic acids, antisense GGCCCC (G2C4) repeat-expansion RNA, and any combination thereof. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody has a dissociation constant (K_D) for human Siglec-7 and mammalian Siglec-7 that ranges from about 10 nM to about10 pM, or less than 10 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody has a dissociation constant (K_D) for human Siglec-7 that ranges from about 9.5 nM to about 17 pM, or less than 17 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to human dendritic cells with an EC_{50} that ranges from 2 nM to 100 pM. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to human dendritic cells with an EC_{50} that ranges from 1.4 nM to 300 pM. In some embodiments, the EC_{50} for binding to human dendritic cells is determined at a temperature of approximately 4°C. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 with an EC_{50} that ranges from 500 pM to 18 pM. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 with an EC_{50} that ranges from 350 pM to 33 pM. In some embodiments, the EC_{50} is determined at a temperature of approximately 37°C.

[0028] Other aspects of the present disclosure relate to an isolated nucleic acid comprising a nucleic acid sequence encoding the anti-Siglec-7 antibody of any of the preceding embodiments.

Other aspects of the present disclosure relate to a vector comprising the nucleic acid of any of the preceding embodiments. Other aspects of the present disclosure relate to an isolated host cell comprising the vector of any of the preceding embodiments. Other aspects of the present disclosure relate to a method of producing an anti-Siglec-7 antibody, comprising culturing the host cell of any of the preceding embodiments so that the anti-Siglec-7 antibody is produced. In some embodiments, the method further comprises recovering the anti-Siglec-7 antibody produced by the host cell. Other aspects of the present disclosure relate to an isolated anti-Siglec-7 antibody produced by the method of any of the preceding embodiments. Other aspects of the present disclosure relate to a pharmaceutical composition comprising the anti-Siglec-7 antibody of any of the preceding embodiments, and a pharmaceutically acceptable carrier.

[0029] Other aspects of the present disclosure relate to a method of preventing, reducing risk, or treating a disease, disorder, or injury selected from 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, and 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, tumors that express one or more Siglec-7 ligands, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7

ligands, or both. In some embodiments, the cancer is selected from the group consisting of 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), and multiple myeloma. Other aspects of the present disclosure relate to an agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both for use in preventing, reducing risk, or treating a disease, disorder, or injury selected from 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, and 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, tumors that express one or more Siglec-7 ligands, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza. Other aspects of the present disclosure relate to use of an agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both in the manufacture of a medicament for preventing, reducing risk, or treating a disease, disorder, or injury selected from 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, and 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, tumors that express one or more Siglec-7 ligands, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza. In some embodiments, the agent is selected from an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In some embodiments, the agent is an isolated anti-Siglec-7 antibody. In some embodiments, the anti-Siglec-7 antibody is the anti-Siglec-7 antibody of any of the preceding embodiments. In some embodiments, the one or more immune cells are selected from dendritic cells, macrophages, neutrophils, NK cells, microglia, T cells, T helper cells, cytotoxic T cells, and any combination thereof. Other aspects of the present disclosure relate to a method of preventing, reducing risk, or treating a disease, disorder, or injury selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, taupathy disease, infections, and cancer, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both. Other aspects of the present disclosure relate to an agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both for use in preventing, reducing risk, or treating a disease, disorder, or injury selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, taupathy disease, infections, and cancer. Other aspects of the present disclosure relate to use of an agent that decreases cellular levels of Siglec-7, inhibits

interaction between Siglec-7 and one or more Siglec-7 ligands, or both in the manufacture of a medicament for preventing, reducing risk, or treating a disease, disorder, or injury selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, taupathy disease, infections, and cancer.

[0030] In some embodiments that may be combined with any of the preceding embodiments, the disease, disorder, or injury is cancer, and wherein the agent inhibits one or more Siglec-7 activities selected from: (a) promoting proliferation, maturation, migration, differentiation, and/or functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated suppressor neutrophils, tumor-associated suppressor NK cells, and regulatory T cells; (b) enhancing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated suppressor neutrophils, tumor-associated suppressor NK cells, and regulatory T cells into tumors; (c) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; (d) enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); (e) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; (f) increasing tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes; (g) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (h) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (i) decreasing infiltration of tumor-specific NK cells with tumor killing potential; (j) decreasing the tumor killing potential of NK cells; (k) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (l) increasing tumor volume; (m) increasing tumor growth rate; (n) increasing metastasis; (o) increasing rate of tumor recurrence; (p) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more target proteins selected from PD1/PDL1, CTLA4, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27 , GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, and any combination thereof, or one or more cancer vaccines; (q) inhibition of PLCγ/PKC/calcium mobilization; and (r) inhibition of PI3K/Akt, Ras/MAPK signaling. In some embodiments that may be combined with any of the preceding embodiments, the cancer expresses Siglec-7 or one or more Siglec-7 ligands. In some embodiments that may be combined with any of the preceding embodiments, the cancer is selected from 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), and multiple myeloma. In some embodiments that may be combined with any of the preceding embodiments, the agent exhibits one or more activities selected from the group consisting of: (a) increasing the number of tumor infiltrating $CD3^+$ T cells; (b) inhibiting Siglec-7 binding to one or more Siglec-7 ligands; (c) decreasing cellular levels of Siglec-7 in peripheral immune cells; (d) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in blood; (e) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in the tumor; (f) reducing PD-L1 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (g) reducing PD-L2 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (h) reducing CD11b levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (i) reducing B7-H3 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (j) reducing CD200R levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (k) reducing CD163 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (l) reducing CD206 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (m) decreasing tumor growth rate of solid tumors; (n) reducing tumor volume; (o) increasing efficacy of one or more PD-1 inhibitors; (p) increasing efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, optionally wherein the one or more checkpoint inhibitor therapies and/or immune-modulating therapies target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, LAG3, or any combination thereof; (q) inhibiting differentiation, survival, and/or one or more functions of non-tumorigenic myeloid-derived suppressor cells (MDSC); (r) inducing cell death of one or more myeloid-derived suppressor cells (MDSC); and (s) increasing proliferation of T cells in the presence of non-tumorigenic myeloid-derived suppressor cells (MDSC).

[0031] Other aspects of the present disclosure relate to a method of inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an agent that that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both. Other aspects of the present disclosure relate to an agent

that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both for use in inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof. Other aspects of the present disclosure relate to use of an agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both in the manufacture of a medicament for inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof. In some embodiments, the agent is selected from an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In some embodiments, the agent is an isolated anti-Siglec-7 antibody. In some embodiments, the anti-Siglec-7 antibody is the anti-Siglec-7 antibody of any of the preceding embodiments. In some embodiments, the one or more immune cells are selected from dendritic cells, macrophages, neutrophils, NK cells, microglia, T cells, T helper cells, cytotoxic T cells, and any combination thereof.

[0032] Other aspects of the present disclosure relate to a method of decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an agent that binds or interacts with Siglec-7. Other aspects of the present disclosure relate to use of an agent that binds or interacts with Siglec-7 for use in decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual in need thereof. Other aspects of the present disclosure relate to use of an agent that binds or interacts with Siglec-7 in the manufacture of a medicament for decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual in need thereof. In some embodiments, the e agent is an isolated anti-Siglec-7 antibody or anti-Siglec-7 antibody conjugate. In some embodiments, the anti-Siglec-7 antibody is the anti-Siglec-7 antibody of any of the preceding embodiments.

[0033] Other aspects of the present disclosure relate to a method of decreasing cellular levels of Siglec-7 on one or more cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated anti-Siglec-7 antibody. Other aspects of the present disclosure relate to use of an isolated anti-Siglec-7 antibody for use in decreasing cellular levels of Siglec-7 on one or more cells in an individual in need thereof. Other aspects of the present disclosure relate to use of an isolated anti-Siglec-7 antibody in the manufacture of a medicament for decreasing cellular levels of Siglec-7 on one or more cells in an individual in need thereof. In some embodiments, the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 *in vivo*. In some embodiments, the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 with an EC_{50} that ranges from 500 pM to 18 pM. In some embodiments, the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 with an EC_{50} that ranges from 350 pM to 33 pM. In some embodiments, the EC_{50} is determined at a temperature of approximately 37°C. In some embodiments, the anti-Siglec-7 antibody has a dissociation constant (K_D) for human Siglec-7 that ranges from about 10 nM to 10 pM, or less than 10 pM. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody has a dissociation constant (K_D) for human Siglec-7 that ranges from about 9.5 nM to about 17 pM, or less than 17 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments, the anti-Siglec-7 antibody binds to human dendritic cells with an EC_{50} that ranges from 2 nM to 100 pM. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody binds to human dendritic cells with an EC_{50} that ranges from 1.4 nM to 300 pM. In some embodiments, the an EC_{50} for binding to human dendritic cells is determined at a temperature of approximately 4°C. In some embodiments, the anti-Siglec-7 antibody is the anti-Siglec-7 antibody of any of the preceding embodiments.

[0034] In some embodiments that may be combined with any of the preceding embodiments, the method further comprising administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or one or more standard or investigational anti-cancer therapies. In some embodiments that may be combined with any of the preceding embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the anti-Siglec-7 antibody. In some embodiments that may be combined with any of the preceding embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti- B- and T-lymphocyte attenuator (BTLA) antibody, an anti-Killer inhibitory receptor (KIR) antibody, an anti-GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, an anti-TNFa

antibody,

an anti-CD33 antibody, an anti-Siglec-5 antibody, an anti-Siglec-9 antibody, an anti-Siglec-11 antibody, an antagonistic anti-TREM1 antibody, an antagonistic anti-TREM2 antibody, and any combination thereof. In some embodiments that may be combined with any of the preceding embodiments, the one or more standard or investigational anti-cancer therapies are selected from radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib therapy, trastuzumab therapy, etanercept therapy, adoptive cell transfer (ACT) therapy, chimeric antigen receptor T cell transfer (CAR-T) therapy, vaccine therapy, and cytokine therapy. In some embodiments that may be combined with any of the preceding embodiments, the method further comprising administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some embodiments that may be combined with any of the preceding embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the anti-Siglec-7 antibody. In some embodiments that may be combined with any of the preceding embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is selected from an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof. In some embodiments that may be combined with any of the preceding embodiments, the method further comprising administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In some embodiments that may be combined with any of the preceding embodiments, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the anti-Siglec-7 antibody. In some embodiments that may be combined with any of the preceding embodiments, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonistic anti-TREM1 antibody, an agonistic anti-TREM2 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, and any combination thereof. In some embodiments that may be combined with any of the preceding embodiments, the method further comprising administering to the individual at least one stimulatory cytokine. In some embodiments that may be combined with any of the preceding embodiments, the at least one stimulatory cytokine is administered in combination with the anti-Siglec-7 antibody. In some embodiments that may be combined with any of the preceding embodiments, the at least one stimulatory cytokine is selected from IFN-a4, IFN-b, IL-1β, TNF-α, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, IL-33, MCP-1, MIP-1-beta, and any combination thereof.

[0035] Other aspects of the present disclosure relate to a method of assessing responsiveness of an individual to an agent that binds or interacts with Siglec-7, the method comprising: a) measuring the expression levels of $CD45^+$ and $CD14^+$ on non-tumorigenic myeloid cells in a blood sample obtained from the individual prior to administering to the individual an agent that binds or interacts with Siglec-7; b) administering to the individual a therapeutically effective amount of the agent; and c) measuring the expression levels of $CD45^+$ and $CD14^+$ on non-tumorigenic myeloid cells in a blood sample obtained from the individual after administration of the agent. In some embodiments, a reduction in the levels of $CD45^+$ and $CD14^+$ on non-tumorigenic myeloid cells after administration of the agent that binds or interacts with Siglec-7 indicates the individual is responsive to the agent. In some embodiments, the method further comprises administering one or more additional therapeutically effective amounts of the agent. In some embodiments, the agent is selected from the group consisting of an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and peptide. In some embodiments, the agent is an isolated anti-Siglec-7 antibody or anti-Siglec-7 antibody-conjugate. In some embodiments, the anti-Siglec-7 antibody is any of the anti-Siglec-7 antibodies disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] **FIG. 1A** depicts an amino acid sequence alignment between human Siglec-7 (SEQ ID NO: 1), chimpanzee Siglec-7 (SEQ ID NO: 2), pygmy chimpanzee Siglec-7 (SEQ ID NO: 3), orangutan Siglec-7 (SEQ ID NO: 4), gorilla Siglec-7(SEQ ID NO: 5), and gibbon Siglec-7 (SEQ ID NO: 6). An asterisk ("*") indicates positions which have a single, fully conserved residue; A colon (":") indicates conservation between groups of strongly similar properties - scoring > 0.5 in the Gonnet PAM 250 matrix; and a period (".") indicates conservation between groups of weakly similar properties - scoring =< 0.5 in the Gonnet PAM 250 matrix. **FIG. 1B** depicts the 3D structure of Siglec-7. Amino acid residues 19-150 of the Siglec-7 amino acid sequence of SEQ ID NO: 1 are depicted in a cartoon representation. Also depicted is a cartoon rendering of an epitope for antibody 4A1. The binding region ^{113}ARMSDAGRYFFRM^{125} (SEQ ID NO: 1) is listed in the figure. The protein surface of Siglec-7 is shown as mesh.

[0037] **FIG. 1C** depicts a cartoon rendering of binding sites of a discontinuous epitope for antibodies 2G4, 3E11, 10B5, 2G1, and 7F12.The discontinuous binding regions ^{60}PVHGYWFRAG^{69} (SEQ ID NO: 1) and ^{117}DAGRYFFRMEK^{127} (SEQ ID NO: 1) are listed in the figure. **FIG. 1D** depicts a cartoon rendering of binding sites of a discontinuous epitope for antibody 10G8 antibodies 2G4, 3E11, 10B5, 2G1, and 7F12.The discontinuous binding regions ^{60}PVHGYWFRAG^{69} (SEQ ID NO: 1) and ^{84}AWAVQEETRDRF^{95} (SEQ ID NO: 1) are listed in the figure. **FIG. 1E** depicts a cartoon rendering of an epitope for antibody 4A1. The binding region ^{113}ARMSDAGRYFFRM^{125}

(SEQ ID NO: 1) is listed in the figure. Binding sites of a conformational epitope for antibody 7E11 is also depicted. The binding regions ^{68}AGNDISWKAPV^{78} (SEQ ID NO: 1) is listed in the figure. **FIG. 1F** depicts binding reactivity in percentage to wild-type Siglec-7 (% WT) of antibodies of the present disclosure to the indicated Siglec-7 mutants. **FIG. 1G** depicts models of Siglec-7 indicating amino acid residues involved in antibody binding. Critical residues for binding are indicated with red spheres; secondary residues for binding are indicated with pink spheres.

[0038] **FIG. 2** shows glycan-binding specificities of human Siglec proteins, such as Siglec-7. This figure shows a summary of the most commonly reported specificities for the most commonly studied sialylated glycans. Relative binding within studies of each Siglec is indicated as ++, strong binding; +, detectable binding; and –, very weak or undetectable binding. Not shown is the recently reported strong-binding preference of hSiglec-8 and mSiglec-F for 6′-sulfated-sialyl-Lewis x (sLex) and of hSiglec-9 for 6-sulfated-sLex. With a few exceptions (CD22 and MAG), results of binding specificity studies of human Siglecs by different investigators using different assays have varied significantly. In addition to assay formats and glycan linker issues, the density and arrangement of the ligands studied could be responsible for this variation (Varki et al., (2006) Glycobiol. 16:1R-27R).

[0039] **FIG. 3** shows the structure and metabolism of disialogangliosides in mammalian brain. The nomenclature of disialogangliosides in the figure follows the system of Svennerholm (1964) J. Lipid Res. 5:145–155 (Ariga T et al. (2008) J. Lipid Res. 49:1157-1175).

[0040] **FIG. 4** depicts results of FACS analysis demonstrating Siglec-7 expression in human primary immune cells.

[0041] **FIG. 5A** depicts FACS analysis of Siglec-7 antibodies binding to human primary dendritic cells compared to isotype controls. **FIG. 5B** depicts a 12-point titration curve to assess binding and calculate the half-maximal effective concentration values (EC_{50}) for binding of Siglec-7 antibodies 4E3 and 10B5 to the surface of primary human dendritic cells.

[0042] **FIG. 6A** depicts Biacore sensorgrams showing binding affinity of Siglec-7 antibodies of the present disclosure to purified Siglec-7-his tagged protein. **FIG. 6B** shows a schematic for combining antibody light chain variable region (VL) sequences of humanized versions of anti-Siglec-7 antibody 4E3 (mAb S7-4E3). Additioanl variations are listed below each sequence. The figure includes sequences for versions of humanized antibody 4E3. IGKV3-11*01 (SEQ ID NO: 497); Joining region (SEQ ID NO: 498); S7-4E3 (SEQ ID NO: 499); 3-11*01 (SEQ ID NO: 500); h4E3-L1 (SEQ ID NO: 501); h4E3-L2 (SEQ ID NO: 502); h4E3-L3 (SEQ ID NO: 503). **FIG. 6C** shows a schematic for combining antibody heavy chain variable region (VH) sequences of humanized versions of anti-Siglec-7 antibody 4E3 (mAb S7-4E3). Additioanl variations are listed below each sequence. The figure includes sequences for versions of humanized antibody 4E3. IGHV3-21*01

(SEQ ID NO: 504); Joining region (SEQ ID NO: 505); S7-4E3 (SEQ ID NO: 506); 3-21*01 (SEQ ID NO: 507); h4E3-H1 (SEQ ID NO: 508); h4E3-H2 (SEQ ID NO: 509); h4E3-H3 (SEQ ID NO: 510). **FIG. 6D** shows a schematic for combining antibody light chain variable region (VL) sequences of humanized versions of anti-Siglec-7 antibody 10B5 (mAb S7-10B5). Additioanl variations are listed below each sequence. The figure includes sequences for versions of humanized antibody 10B5. IGKV1-39*01 (SEQ ID NO: 511); Joining region (SEQ ID NO: 512); S7-10B5.1 (SEQ ID NO: 513); 1-39*01 (SEQ ID NO: 514); h10B5-L1 (SEQ ID NO: 515); h10B5-L2 (SEQ ID NO: 516); h10B5-L3 (SEQ ID NO: 517). **FIG. 6E** shows a schematic for combining antibody heavy chain variable region (VH) sequences of humanized versions of anti-Siglec-7 antibody 10B5 (mAb S7-10B5). Additioanl variations are listed below each sequence. The figure includes sequences for versions of humanized antibody 10B5. IGHV1-46*01 (SEQ ID NO: 518); Joining region (SEQ ID NO: 519); S7-10B5.1 (SEQ ID NO: 520); 1-46*01 (SEQ ID NO: 521); h10B5-H1 (SEQ ID NO: 522); h10B5-H2 (SEQ ID NO: 523); h10B5-H3 (SEQ ID NO: 524); h10B5-H4 (SEQ ID NO: 525). For **FIG. 6B-6E**, CDR sequences are depicted in bold; residue numbering shown as sequential (seq) or according to Chothia; "b" refers to buried sidechain; "p" refers to partially buried; "i" refers to sidechain at interface between VH and VL domains; sequence differences between human and murine germlines are noted by an asterisk (*); potential additional mutations in frameworks are noted below the sequence; potential changes in CDR sequences are noted below each CDR sequence (such changes may prevent asparagine (N) deamidation, tryptophan (W) oxidation, or isoaspartate (DG) formation).

[0043] **FIG. 7A-7N** depict Siglec-7 antibody-dependent downregulation of cell surface Siglec-7 receptor *in vitro* and *in vivo*. **FIG. 7A** depicts U937 histiocytic lymphoma. **FIG. 7B** depicts human primary monocytes. **FIG. 7C** depicts human primary dendritic cells. **FIG. 7D** depicts human primary macrophages. **FIG. 7E** depicts human primary natural killer (NK) cells. **FIG. 7F** depicts human primary monocyte-derived microglia. **FIG. 7G** depicts levels of Siglec-7 surface expression and TREM2 surface expression on human dendritic cells after treatment with an anti-Siglec-7 antibody 10B5 or an isotype control antibody, as compared to a no antibody control. **FIG. 7H** depicts levels of CD11c surface expression, Siglec-7 surface expression, and TREM2 surface expression on human dendritic cells after treatment with an anti-Siglec-7 antibody 10B5. **FIG. 7I** depicts Siglec-7 and CD33 expression in peripheral blood samples from humanized NOG mice 14 days after treatment with anti-Siglec-7 antibodies of the present disclosure. **FIG. 7J** shows *in vivo* reduction in cell surface levels of Siglec-7 following antibody treatment *in vivo*. **FIG. 7K** shows expression of unrelated receptor CD33. CD33 was used as a control. Cell surface levels of CD33 were not significantly reduced following antibody treatment *in vivo*. **FIG. 7L** shows FACS gating strategy for blood samples from humanized NOG mice 14 days after treatment with anti-Siglec-7 antibodies of the present disclosure. **FIG. 7M** depicts a 12-point titration curve showing the half-maximal effective

concentration (EC_{50}) of Siglec-7 antibodies 4E3 and 10B5 for reducing cell surface expression of Siglec-7. **FIG. 7N** depicts a 12-point titration curve showing the half-maximal effective concentration (EC_{50}) of Siglec-7 antibodies 4E3 and 10B5 for reducing cell surface expression of CD11c.

[0044] **FIG. 8** depicts results demonstrating that Siglec-7 antibodies of the present disclosure can block binding of Siglec-7 ligand that is expressed on red blood cells to plate immobilized Siglec-7-Fc protein.

[0045] **FIG. 9** depicts FACS analysis showing that sialic acid ligands on dendritic cells restrict T cell proliferation during mixed lymphocyte reaction with human primary cells.

[0046] **FIG. 10** depicts results showing that sialic acid Siglec-7 ligands on dendritic cells restrict T cell proliferation during mixed lymphocyte reaction.

[0047] **FIG. 11A-11H** depict results showing Siglec-7 receptor and increased Siglec-7 ligand expression on human myeloid cells induced by various stimuli. **FIG. 11A and 11B** depict results showing Siglec-7 receptor and increased Siglec-7 ligand expression on human primary dendritic cells after treatment with tumor supernatant. **FIG. 11C and 11D** depict results showing increased Siglec-7 ligand expression on human primary dendritic cells after treatment with tumor supernatant. **FIG. 11E and 11F** depict results showing Siglec-7 receptor expression on human dendritic cells during LPS-induced inflammation. **FIG. 11G and 11H** depict results showing an increase in sialic acid expression on human myeloid cells during LPS-induced inflammation. These finding indicate that tumors can evade immune surveillance by upregulating the level of inhibitory ligands to Siglec-7 on the tumor cells and on immune cells.

[0048] **FIG. 12** depicts results showing that sialidase treatment to remove Siglec-7 ligands from *E. coli* increases phagocytosis by human primary dendritic cells.

[0049] **FIG. 13A and 13B** depict Siglec-7 ligand expression in brain sections from an Alzheimer's disease brain (AD) and a healthy brain (non-AD). **FIG. 13A** depicts immunohistochemistry staining of Siglec-7-Fc in AD and non-AD brain samples from two donors (Donor 1 and Donor 2). **FIG 13B** depicts results of one-way ANOVA statistical analysis of Siglec-7-Fc staining from 5 AD and 5 non-AD brain samples, indicating that inhibitory Siglec-7 ligand is upregulated and contributes to AD pathology.

[0050] **FIG. 14** depicts results showing that expression of inhibitory Siglec-7 ligands is increased in lung tumor cells, melanoma cells, and colon cancer cells. The results indicate that inhibitory Siglec-7 ligands contribute to cancer pathology in these tumor types.

[0051] **FIG. 15** depicts expression of Siglec-7 in cells of NOG mice injected with human peripheral blood cells. 12 weeks after engraftment with human fetal liver $CD34^+$ cells, humanized mice were transplanted with patient-derived melanoma. Peripheral blood, spleen, and tumor tissues were dissociated and analyzed for immune cell markers and Siglec-7 expression. For FACS analysis,

human hematopoietic cells were identified by CD45 expression, then gated CD14+, CD3+ populations. The results indicate that inhibitory Siglec-7 ligands contribute to cancer pathology in this tumor type.

[0052] **FIG. 16A** depicts a PD-1/Siglec-7 combination antibody treatment protocol for a mouse model of patient-derived cancer in immunologically humanized mice. **FIG. 16B** depicts tumor volume after antibody treatment in individual mice that were engrafted with human immune stem cells. Mice were treated either with Keytruda® (pembrolizumab) anti-PD-1 antibody alone or in combination with anti-Siglec-7 antibody 10B5. **FIG. 16C** depicts mean tumor volume after treatment for 28 days with Keytruda® (pembrolizumab) anti-PD-1 antibody alone or in combination with anti-Siglec-7 antibody 10B5 in mice that were engrafted with human immune stem cells. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$ for Keytruda® (pembrolizumab) + 10B5 vs Keytruda® (pembrolizumab). Means per treatment groups are presented. Error bars represent SEM. **FIG. 16D** depicts the mean tumor volume after treatment for 28 days with Keytruda® (pembrolizumab) anti-PD-1 antibody alone or in combination with anti-Siglec-7 antibody 10B5 in mice that were engrafted with human immune stem cells from the human donor 984480112. Means per treatment groups are presented. Error bars represent SEM. **FIG. 16E** depicts the mean tumor volume after treatment for 28 days with Keytruda® (pembrolizumab) anti-PD-1 antibody alone or in combination with anti-Siglec-7 antibody 10B5 in mice that were engrafted with human immune stem cells from either of the human donors 165547112 or 17509112. **: $p<0.01$ for Keytruda® (pembrolizumab) + 10B5 vs Keytruda® (pembrolizumab). Means per treatment groups are presented. Error bars represent SEM. **FIG. 16F** depicts *in vivo* reduction in cell surface levels of Siglec-7 in peripheral blood human (h) $CD45^+CD14^+$ myeloid cells from mice treated with Keytruda® (pembrolizumab) anti-PD-1 antibody alone or in combination with anti-Siglec-7 antibody 10B5. ***: $p<0.001$ for Keytruda® (pembrolizumab) + 10B5 vs Keytruda® (pembrolizumab), correcting for donor and day of animal sacrifice. +: mean; boxplot midline: median; upper and lower boundaries of the boxes correspond to the first and third quartiles (25th and 75th percentiles). **FIG. 16G** depicts *in vivo* reduction in tumor infiltrating human (h) $CD45^+$ $CD14^+$ myeloid cells from mice treated with Keytruda® (pembrolizumab) anti-PD-1 antibody alone or in combination with anti-Siglec-7 antibody 10B5. ***: $p<0.001$ for Keytruda® (pembrolizumab) + 10B5 vs Keytruda® (pembrolizumab), correcting for donor. +: mean; boxplot midline: median; upper and lower boundaries of the boxes correspond to the first and third quartiles (25th and 75th percentiles). **FIG. 16H** depicts *in vivo* increase in tumor infiltrating human (h) $CD45^+$ $CD3^+$ T cells from mice treated with Keytruda® (pembrolizumab) anti-PD-1 antibody alone or in combination with anti-Siglec-7 antibody 10B5. ***: $p<0.001$ for Keytruda® (pembrolizumab) + 10B5 vs Keytruda® (pembrolizumab), correcting for donor. +: mean; boxplot midline: median; upper and lower boundaries of the boxes correspond to the first and third

quartiles (25th and 75th percentiles). **FIG. 16I** depicts *in vivo* reduction in peripheral blood human (h) $CD45^+$ $CD14^+$ myeloid cells from mice treated with Keytruda® (pembrolizumab) anti-PD-1 antibody alone or in combination with anti-Siglec-7 antibody 10B5. **: $p<0.01$ for Keytruda® (pembrolizumab) + 10B5 vs Keytruda® (pembrolizumab), correcting for donor. +: mean; boxplot midline: median; upper and lower boundaries of the boxes correspond to the first and third quartiles (25th and 75th percentiles).

[0053] **FIG. 17A** depicts change in expression quantified by mean fluorescence intensity (MFI) of PD-L1, PD-L2, CD200R, B7-H3, Siglec-7, and CD206 between myeloid-derived suppressor cells (MDSCs) treated with isotype control antibody (mIgG1) compared to cells treated with anti-Siglec-7 antibody 10B5. **FIG. 17B** depicts change in expression quantified by mean fluorescence intensity (MFI) of CD200R, CD163, PD-L2, B7-H3, PD-L1, CD11b, and Siglec-7 between myeloid-derived suppressor cells (MDSCs) treated with isotype control antibody (mIgG1) compared to cells treated with anti-Siglec-7 antibody 4E3. **FIG. 17C** depicts the percentage of activated T cell proliferation in the absence and presence of co-cultured myeloid-derived suppressor cells (MDSCs). Additionally, co-cultured T cells/MDSCs were left untreated, or were treated with anti-Siglec-7 antibody 4E3, a mouse isotype control antibody (mIgG1), or an anti-PD-L1 antibody (PDL1). ****: $p<0.00001$. **FIG. 17D** depicts the percentage of activated T cell proliferation for T cells treated with glioblastoma-conditioned media, cultured in the absence and presence of co-cultured myeloid-derived suppressor cells (MDSCs). Additionally, co-cultured T cells/MDSCs were left untreated, or were treated with anti-Siglec-7 antibody 4E3, a mouse isotype control antibody (mIgG1), or an anti-PD-L1 antibody (PDL1). **: $p<0.01$; ***: $p<0.001$.

[0054] **FIG. 18** depicts results showing anti-Siglec-7 antibodies 4E3 and 10B5 selectively kill a subset of myeloid-derived suppressor cells (MDSCs). Top row: Live/Dead Gates by cell morphology: increase in dead cell gate with S7-4E3 and S7-10B5. Middle row: Gating on Live/Dead cells using dye: Dye HIGH positive cells are DEAD, dye low cells are alive. Histograms: showing Live/Dead cell dye in histogram format.

DETAILED DESCRIPTION OF THE INVENTION

General techniques

[0055] The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodology by those skilled in the art, such as, for example, the widely utilized methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 3d edition (2001) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; *Current Protocols in Molecular Biology* (F.M. Ausubel, et al. eds., (2003)); the series *Methods in Enzymology* (Academic Press, Inc.): *PCR 2: A Practical Approach* (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)), Harlow and Lane, eds. (1988) *Antibodies, A Laboratory Manual*, and

Animal Cell Culture (R.I. Freshney, ed. (1987)); *Oligonucleotide Synthesis* (M.J. Gait, ed., 1984); *Methods in Molecular Biology*, Humana Press; *Cell Biology: A Laboratory Notebook* (J.E. Cellis, ed., 1998) Academic Press; *Animal Cell Culture* (R.I. Freshney), ed., 1987); *Introduction to Cell and Tissue Culture* (J.P. Mather and P.E. Roberts, 1998) Plenum Press; *Cell and Tissue Culture: Laboratory Procedures* (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., 1993-8) J. Wiley and Sons; *Handbook of Experimental Immunology* (D.M. Weir and C.C. Blackwell, eds.); *Gene Transfer Vectors for Mammalian Cells* (J.M. Miller and M.P. Calos, eds., 1987); *PCR: The Polymerase Chain Reaction*, (Mullis et al., eds., 1994); *Current Protocols in Immunology* (J.E. Coligan et al., eds., 1991); *Short Protocols in Molecular Biology* (Wiley and Sons, 1999); *Immunobiology* (C.A. Janeway and P. Travers, 1997); *Antibodies* (P. Finch, 1997); *Antibodies: A Practical Approach* (D. Catty., ed., IRL Press, 1988-1989); *Monoclonal Antibodies: A Practical Approach* (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); *Using Antibodies: A Laboratory Manual* (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); *The Antibodies* (M. Zanetti and J. D. Capra, eds., Harwood Academic Publishers, 1995); and *Cancer: Principles and Practice of Oncology* (V.T. DeVita et al., eds., J.B. Lippincott Company, 1993).

Definitions

[0056] As used herein, the term "*preventing*" includes providing prophylaxis with respect to occurrence or recurrence of a particular disease, disorder, or condition in an individual. An individual may be predisposed to, susceptible to a particular disease, disorder, or condition, or at risk of developing such a disease, disorder, or condition, but has not yet been diagnosed with the disease, disorder, or condition.

[0057] As used herein, an individual "*at risk*" of developing a particular disease, disorder, or condition may or may not have detectable disease or symptoms of disease, and may or may not have displayed detectable disease or symptoms of disease prior to the treatment methods described herein. "At risk" denotes that an individual has one or more risk factors, which are measurable parameters that correlate with development of a particular disease, disorder, or condition, as known in the art. An individual having one or more of these risk factors has a higher probability of developing a particular disease, disorder, or condition than an individual without one or more of these risk factors.

[0058] As used herein, the term "*treatment*" refers to clinical intervention designed to alter the natural course of the individual being treated during the course of clinical pathology. Desirable effects of treatment include decreasing the rate of progression, ameliorating or palliating the pathological state, and remission or improved prognosis of a particular disease, disorder, or condition. An individual is successfully "treated", for example, if one or more symptoms associated with a particular disease, disorder, or condition are mitigated or eliminated.

[0059] An "*effective amount*" refers to at least an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result. An effective amount can be provided in one or more administrations. An effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the treatment to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. An effective amount of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective amount of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective amount" may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved

[0060] A "*therapeutically effective amount*" is at least the minimum concentration required to effect a measurable improvement of a particular disease, disorder, or condition. A therapeutically effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the Siglec-7 protein antagonist to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the Siglec-7 protein antagonist are outweighed by the therapeutically beneficial effects.

[0061] As used herein, administration "*in conjunction*" with another compound or composition includes simultaneous administration and/or administration at different times. Administration in conjunction also encompasses administration as a co-formulation or administration as separate compositions, including at different dosing frequencies or intervals, and using the same route of administration or different routes of administration.

[0062] An "*individual*" for purposes of treatment, prevention, or reduction of risk refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sport, or pet

animals, such as dogs, horses, rabbits, cattle, pigs, hamsters, gerbils, mice, ferrets, rats, cats, and the like. Preferably, the individual is human.

[0063] The term "*immunoglobulin*" (Ig) is used interchangeably with "*antibody*" herein. The term "antibody" herein is used in the broadest sense and specifically covers monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.* bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity.

[0064] The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, *see, e.g.*, *Basic and Clinical Immunology*, 8th Ed., Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

[0065] The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa ("κ") and lambda ("λ"), based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (CH), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated alpha ("α"), delta ("δ"), epsilon ("ε"), gamma ("γ") and mu ("μ"), respectively. The γ and α classes are further divided into subclasses (isotypes) on the basis of relatively minor differences in the CH sequence and function, *e.g.*, humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The subunit structures and three dimensional configurations of different classes of immunoglobulins are well known and described generally in, for example, Abbas *et al.*, Cellular and Molecular Immunology, 4th ed. (W.B. Saunders Co., 2000).

[0066] "*Native antibodies*" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains.

[0067] An "*isolated*" antibody, such as an anti-Siglec-7 antibody of the present disclosure, is one that has been identified, separated and/or recovered from a component of its production environment (*e.g.*, naturally or recombinantly). Preferably, the isolated polypeptide is free of association with all

other contaminant components from its production environment. Contaminant components from its production environment, such as those resulting from recombinant transfected cells, are materials that would typically interfere with research, diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified: (1) to greater than 95% by weight of antibody as determined by, for example, the Lowry method, and in some embodiments, to greater than 99% by weight; (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant T cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, an isolated polypeptide or antibody will be prepared by at least one purification step.

[0068] The "*variable region*" or "*variable domain*" of an antibody, such as an anti-Siglec-7 antibody of the present disclosure, refers to the amino-terminal domains of the heavy or light chain of the antibody. The variable domains of the heavy chain and light chain may be referred to as "V_H" and "V_L", respectively. These domains are generally the most variable parts of the antibody (relative to other antibodies of the same class) and contain the antigen binding sites.

[0069] The term "*variable*" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies, such as anti-Siglec-7 antibodies of the present disclosure,. The V domain mediates antigen binding and defines the specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the entire span of the variable domains. Instead, it is concentrated in three segments called hypervariable regions (HVRs) both in the light-chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a beta-sheet configuration, connected by three HVRs, which form loops connecting, and in some cases forming part of, the beta-sheet structure. The HVRs in each chain are held together in close proximity by the FR regions and, with the HVRs from the other chain, contribute to the formation of the antigen binding site of antibodies (*see* Kabat et al., *Sequences of Immunological Interest*, Fifth Edition, National Institute of Health, Bethesda, MD (1991)). The constant domains are not involved directly in the binding of antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent-cellular toxicity.

[0070] The term "*monoclonal antibody*" as used herein refers to an antibody, such as an anti-Siglec-7 antibody of the present disclosure, obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible

naturally occurring mutations and/or post-translation modifications (*e.g.*, isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against one or more antigenic sites. In some embodiments, a monoclonal antibody of the present disclosure can be a bispecific antibody. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the one or more antigenic sites. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by a variety of techniques, including, for example, phage-display technologies (*see, e.g.*, Clackson *et al.*, *Nature*, 352:624-628 (1991); Marks *et al.*, *J. Mol. Biol.* 222:581-597 (1992); Sidhu *et al.*, *J. Mol. Biol.* 338(2): 299-310 (2004); Lee et al., *J. Mol. Biol.* 340(5):1073-1093 (2004); Fellouse, *Proc. Nat'l Acad. Sci. USA* 101(34):12467-472 (2004); and Lee *et al.*, *J. Immunol. Methods* 284(1-2):119-132 (2004), the hybridoma method (*e.g.*, Kohler and Milstein., *Nature*, 256:495-97 (1975); Hongo et al., *Hybridoma,* 14 (3):253-260 (1995), Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2d ed. 1988); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981)), recombinant DNA methods (see, *e.g.*, U.S. Patent No. 4,816,567), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, *e.g.*, WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits et al., *Proc. Nat'l Acad. Sci. USA* 90:2551 (1993); Jakobovits *et al.*, *Nature* 362:255-258 (1993); Bruggemann *et al.*, *Year in Immunol.* 7:33 (1993); U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016; Marks *et al.*, *Bio/Technology* 10:779-783 (1992); Lonberg *et al.*, *Nature* 368:856-859 (1994); Morrison, *Nature* 368:812-813 (1994); Fishwild et al., *Nature Biotechnol.* 14:845-851 (1996); Neuberger, *Nature Biotechnol.* 14:826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.* 13:65-93 (1995).

[0071] The terms "*full-length antibody*," "*intact antibody*" or "*whole antibody*" are used interchangeably to refer to an antibody, such as an anti-Siglec-7 antibody of the present disclosure, in its substantially intact form, as opposed to an antibody fragment. Specifically whole antibodies include those with heavy and light chains including an Fc region. The constant domains may be native sequence constant domains (*e.g.*, human native sequence constant domains) or amino acid sequence variants thereof. In some cases, the intact antibody may have one or more effector functions.

[0072] An "*antibody fragment*" comprises a portion of an intact antibody, preferably the antigen binding and/or the variable region of the intact antibody. Examples of antibody fragments include

Fab, Fab', $F(ab')_2$ and Fv fragments; diabodies; linear antibodies (*see* U.S. Patent 5,641,870, Example 2; Zapata et al., *Protein Eng.* 8(10):1057-1062 (1995)); single-chain antibody molecules and multispecific antibodies formed from antibody fragments.

[0073] Papain digestion of antibodies, such as anti-Siglec-7 antibodies of the present disclosure, produces two identical antigen-binding fragments, called "*Fab*" fragments, and a residual "*Fc*" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_H1). Each Fab fragment is monovalent with respect to antigen binding, *i.e.*, it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large $F(ab')_2$ fragment which roughly corresponds to two disulfide linked Fab fragments having different antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having a few additional residues at the carboxy terminus of the C_H1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[0074] The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, the region which is also recognized by Fc receptors (FcR) found on certain types of cells.

[0075] "*Fv*" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three HVRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0076] *"Single-chain Fv"* also abbreviated as *"sFv"* or *"scFv"* are antibody fragments that comprise the VH and VL antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of the sFv, *see* Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

[0077] "*Functional fragments*" of antibodies, such as anti-Siglec-7 antibodies of the present disclosure, comprise a portion of an intact antibody, generally including the antigen binding or variable region of the intact antibody or the F region of an antibody which retains or has modified

FcR binding capability. Examples of antibody fragments include linear antibody, single-chain antibody molecules and multispecific antibodies formed from antibody fragments.

[0078] The term "*diabodies*" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10) residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, thereby resulting in a bivalent fragment, *i.e.*, a fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described in greater detail in, for example, EP 404,097; WO 93/11161; Hollinger et al., *Proc. Nat'l Acad. Sci. USA* 90:6444-48 (1993).

[0079] As used herein, a "chimeric antibody" refers to an antibody (immunoglobulin), such as an anti-Siglec-7 antibody of the present disclosure, in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is(are) identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; Morrison et al., *Proc. Nat'l Acad. Sci. USA*, 81:6851-55 (1984)). Chimeric antibodies of interest herein include PRIMATIZED® antibodies wherein the antigen-binding region of the antibody is derived from an antibody produced by, *e.g.*, immunizing macaque monkeys with an antigen of interest. As used herein, "humanized antibody" is used a subset of "chimeric antibodies."

[0080] "*Humanized*" forms of non-human (*e.g.*, murine) antibodies, such as anti-Siglec-7 antibodies of the present disclosure, are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. In one embodiment, a humanized antibody is a human immunoglobulin (recipient antibody) in which residues from an HVR of the recipient are replaced by residues from an HVR of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired specificity, affinity, and/or capacity. In some instances, FR residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications may be made to further refine antibody performance, such as binding affinity. In general, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin sequence, and all or substantially all of the FR regions are those of a human immunoglobulin sequence, although the FR regions may include one or more individual FR residue substitutions that improve antibody

performance, such as binding affinity, isomerization, immunogenicity, and the like. The number of these amino acid substitutions in the FR is typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally will also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, *see, e.g.*, Jones et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992). *See also*, for example, Vaswani and Hamilton, *Ann. Allergy, Asthma & Immunol.* 1:105-115 (1998); Harris, *Biochem. Soc. Transactions* 23:1035-1038 (1995); Hurle and Gross, *Curr. Op. Biotech.* 5:428-433 (1994); and U.S. Patent Nos. 6,982,321 and 7,087,409.

[0081] A "*human antibody*" is one that possesses an amino-acid sequence corresponding to that of an antibody, such as an anti-Siglec-7 antibody of the present disclosure, produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries. Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991). Also available for the preparation of human monoclonal antibodies are methods described in Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner et al., *J. Immunol.*, 147(1):86-95 (1991). *See also* van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5:368-74 (2001). Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, *e.g.*, immunized xenomice (*see, e.g.*, U.S. Patent Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). *See also*, for example, Li et al., *Proc. Nat'l Acad. Sci. USA*, 103:3557-3562 (2006) regarding human antibodies generated via a human B-cell hybridoma technology.

[0082] The term "*hypervariable region*," "*HVR*," or "*HV*," when used herein refers to the regions of an antibody-variable domain, such as that of an anti-Siglec-7 antibody of the present disclosure, that are hypervariable in sequence and/or form structurally defined loops. Generally, antibodies comprise six HVRs; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). In native antibodies, H3 and L3 display the most diversity of the six HVRs, and H3 in particular is believed to play a unique role in conferring fine specificity to antibodies. *See, e.g.*, Xu et al., *Immunity* 13:37-45 (2000); Johnson and Wu in *Methods in Molecular Biology* 248:1-25 (Lo, ed., Human Press, Totowa, NJ, 2003)). Indeed, naturally occurring camelid antibodies consisting of a heavy chain only are functional and stable in the absence of light chain. See, *e.g.*, Hamers-Casterman et al., *Nature* 363:446-448 (1993) and Sheriff et al., *Nature Struct. Biol.* 3:733-736 (1996).

[0083] A number of HVR delineations are in use and are encompassed herein. The HVRs that are EU or Kabat complementarity-determining regions (CDRs) are based on sequence variability and are the most commonly used (Kabat et al., *supra*). Chothia refers instead to the location of the structural loops (Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)). The AbM HVRs represent a compromise between the EU or Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody-modeling software. The "contact" HVRs are based on an analysis of the available complex crystal structures. The residues from each of these HVRs are noted below.

Loop	Kabat	AbM	Chothia	Contact
L1	L24-L34	L24-L34	L26-L32	L30-L36
L2	L50-L56	L50-L56	L50-L52	L46-L55
L3	L89-L97	L89-L97	L91-L96	L89-L96
H1	H31-H35B	H26-H35B	H26-H32	H30-H35B (Kabat numbering)
H1	H31-H35	H26-H35	H26-H32	H30-H35 (Chothia numbering)
H2	H50-H65	H50-H58	H53-H55	H47-H58
H3	H95-H102	H95-H102	H96-H101	H93-H101

[0084] HVRs may comprise "extended HVRs" as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2), and 89-97 or 89-96 (L3) in the VL, and 26-35 (H1), 50-65 or 49-65 (a preferred embodiment) (H2), and 93-102, 94-102, or 95-102 (H3) in the VH. The variable-domain residues are numbered according to EU or Kabat et al., *supra*, for each of these extended-HVR definitions.

[0085] "*Framework*" or "*FR*" residues are those variable-domain residues other than the HVR residues as herein defined.

[0086] The phrase "*variable-domain residue-numbering as in EU or Kabat*" or "*amino-acid-position numbering as in EU or Kabat*," and variations thereof, refers to the numbering system used for heavy-chain variable domains or light-chain variable domains of the compilation of antibodies in EU or Kabat et al., *supra*. Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or HVR of the variable domain. For example, a heavy-chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (*e.g.*, residues 82a, 82b, and 82c, *etc.* according to Kabat) after heavy-chain FR residue 82. The EU or Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence.

[0087] The EU or Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (*e.g.*, Kabat et al., Sequences of Immunological Interest. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The "EU or Kabat numbering system" or "EU index" is generally used when referring to a residue in an immunoglobulin heavy chain constant region (*e.g.*, the EU index reported in Kabat *et al., supra*). The "EU index as in Kabat" refers to the

residue numbering of the human IgG1 EU antibody. Unless stated otherwise herein, references to residue numbers in the variable domain of antibodies means residue numbering by the Kabat numbering system. Unless stated otherwise herein, references to residue numbers in the constant domain of antibodies means residue numbering by the EU or Kabat numbering system (*e.g., see* United States Patent Publication No. 2010-280227).

[0088] An "*acceptor human framework*" as used herein is a framework comprising the amino acid sequence of a VL or VH framework derived from a human immunoglobulin framework or a human consensus framework. An acceptor human framework "derived from" a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain pre-existing amino acid sequence changes. In some embodiments, the number of pre-existing amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. Where pre-existing amino acid changes are present in a VH, preferable those changes occur at only three, two, or one of positions 71H, 73H and 78H; for instance, the amino acid residues at those positions may by 71A, 73T and/or 78A. In one embodiment, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

[0089] A "*human consensus framework*" is a framework that represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991). Examples include for the VL, the subgroup may be subgroup kappa I, kappa II, kappa III or kappa IV as in Kabat *et al., supra.* Additionally, for the VH, the subgroup may be subgroup I, subgroup II, or subgroup III as in Kabat *et al., supra.*

[0090] An "*amino-acid modification*" at a specified position, *e.g.*, of an anti-Siglec-7 antibody of the present disclosure, refers to the substitution or deletion of the specified residue, or the insertion of at least one amino acid residue adjacent the specified residue. Insertion "adjacent" to a specified residue means insertion within one to two residues thereof. The insertion may be N-terminal or C-terminal to the specified residue. The preferred amino acid modification herein is a substitution.

[0091] An "*affinity-matured*" antibody, such as an anti-Siglec-7 antibody of the present disclosure, is one with one or more alterations in one or more HVRs thereof that result in an improvement in the affinity of the antibody for antigen, compared to a parent antibody that does not possess those alteration(s). In one embodiment, an affinity-matured antibody has nanomolar or even picomolar affinities for the target antigen. Affinity-matured antibodies are produced by procedures known in the art. For example, Marks et al., *Bio/Technology* 10:779-783 (1992) describes affinity

maturation by VH- and VL-domain shuffling. Random mutagenesis of HVR and/or framework residues is described by, for example: Barbas et al. *Proc Nat. Acad. Sci. USA* 91:3809-3813 (1994); Schier et al. *Gene* 169:147-155 (1995); Yelton et al. *J. Immunol.* 155:1994-2004 (1995); Jackson et al., *J. Immunol.* 154(7):3310-9 (1995); and Hawkins *et al, J. Mol. Biol.* 226:889-896 (1992).

[0092] As use herein, the term "*specifically recognizes*" or "*specifically binds*" refers to measurable and reproducible interactions such as attraction or binding between a target and an antibody, such as an anti-Siglec-7 antibody of the present disclosure, that is determinative of the presence of the target in the presence of a heterogeneous population of molecules including biological molecules. For example, an antibody, such as an anti-Siglec-7 antibody of the present disclosure, that specifically or preferentially binds to a target or an epitope is an antibody that binds this target or epitope with greater affinity, avidity, more readily, and/or with greater duration than it binds to other targets or other epitopes of the target. It is also understood by reading this definition that, for example, an antibody (or a moiety) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "*specific binding*" or "*preferential binding*" does not necessarily require (although it can include) exclusive binding. An antibody that specifically binds to a target may have an association constant of at least about $10^{3}\,M^{-1}$ or $10^{4}\,M^{-1}$, sometimes about $10^{5}\,M^{-1}$ or $10^{6}\,M^{-1}$, in other instances about $10^{6}\,M^{-1}$ or $10^{7}\,M^{-1}$, about $10^{8}\,M^{-1}$ to $10^{9}\,M^{-1}$, or about $10^{10}\,M^{-1}$ to $10^{11}\,M^{-1}$ or higher. A variety of immunoassay formats can be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select monoclonal antibodies specifically immunoreactive with a protein. *See, e.g.*, Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Publications, New York, for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity.

[0093] As used herein, an "*interaction*" between a Siglec-7 protein and a second protein encompasses, without limitation, protein-protein interaction, a physical interaction, a chemical interaction, binding, covalent binding, and ionic binding. As used herein, an antibody "inhibits interaction" between two proteins when the antibody disrupts, reduces, or completely eliminates an interaction between the two proteins. An antibody of the present disclosure, or fragment thereof, "inhibits interaction" between two proteins when the antibody or fragment thereof binds to one of the two proteins.

[0094] An "*agonist*" antibody or an "*activating*" antibody is an antibody, such as an agonist anti-Siglec-7 antibody of the present disclosure, that induces (*e.g.*, increases) one or more activities or functions of the antigen after the antibody binds the antigen.

[0095] A "*blocking*" antibody, an "*antagonist*" antibody, or an "*inhibitory*" antibody is an antibody, such as an anti-Siglec-7 antibody of the present disclosure, that inhibits or reduces (*e.g.*,

decreases) antigen binding to one or more ligand after the antibody binds the antigen, and/or that inhibits or reduces (*e.g.*, decreases) one or more activities or functions of the antigen after the antibody binds the antigen. In some embodiments, blocking antibodies, antagonist antibodies, or inhibitory antibodies substantially or completely inhibit antigen binding to one or more ligand and/or one or more activities or functions of the antigen.

[0096] Antibody "*effector functions*" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype.

[0097] The term "*Fc region*" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native-sequence Fc regions and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy-chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU or Kabat numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue. Suitable native-sequence Fc regions for use in the antibodies of the present disclosure include human IgG1, IgG2, IgG3 and IgG4.

[0098] A "*native sequence Fc region*" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

[0099] A "*variant Fc region*" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, *e.g.* from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% homology therewith, more preferably at least about 95% homology therewith.

[0100] "*Fc receptor*" or "*FcR*" describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors, FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif ("ITAM") in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif ("ITIM") in its cytoplasmic domain. (*see, e.g.*, M. Daëron, *Annu. Rev. Immunol.* 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-92 (1991); Capel et al., *Immunomethods* 4:25-34 (1994); and de Haas et al., *J. Lab. Clin. Med.* 126: 330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. FcRs can also increase the serum half-life of antibodies.

[0101] Binding to FcRn *in vivo* and serum half-life of human FcRn high-affinity binding polypeptides can be assayed, *e.g.*, in transgenic mice or transfected human cell lines expressing human FcRn, or in primates to which the polypeptides having a variant Fc region are administered. WO 2004/42072 (Presta) describes antibody variants with improved or diminished binding to FcRs. *See also, e.g.*, Shields et al., *J. Biol. Chem.* 9(2):6591-6604 (2001).

[0102] As used herein, "*percent (%) amino acid sequence identity*" and "*homology*" with respect to a peptide, polypeptide or antibody sequence refers to the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or MEGALIGN™ (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms known in the art needed to achieve maximal alignment over the full length of the sequences being compared.

[0103] An "*isolated*" cell is a molecule or a cell that is identified and separated from at least one contaminant cell with which it is ordinarily associated in the environment in which it was produced. In some embodiments, the isolated cell is free of association with all components associated with the production environment. The isolated cell is in a form other than in the form or setting in which it is found in nature. Isolated cells are distinguished from cells existing naturally in tissues, organs, or individuals. In some embodiments, the isolated cell is a host cell of the present disclosure.

[0104] An "*isolated*" nucleic acid molecule encoding an antibody, such as an anti-Siglec-7 antibody of the present disclosure, is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the environment in which it was produced. Preferably, the isolated nucleic acid is free of association with all components associated with the production environment. The isolated nucleic acid molecules encoding the polypeptides and antibodies herein is in a form other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from nucleic acid encoding the polypeptides and antibodies herein existing naturally in cells.

[0105] The term "*vector*," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA into which additional DNA segments may be ligated. Another type of vector is a phage vector. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors," or simply, "expression vectors." In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector.

[0106] "*Polynucleotide*," or "*nucleic acid*," as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase or by a synthetic reaction. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may comprise modification(s) made after synthesis, such as conjugation to a label. Other types of modifications include, for example, "caps," substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, *etc.*) and with charged linkages (*e.g.*, phosphorothioates, phosphorodithioates, *etc.*), those containing pendant moieties, such as, for example, proteins (*e.g.*, nucleases, toxins, antibodies, signal

peptides, ply-L-lysine, *etc.*), those with intercalators (*e.g.*, acridine, psoralen, *etc.*), those containing chelators (*e.g.*, metals, radioactive metals, boron, oxidative metals, *etc.*), those containing alkylators, those with modified linkages (*e.g.*, alpha anomeric nucleic acids, *etc.*), as well as unmodified forms of the polynucleotides(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid or semi-solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl-, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, α-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs, and basic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S ("thioate"), P(S)S ("dithioate"), (O)NR2 ("amidate"), P(O)R, P(O)OR', CO, or CH2 ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

[0107] A "*host cell*" includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected *in vivo* with a polynucleotide(s) of the present disclosure.

[0108] "*Carriers*" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming

counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

[0109] As used herein, the term "*apoptosis*" refers to gene-directed process of intracellular cell destruction. Apoptosis is distinct from necrosis; it includes cytoskeletal disruption, cytoplasmic shrinkage and condensation, expression of phosphatidylserine on the outer surface of the cell membrane and blebbing, resulting in the formation of cell membrane bound vesicles or apoptotic bodies. The process is also referred to as "programmed cell death." During apoptosis, characteristic phenomena such as curved cell surfaces, condensation of nuclear chromatin, fragmentation of chromosomal DNA, and loss of mitochondrial function are observed. Various known technologies may be used to detect apoptosis, such as staining cells with Annexin V, propidium iodide, DNA fragmentation assay and YO-PRO-1 (Invitrogen). In some embodiments, staining with Annexin V and propidium iodide may be used, and the combined percentages of the Annexin V+/PI+, Annexin V+/PI- and Annexin V-/PI+ populations are considered as dead cells.

[0110] As used herein, the term "*agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both*" refers to a molecule that reduces (including significantly), decreases, blocks, inhibits, or interferes with a Siglec-7 (mammalian, such as a human Siglec-7) biological activity *in vitro*, *in situ*, and/or *in vivo*. The term "agent" implies no specific mechanism of biological action whatsoever, and expressly includes and encompasses all possible pharmacological, physiological, and biochemical interactions with a Siglec-7 whether direct or indirect, and whether interacting with a Siglec-7, one or more of its ligands, or through another mechanism, and its consequences which can be achieved by a variety of different, and chemically divergent, compositions. Exemplary agents include, without limitation, an anti-Siglec-7 antibody that specifically binds to a Siglec-7, a soluble Siglec-7 receptor protein, a soluble Siglec-7-Fc fusion protein (e.g., Siglec-7 immunoadhesin), a soluble Siglec receptor that binds to a Siglec-7 ligand, a Siglec-Fc fusion protein (e.g., Siglec immunoadheisn) that binds to a Siglec-7 ligand, an anti-sense molecule directed to a nucleic acid encoding a Siglec-7, a short interfering RNA ("siRNA") molecule directed to a nucleic acid encoding a Siglec-7, a Siglec-7 inhibitory compound, an RNA or DNA aptamer that binds to a Siglec-7, and a Siglec-7 structural analog. In some embodiments, a Siglec-7 inhibitor (*e.g.,* an antibody) binds (physically interacts with) an agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both, binds to a Siglec-7 ligand, and/or inhibits (reduces) Siglec-7 synthesis or production. In other embodiments, an agent of the present disclosure inhibitor binds a Siglec-7 and prevents its binding to one or more of its ligands. In still other embodiments, an agent of the present disclosure reduces or eliminates expression (*i.e.,* transcription or translation) of a Siglec-7. Examples of types

of agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both are provided herein.

[0111] As used herein, the term "*agent that binds or interacts with Siglec-7*" refers to a molecule that either directly or indirectly interacts with a Siglec-7 protein. The term "agent" implies no specific mechanism of biological action whatsoever, and expressly includes and encompasses all possible pharmacological, physiological, and biochemical interactions with a Siglec-7 whether direct or indirect, and whether interacting with a Siglec-7or through another mechanism, and its consequences which can be achieved by a variety of different, and chemically divergent, compositions. Exemplary agents include, without limitation, an anti-Siglec-7 antibody that specifically binds to a Siglec-7.

[0112] As used herein, the term "RNA interference" or "RNAi" refers generally to a process in which a double-stranded RNA molecule or a short hairpin RNA molecule reducing or inhibiting the expression of a nucleic acid sequence with which the double-stranded or short hairpin RNA molecule shares substantial or total homology. The term "short interfering RNA" or "siRNA" or "RNAi agent" refers to an RNA sequence that elicits RNA interference. *See* Kreutzer et al., WO 00/44895; Zernicka-Goetz et al., WO 01/36646; Fire, WO 99/32619; Mello and Fire, WO 01/29058. As used herein, siRNA molecules include RNA molecules encompassing chemically modified nucleotides and non-nucleotides. The term "ddRNAi agent" refers to a DNA-directed RNAi agent that is transcribed from an exogenous vector. The terms "short hairpin RNA" or "shRNA" refer to an RNA structure having a duplex region and a loop region. In certain embodiments, ddRNAi agents are expressed initially as shRNAs.

[0113] As used herein, the term "aptamer" refers to a heterologous oligonucleotide capable of binding tightly and specifically to a desired molecular target, such as, for example, common metabolic cofactors (*e.g.,* Coenzyme A, S-adenosyl methionine, and the like), proteins (*e.g.,* complement protein C5, antibodies, and the like), or conserved structural elements in nucleic acid molecules (*e.g.,* structures important for binding of transcription factors and the like). Aptamers typically comprise DNA or RNA nucleotide sequences ranging from about 10 to about 100 nucleotides in length, from about 10 to about 75 nucleotides in length, from about 10 to about 50 nucleotides in length, from about 10 to about 35 nucleotides in length, and from about 10 to about 25 nucleotides in length. Synthetic DNA or RNA oligonucleotides can be made using standard solid phase phosphoramidite methods and equipment, such as by using a 3900 High Throughput DNA Synthesizer™, available from Applied Biosystems (Foster City, CA). Aptamers frequently incorporate derivatives or analogs of the commonly occurring nucleotides found in DNA and RNA (*e.g.,* A, G, C, and T/U), including backbone or linkage modifications (*e.g.,* peptide nucleic acid (PNA) or phosphothioate linkages) to increase resistance to nucleases, binding avidity, or to otherwise alter their pharmacokinetic properties. Exemplary modifications are set forth in U.S.

Patent Nos. 6,455,308; 4,469,863; 5,536,821; 5,541,306; 5,637,683; 5,637,684; 5,700,922; 5,717,083; 5,719,262; 5,739,308; 5,773,601; 5,886,165; 5,929,226; 5,977,296; 6,140,482; and in WIPO publications WO 00/56746 and WO 01/14398. Methods for synthesizing oligonucleotides comprising such analogs or derivatives are disclosed, for example, in the patent publications cited above, and in U.S. Patent Nos. 6,455,308; 5,614,622; 5,739,314; 5,955,599; 5,962,674; 6,117,992; and in WO 00/75372.

[0114] The term "*about*" as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to "*about*" a value or parameter herein includes(and describes) embodiments that are directed to that value or parameter *per se*.

[0115] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly indicates otherwise. For example, reference to an "antibody" is a reference to from one to many antibodies, such as molar amounts, and includes equivalents thereof known to those skilled in the art, and so forth.

[0116] It is understood that aspect and embodiments of the present disclosure described herein include "comprising," "consisting," and "consisting essentially of" aspects and embodiments.

Overview

[0117] The present disclosure relates to agents (e.g., anti-Siglec-7 antibodies) that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands, methods of making and using such agents (e.g., anti-Siglec-7 antibodies); pharmaceutical compositions containing such agents (e.g., anti-Siglec-7 antibodies); nucleic acids encoding such agents (e.g., anti-Siglec-7 antibodies); and host cells containing nucleic acids encoding such agents (e.g., anti-Siglec-7 antibodies).

[0118] In some embodiments, anti-Siglec-7 antibodies of the present disclosure have one or more antagonistic activities that are due, at least in part, to the ability of the antibodies inhibit the interaction between Siglec-7 and one or more natural glycan ligands. In some embodiments, the anti-Siglec-7 antibodies of the present disclosure may have one or more antagonistic activities that are due, at least in part, to the ability of the antibodies to reduce cellular expression (*e.g.*, cell surface expression) of Siglec-7 by inducing degradation, down regulation, cleavage, receptor desensitization, and/or lysosomal targeting of Siglec-7.

[0119] In some embodiments, antibody-induced Siglec-7 activity can be determined or tested *in vitro* by any of the techniques disclosed herein (*see, e.g.,* **Examples 1-5**), including, without limitation, testing plate-binding of full-length anti-Siglec-7 antibodies to increase the density of antibodies exposed to Siglec-7, cross-linking anti-Siglec-7 antibodies with a secondary antibody, cross-linking anti-Siglec-7 antibodies with cells that express one or more Fcg receptors (e.g., FcgRIIB), using Siglec-7 antibodies in solution, and using Fab fragments of Siglec-7 antibodies.

[0120] In some embodiments, the anti-Siglec-7 antibodies of the present disclosure have one or more antagonistic activities that are due, at least in part, to the ability of the antibodies inhibit the interaction between Siglec-7 and one or more natural glycan ligands. In some embodiments, the anti-Siglec-7 antibodies of the present disclosure may have one or more antagonistic activities that are due, at least in part, to the ability of the antibodies to reduce cellular expression (*e.g.*, cell surface expression) of Siglec-7 by inducing degradation, down regulation, cleavage, receptor desensitization, and/or lysosomal targeting of Siglec-7. In some embodiments, the anti-Siglec-7 antibodies exhibit one or more of the following properties: a. decrease cellular levels of Siglec-7 with a half-maximal effective concentration (EC_{50}) that is lower than that of the anti-Siglec-7 antibody Mab1138 (R&D Systems; Cat. No. MAB 1138); b. decrease red blood cell binding to Siglec-7-Fc up to 10 fold more effectively than the anti-Siglec-7 antibody Mab1138 (R&D Systems; Cat. No. MAB 1138); c. have a dissociation constant (K_D) for human Siglec-7 that may range from 10 nM to 10 pM, for example when the K_D is determined at a temperature of approximately 25°C; d. have a dissociation constant (K_D) for human cells, such as human dendritic cells, that may range from 2 nM to 100 pM, for example when the K_D is determined at a temperature of approximately 4°C; e. bind to human cells, such as human dendritic cells with a half-maximal effective concentration (EC_{50}) that may range from 2 nM to 100 pM, for example when the EC_{50} is determined at a temperature of approximately 4°C; or f. decrease cellular levels of Siglec-7 with a half-maximal effective concentration (EC_{50}) that may range from 350 pM to 33 pM. As disclosed herein half-maximal effective concentration (EC_{50}) refers to the concentration at which an anti-Siglec-7 antibody of the present disclosure reduces cellular levels of Siglec-7 on a cell or in a cell, or the concentration at which the antibody achieves half-maximal binding to Siglec-7 on a cell.

[0121] Advantageously, anti-Siglec-7 antibodies of the present disclosure have an improved EC_{50} for binding Siglec-7 as compared to commercial anti-Siglec-7 antibodies, such as Mab1138 (R&D Systems; Cat. No. MAB 1138), reduce cell surface expression more potently (e.g., lower EC_{50}) than commercial anti-Siglec-7 antibodies, such as Mab1138 (R&D Systems; Cat. No. MAB 1138), and decreases red blood cell binding to Siglec-7-Fc more effectively (up to 10 fold) as compared to commercial anti-Siglec-7 antibodies, such as Mab1138 (R&D Systems; Cat. No. MAB 1138) (*see, e.g.,* **Examples 3 and 4**).

[0122] Certain aspects of the present disclosure are based, at least in part, on the identification of agents, such as anti-Siglec-7 antibodies, that exhibit the ability to compete with one or more Siglec-7 ligands for binding to Siglec-7 and/or the ability to decrease cell surface levels of Siglec-7 on cells, resulting in the reduction, neutralization, prevention, or curbing of one or more Siglec-7 activities. Exemplary Siglec-7 activities include, without limitation, phosphorylation of Tyr-437 and Tyr-460 by a Src family tyrosine kinase, such as Syk, LCK, FYM, and/or ZAP70; recruitment of and

binding to the tyrosine-specific protein phosphatases SHP1 and SHP2; recruitment of and binding to PLC-gamma1, which acts as a guanine nucleotide exchange factor for Dynamini-1; recruitment of and binding to SH2-domain containing protein (*e.g.*, Crkl); recruitment of and binding to the spleen tyrosine kinase Syk; recruitment of and binding to SH3-SH2-SH3 growth factor receptor-bound protein 2 (Grb2); recruitment of and binding to multiple SH2-containing proteins; modulated expression of one or more pro-inflammatory cytokines, such as IF IFN-a4, IFN-beta, IL-1β, IL-1alpha, TNF-α, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-33, MCP-1, and MIP-1-beta; modulated expression of one or more pro-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; increased expression of one or more anti-inflammatory cytokines, such as IL-4, IL-10, IL-13, IL-35, IL-16, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, or IL-6; modulated expression of one or more anti-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; modulate expression of one or more proteins selected from C1qa, C1qB, C1qC, C1s, C1R, C4, C2, C3, ITGB2, HMOX1, LAT2, CASP1, CSTA, VSIG4, MS4A4A, C3AR1, GPX1, TyroBP, ALOX5AP, ITGAM, SLC7A7, CD4, ITGAX, and PYCARD; inhibition of extracellular signal-regulated kinase (ERK) phosphorylation; decreasing tyrosine phosphorylation on one or more cellular proteins, optionally, wherein the one or more cellular proteins comprise ZAP-70 and the tyrosine phosphorylation occurs on Tyr-319 of ZAP-70; modulated expression of C-C chemokine receptor 7 (CCR7); inhibition of microglial cell chemotaxis toward CCL19-expressing and CCL21-expressing cells; decreasing T cell proliferation induced by one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, M1 microglia, activated M1 microglia, M2 microglia, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, and M2 NK cells; inhibition of osteoclast production, decreased rate of osteoclastogenesis, or both; decreasing survival of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; decreasing proliferation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1

neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibiting migration of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibiting one or more functions of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibiting maturation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibition of one or more types of clearance selected from apoptotic neuron clearance, nerve tissue debris clearance, dysfunctional synapse clearance, non-nerve tissue debris clearance, bacteria clearance, other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, disease-causing nucleic acid clearance, and tumor cell clearance; optionally wherein the disease-causing protein is selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, the disease-causing nucleic acid is an antisense GGCCCC (G2C4) repeat-expansion RNA, and the tumor cell is from a cancer selected from 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, and thyroid cancer; inhibition of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, dysfunctional synapses, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, disease-causing nucleic acids, or tumor cells; optionally wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and the tumor cells are from a cancer selected from 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, or thyroid cancer; binding to Siglec-7 ligand on tumor cells; binding to Siglec-7 ligand on cells selected from neutrophils, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, and NK cells; inhibition of tumor cell killing by one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; inhibiting anti-tumor cell proliferation activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; inhibition of anti-tumor cell metastasis activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; inhibition of one or more ITAM motif containing receptors, optionally wherein the one or more ITAM motif containing receptors are selected from TREM1, TREM2, Sirp beta, FcgR, DAP10, and DAP12; inhibition of signaling by one or more pattern recognition receptors (PRRs), optionally wherein the one or more PRRs are selected from receptors that identify pathogen-associated molecular patterns (PAMPs), receptors that identify damage-associated molecular patterns (DAMPs), and any combination thereof; inhibition of one or more receptors comprising the motif $D/Ex_{0-2}YxxL/IX_{6-8}YxxL/I$ (SEQ ID NO: 537); inhibition of signaling by one or more Toll-like receptors; inhibition of the JAK-STAT signaling pathway; inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NFêB); de-phosphorylation of an

ITAM motif containing receptor; modulated expression of one or more inflammatory receptors, optionally wherein the one or more inflammatory receptors comprise CD86 and the one or more inflammatory receptors are expressed on one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; increasing expression of one or more Siglec-7-dependent genes; normalization of disrupted Siglec-7-dependent gene expression; decreasing expression of one or more ITAM-dependent genes, optionally wherein the one more ITAM-dependent genes are activated by nuclear factor of activated T cells (NFAT) transcription factors; promoting or rescuing functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells; increasing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells into tumors; increasing the number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; enhancing tumor-promoting activity of myeloid-derived suppressor cells; increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; increasing tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes; enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); decreasing activation of tumor-specific T lymphocytes with tumor killing potential; decreasing infiltration of tumor-specific NK cells with tumor killing potential; decreasing the tumor killing potential of NK cells; decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; increasing tumor volume; increasing tumor growth rate; increasing metastasis; increasing rate of tumor recurrence; decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more target proteins selected from PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines; inhibition of PLCã/PKC/calcium mobilization; and inhibition of PI3K/Akt, Ras/MAPK signaling.

[0123] In some embodiments, treatment of cancer with agents, such as Siglec-7 blocking antibodies: (i) directly or indirectly decrease the survival, proliferation, maturation, differentiation, and/or functionality of tumor-promoting myeloid/granulocytic immune-suppressive cells that

accumulate in the tumor, in peripheral blood, and in lymphoid organs of cancer patients; (ii) decrease the number of tumor-promoting myeloid/granulocytic immune-suppressive cells in the tumor, in the peripheral blood, and in other lymphoid organs of a cancer patient; (iii) block tumor-promoting activity of myeloid-derived suppressor cells (MDSC); (iv) decrease expression of tumor-promoting cytokines, such as TGF-beta and IL-10, in the tumor and in the peripheral blood of a cancer patient; (v) decrease tumor-promoting FoxP3+ regulatory T lymphocyte infiltration in the tumor; (vi) increase infiltration and activation of T lymphocytes with tumor killing potential; (vii) increase infiltration of tumor-specific NK cells with tumor killing potential; (viii) increase the tumor killing potential of NK cells; (ix) increase infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (x) decrease tumor volume; (xi) reduce tumor growth rate; (xii) reduce and/or inhibit metastasis; (xiii) reduce rate of tumor recurrence; (xiv) increase efficacy of immune-therapy that modulates anti-tumor T cell responses, such as PD1/PDL1, CTLA4, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, and cancer vaccines, (xv) induce, activate, or otherwise increase PLCã/PKC/calcium mobilization; and (xvi) induce, activate, or otherwise increase PI3K/Akt, Ras/MAPK signaling.

[0124] Immunosuppressor cells are sometimes also referred to as myeloid-derived suppressor cells (MDSC). In humans, MDSCs can be defined by one of the following combination of markers: (1) $CD14^+$ $HLA\text{-}DR^{low/-}$, (2) $CD14^+$ $IL4R\alpha^+$, (3) $CD14^+$ $HLA\text{-}DR^-$ $IL4R\alpha^+$, (4) $CD34^+$ $CD14^+$ $CD11b^+$ $Siglec\text{-}7^+$, (5) $CD11b^+$ $CD14^+$ $Siglec\text{-}7^+$, (6) $Siglec\text{-}7^+$ $HLA\text{-}DR^-$, (7) Lin^- $HLA\text{-}DR^-$, (8) Lin^- $HLA\text{-}DR^-$ $Siglec\text{-}7^+$, (9) Lin^- $HLA\text{-}DR^-$ $Siglec\text{-}7^+$ $CD11b^+$, (10) Lin^- $Siglec\text{-}7^+$ $CD11b^+$ $CD15^+$, (11) Lin^- $HLA\text{-}DR^-$ $Siglec\text{-}7^+$ $CD11b^+$ $CD14^-$ $CD15^+$, (12) $CD11b^+$ $CD14^-$ $Siglec\text{-}7^+$, (13) $CD11b^+$ $CD14^-$ $HLA\text{-}DR^-$ $Siglec\text{-}7^+$ $CD15^+$, (14) $Siglec\text{-}7^+$ $HLA\text{-}DR^-$ $CD15^+$, (15) $CD15^+$ $IL4R\alpha^+$, (16) $CD11b^+$ $CD15^+$ $CD66b^+$, (17) $CD15^+$ FSC^{low} SSC^{high}, (18) $CD15^{high}$ $Siglec\text{-}7^+$, (19) $CD11b^+$ $CD14^-$ $CD15^+$, (20) $CD66b^+$ SSC^{high}, and (21) $CD11b^+$ $CD15^+$ (see also Solito S et al. Annals of the NY Academy of Sciences, 2014). In mice, MDSCs can be defined by the expression of the surface markers $CD45^+$, $CD11b^+$, $Gr1^+$, and/or $Il4Ra^+$. Additional exemplary immunosuppressive monocytic lineages are $CD45^+$, $CD11b^+$, $Gr1^{low}$; and $CD45^+$, $CD11c^+$.

[0125] The present disclosure further relates to agents that bind or interact with Siglec-7, such as anti-Siglec-7 antibodies. In certain embodiments, the anti-Siglec-7 antibodies do not significantly decrease cell surface levels of Siglec-7, and/or do not inhibit interaction between Siglec-7 and one or more Siglec-7 ligands.

Siglec-7 proteins

[0126] In one aspect, the present disclosure provides agents, such as isolated (*e.g.*, monoclonal) antibodies, that interact with or otherwise bind to regions, such as epitopes, within a Siglec-7 protein

of the present disclosure. In some embodiments, agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, bind to a Siglec-7 protein and modulate one or more Siglec-7 activities after binding to the Siglec-7 protein, for example, an activity associated with Siglec-7 expression in a cell. Siglec-7 proteins of the present disclosure include, without limitation, a mammalian Siglec-7 protein, human Siglec-7 protein, mouse Siglec-7 protein, and rat Siglec-7 protein.

[0127] Siglec-7 is variously referred to as a Siglec-7 molecule, Sialic acid-binding Ig-like lectin 7, AIRM1, CD328, CDw328, D-Siglec, QA79, SIGLEC19P, SIGLECP2, p75, and p75/AIRM1.

[0128] Siglec-7 is an immunoglobulin-like receptor primarily expressed on immune and hematopoietic cells, including without limitation monocytes, macrophages, dendritic cells, neutrophils, mast cells, microglial cells, lymphoid cells, natural killer cells, and subsets of T cells.

[0129] Various Siglec-7 homologs are known, including without limitation, human Siglec-7, chimpanzee Siglec-7, pygmy chimpanzee Siglec-7, orangutan Siglec-7, gorilla Siglec-7, and gibbon Siglec-7. The amino acid sequence of human Siglec-7 is set forth below as SEQ ID NO: 1:

```
        10         20         30         40         50
MLLLLLLPLL WGRERVEGQK SNRKDYSLTM QSSVTVQEGM CVHVRCSFSY
        60         70         80         90        100
PVDSQTDSDP VHGYWFRAGN DISWKAPVAT NNPAWAVQEE TRDRFHLLGD
       110        120        130        140        150
PQTKNCTLSI RDARMSDAGR YFFRMEKGNI KWNYKYDQLS VNVTALTHRP
       160        170        180        190        200
NILIPGTLES GCFQNLTCSV PWACEQGTPP MISWMGTSVS PLHPSTTRSS
       210        220        230        240        250
VLTLIPQPQH HGTSLTCQVT LPGAGVTTNR TIQLNVSYPP QNLTVTVFQG
       260        270        280        290        300
EGTASTALGN SSSLSVLEGQ SLRLVCAVDS NPPARLSWTW RSLTLYPSQP
       310        320        330        340        350
SNPLVLELQV HLGDEGEFTC RAQNSLGSQH VSLNLSLQQE YTGKMRPVSG
       360        370        380        390        400
VLLGAVGGAG ATALVFLSFC VIFIVVRSCR KKSARPAADV GDIGMKDANT
       410        420        430        440        450
IRGSASQGNL TESWADDNPR HHGLAAHSSG EEREIQYAPL SFHKGEPQDL
       460
SGQEATNNEY SEIKIPK
```

[0130] In some embodiments, the Siglec-7 is a preprotein that includes a signal sequence. In some embodiments, the Siglec-7 is a mature protein. In some embodiments, the mature Siglec-7 protein does not include a signal sequence. In some embodiments, the mature Siglec-7 protein is expressed on a cell. In some embodiments, the mature Siglec-7 protein is expressed on a cell, such as the surface of a cell, including, without limitation, human dendritic cells, human macrophages, human monocytes, human osteoclasts, human neutrophils, human T cells, human helper T cell, human cytotoxic T cells, human granulocytes, and human microglia. Agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may bind any of the Siglec-7 proteins of the present disclosure expressed on any cell disclosed herein.

[0131] Siglec-7 proteins of the present disclosure, such as human Siglec-7, contain several domains, including without limitation, a signal sequence located at amino acid residues 1-18 of SEQ ID NO: 1, an extracellular immunoglobulin-like variable-type (IgV) domain located at amino acid residues 39-122 of SEQ ID NO: 1, two Ig-like C2-type domains located at amino acid residues 150-233 and 240-336 of SEQ ID NO: 1, a transmembrane domain located at amino acid residues 354-376 of SEQ ID NO: 1, an ITIM motif 1 located at amino acid residues 435-440 of SEQ ID NO: 1, and an ITIM motif 2 located at amino acid residues 459-463 of SEQ ID NO: 1. As one of skill in the art will appreciate, the beginning and ending residues of the domains of the present disclosure may vary depending upon the computer modeling program used or the method used for determining the domain.

[0132] Certain aspects of the present disclosure provide anti-Siglec-7 antibodies that bind to a human Siglec-7, or a homolog thereof, including without limitation a mammalian Siglec-7 protein and Siglec-7 orthologs from other species. Exemplary Siglec-7 homologs and orthologs are listed in **Table A**.

Table A: Siglec-7 homologs and orthologs

Organism	Siglec-7 Accession Number
Chimpanzee *(Pan troglodytes)*	NCBI Accession No. XP_009434417.1
Pygmy chimpanzee (*Pan paniscus*)	NCBI Accession No. XP_008964443.1
Orangutan (*Pongo abelii*)	NCBI Accession No. XP_009231247
Gorilla (*Gorilla gorilla gorilla*)	NCBI Accession No. XP_004061321.1
Gibbon (*Nomascus leucogenys*)	NCBI Accession No. XP_003269883.1

[0133] Accordingly, as used herein a "Siglec-7" protein of the present disclosure includes, without limitation, a mammalian Siglec-7 protein, human Siglec-7 protein, and primate Siglec-7 protein. Additionally, anti-Siglec-7 antibodies of the present disclosure may bind an epitope within one or more of a mammalian Siglec-7 protein, human Siglec-7 protein, and primate Siglec-7. In some embodiments, anti-Siglec-7 antibodies of the present disclosure may bind specifically to a mammalian Siglec-7 protein, human Siglec-7 protein, or both. In certain embodiments, anti-Siglec-7 antibodies of the present disclosure may bind specifically to human Siglec-7, primate Siglec-7, or both.

[0134] In some embodiments, agents of the present disclosure that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands, or that bind or interact with Siglec-7, such as anti-Siglec-7 antibodies of the present disclosure, may bind Siglec-7 in a pH dependent manner. In some embodiments, agents of the present disclosure, such as anti-Siglec-7 antibodies, can bind to Siglec-7 at a neutral pH and be internalized without dissociating from the Siglec-7 protein. Alternatively, at an acidic pH agents of the present disclosure, such as anti-Siglec-7 antibodies, may dissociate from Siglec-7 once they are internalized and are then degraded by

endosome/lysosome pathway. In certain embodiments, an anti-Siglec-7 antibody binds Siglec-7 at a pH that ranges from 5.5 to 8.0, from 5.5 to 7.5, from 5.5 to 7.0, from 5.5 to 6.5, from 5.5 to 6.0, from 6.0 to 8.0, from 6.5 to 8.0, from 7.0 to 8.0, from 7.5 to 8.0, from 6.0 to 7.5, from 6.0 to 7.0, from 6.5 to 7.5. In certain embodiments, an anti-Siglec-7 antibody dissociates from Siglec-7 at a pH of less than 6.0, less than 5.5, less than 5.0, less than 4.5, less than 4.0, less than 3.5, less than 3.0, less than 2.5, or less than 2.0.

[0135] In some embodiments, agents of the present disclosure that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands, or that bind or interact with Siglec-7, such as anti-Siglec-7 antibodies of the present disclosure, bind to a wild-type Siglec-7 protein of the present disclosure, naturally occurring variants thereof, and/or disease variants thereof.

[0136] In some embodiments, agents of the present disclosure that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands, or that bind or interact with Siglec-7, such as anti-Siglec-7 antibodies of the present disclosure, bind a variant of human Siglec-7.

[0137] In some embodiments, agents of the present disclosure that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands, or that bind or interact with Siglec-7, such as anti-Siglec-7 antibodies of the present disclosure, bind to a Siglec-7 protein expressed on the surface of a cell including, without limitation, human dendritic cells, human macrophages, human NK cells, human monocytes, human osteoclasts, human neutrophils, human T cells, human T helper cell, human cytotoxic T cells, human granulocytes, and human microglia. In some embodiments, agents of the present disclosure that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands, or that bind or interact with Siglec-7, such as anti-Siglec-7 antibodies of the present disclosure, bind to a Siglec-7 protein expressed on the surface of a cell and modulate (*e.g.*, induce or inhibit) at least one Siglec-7 activity of the present disclosure after binding to the surface expressed Siglec-7 protein. In some embodiments of the present disclosure, the anti-Siglec-7 antibody binds specifically to a Siglec-7 protein. In some embodiments of the present disclosure, the anti-Siglec-7 antibody further binds to at least one additional Siglec protein. In some embodiments, the anti-Siglec-7 antibody modulates one or more activities of the at least one additional Siglec protein or of a cell expressing the at least one additional Siglec protein.

Siglec-7 ligands

[0138] Siglec-7 proteins of the present disclosure can interact with (*e.g.*, bind to) one or more Siglec-7 ligands.

[0139] Exemplary Siglec-7 ligands include, without limitation, sialic acid, sialic acid-containing glycolipids, sialic acid-containing glycoproteins, alpha-2,8-disialyl containing glycolipids, branched alpha-2,6-linked sialic acid-containing glycoproteins, terminal alpha-2,6-linked sialic acid-containing glycolipids, terminal alpha-2,3-linked sialic acid-containing glycoproteins, disialogangliosides (*e.g.*, gangliosides or glycolipids containing a ceramide linked to a sialylated glycan), secreted mucins, Siglec-7 ligands expressed on red blood cells,Siglec-7 ligands expressed on bacterial cells, Siglec-7 ligands expressed on apoptotic cells, Siglec-7 ligands expressed on nerve cells, Siglec-7 ligands expressed on glial cells, Siglec-7 ligands expressed on microglia, Siglec-7 ligands expressed on astrocytes, Siglec-7 ligands expressed on tumor cells, Siglec-7 ligands expressed on viruses, Siglec-7 ligands expressed on dendritic cells, Siglec-7 ligands bound to beta amyloid plaques, Siglec-7 ligands bound to Tau tangles, Siglec-7 ligands on disease-causing proteins, Siglec-7 ligands on disease-causing peptides, Siglec-7 ligands expressed on macrophages, Siglec-7 ligands expressed on neutrophils, Siglec-7 ligands expressed on monocytes, Siglec-7 ligands expressed on natural killer cells, Siglec-7 ligands expressed on T cells, Siglec-7 ligands expressed on T helper cells, Siglec-7 ligands expressed on cytotoxic T cells, Siglec-7 ligands expressed on B cells, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor dendritic cells, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor macrophages, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor neutrophils, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor NK cells, Siglec-7 ligands expressed on myeloid-derived suppressor cells, and Siglec-7 ligands expressed on regulatory T cells. In some embodiments, Siglec-7 ligands of the present disclosure are ganglioside (e.g., disialogangliosides). Disialogangliosides generally share a common lacto-ceramide core and one or more sialic acid residues.

[0140] Further examples of suitable Siglec-7 ligands are depicted in **FIG. 2**.

[0141] Further examples of suitable ganglioside (e.g., disialogangliosides) ligands are depicted in **FIG. 3** and listed in **Table B**. Generally, a ganglioside (e.g., disialogangliosides) is a molecule composed of a glycosphingolipid with one or more sialic acids (*e.g.*, n-acetyl-neuraminic acid, NANA) linked on the sugar chain.

Table B: Structures of exemplary ganglioside Siglec-7 ligands

GM2-1 = aNeu5Ac(2-3)bDGalp(1-?)bDGalNAc(1-?)bDGalNAc(1-?)bDGlcp(1-1)Cer
GM3 = aNeu5Ac(2-3)bDGalp(1-4)bDGlcp(1-1)Cer
GM2,GM2a(?) = bDGalpNAc(1-4)[aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GM2b(?) = aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlcp(1-1)Cer
GM1,GM1a = bDGalp(1-3)bDGalNAc[aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
asialo-GM1,GA1 = bDGalp(1-3)bDGalpNAc(1-4)bDGalp(1-4)bDGlcp(1-1)Cer
asialo-GM2,GA2 = bDGalpNAc(1-4)bDGalp(1-4)bDGlcp(1-1)Cer
GM1b = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)bDGalp(1-4)bDGlcp(1-1)Cer
GD3 = aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlcp(1-1)Cer
GD2 = bDGalpNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GD1a = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GD1alpha = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-6)]bDGalp(1-4)bDGlcp(1-1)Cer
GD1b = bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GT1a = aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GT1,GT1b = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
OAc-GT1b = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)aXNeu5Ac9Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GT1c = bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GT3 = aNeu5Ac(2-8)aNeu5Ac(2-8)aNeu5Ac(2-3)bDGal(1-4)bDGlc(1-1)CerGQ1b = aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GGal = aNeu5Ac(2-3)bDGalp(1-1)Cer
where:
aNeu5Ac = 5-acetyl-alpha-neuraminic acid
aNeu5Ac9Ac = 5,9-diacetyl-alpha-neuraminic acid
bDGalp = beta-D-galactopyranose
bDGalpNAc = N-acetyl-beta-D-galactopyranose
bDGlcp = beta-D-glucopyranose
Cer = ceramide (general N-acylated sphingoid)

Siglec-7 agents

[0142] Certain aspects of the present disclosure relate to agents (e.g., Siglec-7 agents) that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands. Other aspects of the present disclosure relate to agents (e.g., Siglec-7 agents) that bind or interact with Siglec-7. In some embodiments, agents of the present disclosure block, inhibit, reduce, or interfere with one or more activities of a Siglec-7 protein *in vitro*, *in situ*, and/or *in vivo*. In some embodiments, agents of the present disclosure do not block, inhibit, reduce, or interfere with one or more activities of a Siglec-7 protein *in vitro*, *in situ*, and/or *in vivo*. In some embodiments, agents of the present disclosure, increase, activate or induce one or more activities of a Siglec-7 protein *in vitro*, *in situ*, and/or *in vivo*.

[0143] In certain embodiments, agents of the present disclosure are agents (e.g., Siglec-7 agents) that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligand. An agent of the present disclosure that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands is a molecule having one or more of the following characteristics: (1) inhibits or reduces one or more Siglec-7activities; (2) the ability to inhibit or reduce binding of a Siglec-7 to one or more of its ligands; (3) the ability to reduce Siglec-7 expression (such as at the mRNA level and/or at protein level) in Siglec-7-expressing cells;

(4) the ability to interact, bind, or recognize a Siglec-7 protein; (5) the ability to specifically interact with or bind to a Siglec-7 protein; and (6) the ability to treat, ameliorate, or prevent any aspect of a disease or disorder described or contemplated herein.

[0144] Exemplary agents that inhibit the production of Siglec-7 include, without limitation, compounds that specifically inhibit Siglec-7 synthesis and/or release, antisense molecules directed to a Siglec-7, or a short interfering RNA (siRNA) molecule directed to a nucleic acid encoding a Siglec-7. Additional exemplary agents that inhibit one or more Siglec-7 activities include, without limitation, anti-Siglec-7 antibodies that specifically bind to a Siglec-7 protein, compounds that specifically inhibit one or more Siglec-7 activities such as small molecule inhibitors and/or peptide inhibitors, compounds that specifically inhibit Siglec-7 binding to one or more ligands, a Siglec-7 structural analog, or an RNA or DNA aptamer that binds a Siglec-7. In some embodiments, an agent that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands is an allosteric inhibitor. In some embodiments, an agent that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands is an orthosteric inhibitor.

[0145] In certain embodiments, an agent that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands is a small molecule inhibitor, including, without limitation, small peptides or peptide-like molecules, soluble peptides, and synthetic non-peptidyl organic or inorganic compounds. A small molecule inhibitor may have a molecular weight of any of about 100 to about 20,000 daltons (Da), about 500 to about 15,000 Da, about 1000 to about 10,000 Da. Methods for making and testing the inhibitory effect a small molecule has on one or more Siglec-7 activities are well known in the art and such methods can be used to assess the effect of the small molecule inhibitor on Siglec-7 activity. For example, any of the methods and assays disclosed herein may be used to screen for small molecule inhibitors that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligand.

[0146] In certain embodiments, an agent that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands is an anti-Siglec-7 antibody that binds or physically interacts with a Siglec-7. The antibody may have nanomolar or even picomolar affinities for the target antigen (*e.g.,* Siglec-7). In certain embodiments, the Kd of the antibody is about 0.002 to about 100 nM. In certain embodiments, the Kd of the antibody is about 0.05 to about 100 nM. In certain embodiments, the Kd of the antibody is about 0.05 to about 50 nM. In certain embodiments, the Kd of the antibody is about 0.05 to about 10 nM. In certain embodiments, the Kd of the antibody is about 0.05 to about 2 nM. In certain embodiments, the Kd of the antibody is about 0.1 to about 2 nM. For example, Kd of the antibody is any of about 100 nM, about 90 nM, about 80

nM, about 70 nM, about 60 nM, about 50 nM, about 45 nM, about 40 nM, about 35 nM, about 30 nM, about 25 nM, about 20 nM, about 15 nM, about 10 nM, about 9 nM, about 8 nM, about 7 nM, about 6 nM, about 5 nM, about 4 nM, about 3 nM, about 2 nM, about 1 nM, about 900 pM, about 800 pM, about 700 pM, about 600 pM, about 500 pM, about 400 pM, about 300 pM, about 200 pM, about 100 pM, about 75 pM, or about 50 pM to any of about 2 pM, about 5 pM, about 10 pM, about 15 pM, about 20 pM, about 25 pM about 50 pM, about 75 pM, about 100 pM, about 200 pM, about 300 pM, about 400 pM, about 500 pM, about 600 pM, about 700 pM, about 800 pM, about 900 pM, about 1 nM, or about 2 nM. In some embodiments, the dissociation constant (K_D) for Siglec-7 is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (e.g., a Fab) or a full-length antibody in a monovalent form. Methods for the preparation and selection of antibodies that interact and/or bind with specificity to a Siglec-7 are described herein. (e.g., see **Example 1**).

[0147] In certain embodiments, an agent that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands comprises at least one antisense molecule capable of blocking or decreasing the expression of a functional Siglec-7 by targeting nucleic acids encoding a Siglec-7. Nucleic acid sequences of Siglec-7 are known in the art. For example, a human Siglec-7 can have a nucleic acid sequence as shown in NCBI Accession number NM_014385.3 and a chimpanzee Siglec-7 can have a nucleic acid sequence as shown in NCBI Accession number XM_009436142.1. Methods are known for the preparation of antisense oligonucleotide molecules and such methods can be used to prepare antisense oligonucleotides that will specifically bind one or more of a Siglec-7 mRNA without cross-reacting with other polynucleotides. Exemplary sites of targeting include, but are not limited to, the initiation codon, the 5' regulatory regions, the coding sequence, including any conserved consensus regions, and the 3' untranslated region. In certain embodiments, the antisense oligonucleotides are about 10 to about 100 nucleotides in length, about 15 to about 50 nucleotides in length, about 18 to about 25 nucleotides in length, or more. In certain embodiments, the oligonucleotides further comprise chemical modifications to increase nuclease resistance and the like, such as, for example, phosphorothioate linkages and 2'-O-sugar modifications known to those of ordinary skill in the art.

[0148] In certain embodiments, an agent that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands comprises at least one siRNA molecule capable of blocking or decreasing the expression of a functional Siglec-7 by targeting nucleic acids encoding a Siglec-7. Methods for preparation of siRNA molecules are well known in the art and such methods can be used to prepare siRNA molecules that will specifically target a Siglec-7 mRNA without cross-reacting with other polynucleotides. siRNA molecules may be generated by methods such as by typical solid phase oligonucleotide synthesis, and often will

incorporate chemical modifications to increase half-life and/or efficacy of the siRNA agent, and/or to allow for a more robust delivery formulation. Alternatively, siRNA molecules are delivered using a vector encoding an expression cassette for intracellular transcription of siRNA.

[0149] In certain embodiments, an agent that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands is an RNA or DNA aptamer that binds or physically interacts with a Siglec-7, and blocks interactions between a Siglec-7 and one or more of its ligands. In certain embodiments, the aptamer comprises at least one RNA or DNA aptamer that binds to a mature form of Siglec-7.

[0150] In certain embodiments, an agent that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands comprises at least one Siglec-7 structural analog. The term Siglec-7 structural analog refers to compounds that have a similar three dimensional structure as part of that of a Siglec-7 and which bind to one or more CD3 ligands under physiological conditions *in vitro* or *in vivo*, wherein the binding at least partially inhibits a Siglec-7 biological activity. Suitable Siglec-7 structural analogs can be designed and synthesized through molecular modeling of Siglec-7 binding to a ligand, such as a Siglec-7 ligand of the present disclosure. The Siglec-7 structural analogs can be monomers, dimers, or higher order multimers in any desired combination of the same or different structures to obtain improved affinities and biological effects. In some embodiments, the agent binds to or interacts with an amino acid sequence of a Siglec-7.

[0151] In certain embodiments, an agent that decreases cellular levels of Siglec-7 and/or inhibits interaction between Siglec-7 and one or more Siglec-7 ligands comprises a soluble Siglec-7 receptor protein, a soluble Siglec-7-Fc fusion protein (e.g., Siglec-7 immunoadhesin), a soluble Siglec receptor that binds to a Siglec-7 ligand, a Siglec-Fc fusion protein (e.g., Siglec immunoadhesin) that binds to a Siglec-7 ligand. In certain embodiments, such agents bind one or more Siglec-7 ligands and thereby prevent the interaction between a given Siglec-7 ligand and a functional Siglec-7 receptor.

[0152] In certain embodiments, agents of the present disclosure are agents (e.g., Siglec-7 agents) that bind or interact with Siglec-7. Exemplary agents that bind or interact with Siglec-7 include, without limitation, inert anti-Siglec-7 antibodies, agonist anti-Siglec-7 antibodies, Siglec-7 ligands, Siglec-7 ligand agonist fragments, Siglec-7 immunoadhesins, Siglec-7 soluble receptors, Siglec-Fc fusion proteins (e.g., Siglec immunoadhesins), soluble Siglec receptors, Siglec-7 ligand mimetics, and small molecule compounds. A small molecule compound may have a molecular weight of any of about 100 to about 20,000 daltons (Da), about 500 to about 15,000 Da, about 1000 to about 10,000 Da. Methods for making and testing the effect an agent has on one or more Siglec-7 activities are well known in the art and such methods can be used to assess the effect of the small molecule

inhibitor on Siglec-7 activity. For example, any of the methods and assays disclosed herein may be used to screen for small molecule inhibitors that bind or interact with Siglec-7.

Assays

[0153] Agents that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands may be identified and/or characterized using methods well known in the art, such as, for example, radiolabeled inhibitor assays, optical assays, protein binding assays, biochemical screening assays, immunoassays, mass shift measurement assays, fluorescence assays, and/or fluorogenic peptide cleavage assays.

Binding assays and other assays

[0154] In certain embodiments, agents that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands can be identified by techniques well known in the art for detecting the presence of a Siglec-7 agent candidate's interaction and/or binding affinity to a Siglec-7.

[0155] In certain embodiments, agents that interact with a Siglec-7 can be identified using a radiolabeled inhibitor assay. For example, a known amount of a radiolabeled agent candidate may be incubated with a known amount of immobilized Siglec-7 and a buffer. Subsequently, the immobilized Siglec-7 may be washed with a buffer and the immobilized Siglec-7 may be measured for the remaining presence of the radiolabeled Siglec-7 agent candidate using techniques known in the art, such as, for example, a gamma counter. A measurement indicating the presence of a radiolabeled substance may indicate the radiolabeled agent candidate is capable of interacting with and/or binding to Siglec-7.

[0156] In certain embodiments, an agent that interacts with a Siglec-7 may be identified using an optical technique. An exemplary optical technique to detect a Siglec-7 agent may include, *e.g.*, attaching Siglec-7 to a colorimetric resonant grafting surface, thereby shifting the wavelength of reflected light due to changes in the optical path the light must take, and subsequently measuring additional changes in the wavelength of reflected light when a candidate agent is allowed to interact with Siglec-7. For example, no change in the measured wavelength of reflected light when an agent is incubated with Siglec-7 may indicate that the agent candidate is unable to interact with Siglec-7. Changes in the measured wavelength of reflected light when an agent candidate is incubated with Siglec-7 may indicate that the agent candidate is capable of binding and/or interacting with Siglec-7.

[0157] In certain embodiments, an agent that interacts with a Siglec-7 may be identified using a protein-binding assay. An exemplary protein-binding assay to detect a Siglec-7 agent may include, *e.g.*, co-immunoprecipitation of a Siglec-7 in the presence of the agent candidate. For example, a Siglec-7 may be incubated with the agent candidate in buffer, and subsequently an immobilized molecule specific to capture a Siglec-7, such as, for example, an anti-Siglec-7 antibody, may be used

to capture Siglec-7 in the presence of the agent candidate and bind the Siglec-7, potentially with an interacting agent candidate, during wash procedures known in the art. Subsequently, Siglec-7, potentially with an interacting agent candidate, can be released and the presence of an agent candidate may be detected, based on the agent candidate characteristics, by techniques, such as, for example, mass spectrometry and/or Western blot.

[0158] In certain embodiments, an agent that interacts with a Siglec-7 may be identified using a biochemical and/or an immunoassay assay well known in the art. An exemplary technique may include, *e.g.*, an assay to quantitatively measure changes in Siglec-7 concentration and/or protein half-life using techniques, such as, for example, Western blot, immunostaining, and co-immunoprecipitation. For example, an agent candidate may be incubated with a sample containing a Siglec-7, such as a cell expressing Siglec-7 and subsequently Siglec-7 protein quantity and/or cellular levels may be measured at points during a time course study. Changes in protein quantity, cellular levels, and/or protein half-life in comparison to a control treatment may indicate that the Siglec-7 agent candidate may be capable of altering Siglec-7 half-life and/or activity.

[0159] In certain embodiments, a mass shift measurement assay may be used to identify an agent that interacts with a Siglec-7. An exemplary mass shift measurement assay may include, *e.g.*, detecting the presence of a strongly and/or covalently bound Siglec-7 agent by measuring a change in Siglec-7 mass when the agent candidate is interacting with Siglec-7 by using instruments, such as, but not limited to, a mass spectrometer. For example, a mass shift assay may be performed on a whole protein and/or a peptide-based analysis, depending on the nature of the agent candidate interaction. Detection of a mass shift correlating with the addition of said agent candidate to Siglec-7 may indicate that the agent candidate may be capable of interacting with or otherwise inhibiting a Siglec-7. Additionally, an exemplary mass shift measurement assay may include, *e.g.*, detecting the addition of mass to Siglec-7 correlating with the respective agent candidate mass when the agent candidate is interacting with Siglec-7 using techniques, such as, for example, surface plasmon resonance. For example, the change in the refractive index of light may be measured and correlated with a change in mass of Siglec-7 attached to a sensor surface.

[0160] In certain embodiments, a chemical cross-linking assay may be used to identify a Siglec-7 agent that interacts with a Siglec-7. For example, an agent candidate may be incubated with a Siglec-7, *in vivo* or *in vitro*, with a molecule cross-linker capable of covalently linking an agent candidate interacting with Siglec-7 to said Siglec-7 molecule. Subsequently, techniques, such as, but not limited to, mass spectrometry and/or Western blot, may be used to identify an agent candidate that may be capable of interacting with or otherwise inhibiting Siglec-7. For example, detection of Siglec-7covalently cross-linked with the agent candidate may indicate that the agent candidate may be capable of interacting with or otherwise inhibiting Siglec-7.

[0161] In certain embodiments, agents that interact with a Siglec-7 may be identified using a fluorescence assay. For example, a known amount of a fluorescent agent candidate may be incubated with a known amount of immobilized Siglec-7 and a buffer. Subsequently, the immobilized Siglec-7 may be washed with a buffer and the immobilized Siglec-7 may be measured for the remaining presence of a fluorescent Siglec-7 agent candidate using techniques known in the art, such as, but not limited to, fluorescence detection. A measurement indicating the presence of a fluorescent substance may indicate the fluorescent agent candidate is capable of interacting with and/or binding to Siglec-7.

Activity assays

[0162] Assays known in the art and described herein (*e.g.,* **Examples 1-10**) can be used for identifying and testing biological activities of Siglec-7 agents of the present disclosure. In some embodiments, assays for testing the ability of Siglec-7 agents for modulating one or more Siglec-7 activities are provided.

Anti-Siglec-7 antibodies

[0163] Certain aspects of the present disclosure relate to anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands. In some embodiments, the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 without inhibiting the interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands. In some embodiments, the anti-Siglec-7 antibody inhibits the interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands. In some embodiments, the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 and inhibits the interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands.

[0164] Cellular levels of Siglec-7 may refer to, without limitation, cell surface levels of Siglec-7, intracellular levels of Siglec-7, and total levels of Siglec-7. In some embodiments, a decrease in cellular levels of Siglec-7 comprises decrease in cell surface levels of Siglec-7. As used herein, an anti-Siglec-7 antibody decreases cell surface levels of Siglec-7 if it induces a decrease of 21% or more in cell surface levels of Siglec-7 as measured by any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art, for example, utilizing flow cytometry, such as fluorescence-activated cell sorting (FACS), to measure cell surface levels of Siglec-7. In some embodiments, a decrease in cellular levels of Siglec-7 comprises a decrease in intracellular levels of Siglec-7. As used herein, an anti-Siglec-7 antibody decreases intracellular levels of Siglec-7 if it induces a decrease of 21% or more in intracellular levels of Siglec-7 as measured by any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art, for example immunostaining, Western blot analysis, co-immunoprecipitation, and cell cytometry. In some embodiments, a decrease in cellular levels of Siglec-7 comprises a decrease in total levels of Siglec-7. As used herein, an anti-Siglec-7 antibody decreases total levels of Siglec-7 if it induces a decrease of

21% or more in total levels of Siglec-7 as measured by any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art, for example immunostaining, Western blot analysis, co-immunoprecipitation, and cell cytometry. In some embodiments, the anti-Siglec-7 antibodies induce Siglec-7 degradation, Siglec-7 cleavage, Siglec-7 internalization, Siglec-7 shedding, and/or downregulation of Siglec-7 expression. In some embodiments, cellular levels of Siglec-7 are measured on primary cells (*e.g.*, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, and macrophages) or on cell lines utilizing an *in vitro* cell assay.

[0165] In some embodiments, anti-Siglec-7 antibodies of the present disclosure decrease cellular levels of Siglec-7 by at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more as compared to cellular levels of Siglec-7 in the absence of the anti-Siglec-7 antibody.

[0166] In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that may be less than 10 nM, less than 9.5 nM, less than 9 nM, less than 8.5 nM, less than 8 nM, less than 7.5 nM, less than 7 nM, less than 6.5 nM, less than 6 nM, less than 5.5 nM, less than 5 nM, less than 4.5 nM, less than 4 nM, less than 3.5 nM, less than 3 nM, less than 2.5 nM, less than 2 nM, less than 1.5 nM, less than 1.4 nM, less than 1.3 nM, less than 1.2 nM, less than 1.1 nM, less than 1 nM, less than 500 pM, less than 450 pM, less than 400 pM, less than 350 pM, less than 300 pM, less than 250 pM, less than 200 pM, less than 175 pM, less than 170 pM, less than 169 pM, less than 168 pM, less than 167 pM, less than 166 pM, less than 166.2 pM, less than 165 pM, less than 164 pM, less than 163 pM, less than 162 pM, less than 161 pM, less than 160 pM, less than 150 pM, less than 145 pM, less than 140 pM, less than 139 pM, less than 138 pM, less than 138.2 pM, less than 137 pM, less than 136 pM, less than 135 pM, less than 134 pM, less than 133 pM, less than 132 pM, less than 131 pM, less than 130 pM, less than 120 pM, less than 110 pM, less than 100 pM, less than 90 pM, less than 80 pM, less than 70 pM, less than 60 pM, less than 50 pM, less than 40 pM, less than 35 pM, less than 33 pM, less than 30 pM, less than 20 pM, less than 19 pM, less than 18 pM, less than 17 pM, less

than 16 pM, less than 15 pM, less than 14 pM, less than 13 pM, less than 12 pM, less than 11 pM, or less than 10 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that ranges from about 10 nM to about 10 pM, or less than 10 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that ranges from about 10 nM to about 100 pM, or less than 100 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that ranges from about 10 nM to about 300 pM, or less than 300 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that ranges from about 2 nM to about 10 pM, or less than 10 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that ranges from about 2 nM to about 100 pM, or less than 100 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that ranges from about 2 nM to about 300 pM, or less than 300 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that ranges from about 1.4 nM to about 10 pM, or less than 10 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that ranges from about 1.4 nM to about 100 pM, or less than 100 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to human cells, such as primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that ranges from about 1.4 nM to about 300 pM, or less than 300 pM. Any suitable methods described herein (e.g., see **Examples 1-3**) may be used to calculate the half-maximal effective concentration (EC_{50}) for anti-Siglec-7 antibodies of the present disclosure binding to human cells, such as primary dendritic cells. In some embodiments, the half-maximal effective concentration (EC_{50}) is determined at a temperature of approximately 4°C.

[0167] In some embodiments, anti-Siglec-7 antibodies of the present disclosure decrease cellular levels of Siglec-7 with a half-maximal effective concentration (EC_{50}) that may be less than 500 pM, less than 450 pM, less than 400 pM, less than 350 pM, less than 300 pM, less than 250 pM, less than 200 pM, less than 175 pM, less than 170 pM, less than 169 pM, less than 168 pM, less than 167 pM, less than 166 pM, less than 166.2 pM, less than 165 pM, less than 164 pM, less than 163 pM, less than 162 pM, less than 161 pM, less than 160 pM, less than 150 pM, less than 145 pM, less than 140 pM, less than 139 pM, less than 138 pM, less than 138.2 pM, less than 137 pM, less than 136 pM,

less than 135 pM, less than 134 pM, less than 133 pM, less than 132 pM, less than 131 pM, less than 130 pM, less than 120 pM, less than 110 pM, less than 100 pM, less than 90 pM, less than 80 pM, less than 70 pM, less than 60 pM, less than 50 pM, less than 40 pM, less than 35 pM, less than 33 pM, less than 30 pM, less than 20 pM, less than 19 pM, less than 18 pM, less than 17 pM, less than 16 pM, less than 15 pM, less than 14 pM, less than 13 pM, less than 12 pM, less than 11 pM, or less than 10 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure decrease cellular levels of Siglec-7 with a half-maximal effective concentration (EC_{50}) that ranges from about 500 pM to about 18 pM, or less than 18 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure decrease cellular levels of Siglec-7 with a half-maximal effective concentration (EC_{50}) that ranges from about 500 pM to about 33 pM, or less than 33 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure decrease cellular levels of Siglec-7 with a half-maximal effective concentration (EC_{50}) that ranges from about 350 pM to about 18 pM, or less than 18 pM. In some embodiments, anti-Siglec-7 antibodies of the present disclosure decrease cellular levels of Siglec-7 with a half-maximal effective concentration (EC_{50}) that ranges from about 350 pM to about 33 pM, or less than 33 pM. Any suitable method (e.g., see **Examples 1-3**) may be used to measure the half-maximal effective concentration (EC_{50}) of the anti-Siglec-7 antibodies of the present disclosure. In some embodiments, the EC_{50} is determined at a temperature of approximately 37°C.

[0168] Any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art may be used to measure inhibition of interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands. In some embodiments, anti-Siglec-7 antibodies of the present disclosure inhibit interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands by at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more at saturating antibody concentrations (*e.g.*, 67 nM) utilizing any *in vitro* assay or cell-based culture assay described herein or known in the art.

[0169] In some embodiments, anti-Siglec-7 antibodies of the present disclosure inhibit cell surface clustering of Siglec-7. In some embodiments, anti-Siglec-7 antibodies of the present

disclosure inhibit one or more activities of a Siglec-7 protein, including, without limitation, phosphorylation of Tyr-437 and Tyr-460 by a Src family tyrosine kinase, such as Syk, LCK, FYM, and/orZAP70; recruitment of and binding to the tyrosine-specific protein phosphatases SHP1 and SHP2; recruitment of and binding to PLC-gamma1, which acts as a guanine nucleotide exchange factor for Dynamini-1; recruitment of and binding to SH2-domain containing protein (*e.g.*, Crkl); recruitment of and binding to the spleen tyrosine kinase Syk; recruitment of and binding to SH3-SH2-SH3 growth factor receptor-bound protein 2 (Grb2); recruitment of and binding to multiple SH2-containing proteins; modulated expression of one or more pro-inflammatory cytokines, optionally wherein the one or more anti-inflammatory cytokines are selected from a group consisting IFN-a4, IFN-beta, IL-1â, IL-1alpha, TNF-á, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-33, MCP-1, and MIP-1-beta; modulated expression of one or more pro-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; modulated expression of one or more anti-inflammatory cytokines, optionally wherein the one or more anti-inflammatory cytokines are selected from IL-4, IL-10, IL-13, IL-35, IL-16, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, or IL-6; modulated expression of one or more anti-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; modulate expression of one or more proteins selected from C1qa, C1qB, C1qC, C1s, C1R, C4, C2, C3, ITGB2, HMOX1, LAT2, CASP1, CSTA, VSIG4, MS4A4A, C3AR1, GPX1, TyroBP, ALOX5AP, ITGAM, SLC7A7, CD4, ITGAX, and PYCARD; inhibition of extracellular signal-regulated kinase (ERK) phosphorylation; decreasing tyrosine phosphorylation on one or more cellular proteins, optionally, wherein the one or more cellular proteins comprise ZAP-70 and the tyrosine phosphorylation occurs on Tyr-319 of ZAP-70; modulated expression of C-C chemokine receptor 7 (CCR7); inhibition of microglial cell chemotaxis toward CCL19-expressing and CCL21-expressing cells; decreasing T cell proliferation induced by one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, M1 microglia, activated M1 microglia, M2 microglia, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, and M2 NK cells; inhibition of osteoclast production, decreased rate of osteoclastogenesis, or both; decreasing survival of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells,

monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; decreasing proliferation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibiting migration of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibiting one or more functions of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibiting maturation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibition of one or more types of clearance selected from apoptotic neuron clearance, nerve tissue debris clearance, dysfunctional synapse clearance, non-nerve tissue debris clearance, bacteria clearance, other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, disease-causing nucleic acid clearance, and tumor cell clearance; optionally wherein the disease-causing protein is selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR)

repeat peptides, the disease-causing nucleic acid is an antisense GGCCCC (G2C4) repeat-expansion RNA, and the tumor cell is from a cancer selected from 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, and thyroid cancer; inhibition of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, dysfunctional synapses, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, disease-causing nucleic acids, or tumor cells; optionally wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and the tumor cells are from a cancer selected from 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, or thyroid cancer; binding to Siglec-7 ligand on tumor cells; binding to Siglec-7 ligand on cells selected from neutrophils, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, and NK cells; inhibition of tumor cell killing by one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; inhibiting anti-tumor cell proliferation activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; inhibition of anti-tumor cell metastasis activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; inhibition of one or more ITAM motif containing receptors, optionally wherein the one or more ITAM motif containing receptors are selected from TREM1, TREM2, Sirp beta, FcgR, DAP10, and DAP12; inhibition of signaling by one or more pattern recognition receptors (PRRs), optionally wherein the one or more PRRs are selected from receptors that identify pathogen-associated molecular patterns (PAMPs), receptors that identify damage-

associated molecular patterns (DAMPs), and any combination thereof; inhibition of one or more receptors comprising the motif D/Ex_{0-2}YxxL/IX_{6-8}YxxL/I (SEQ ID NO: 537); inhibition of signaling by one or more Toll-like receptors; inhibition of the JAK-STAT signaling pathway; inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NFêB); de-phosphorylation of an ITAM motif containing receptor; modulated expression of one or more inflammatory receptors, optionally wherein the one or more inflammatory receptors comprise CD86 and the one or more inflammatory receptors are expressed on one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; increasing expression of one or more Siglec-7-dependent genes; normalization of disrupted Siglec-7-dependent gene expression; decreasing expression of one or more ITAM-dependent genes, optionally wherein the one more ITAM-dependent genes are activated by nuclear factor of activated T cells (NFAT) transcription factors; promoting or rescuing functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells; increasing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells into tumors; increasing the number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; enhancing tumor-promoting activity of myeloid-derived suppressor cells; increasing expression of tumor-promoting cytokines, such as TGF-beta or IL-10, in a tumor or in peripheral blood; increasing tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes; enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); decreasing activation of tumor-specific T lymphocytes with tumor killing potential; decreasing infiltration of tumor-specific NK cells with tumor killing potential; decreasing the tumor killing potential of NK cells; decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; increasing tumor volume; increasing tumor growth rate; increasing metastasis; increasing rate of tumor recurrence; decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, such as immune-therapies are immune-therapies that target one or more target proteins selected from PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines; inhibition of PLCã/PKC/calcium mobilization; and inhibition of PI3K/Akt, Ras/MAPK signaling.

[0170] In some embodiments, anti-Siglec-7 antibodies of the present disclosure exhibit one or more activities, including, without limitation, increasing the number of tumor infiltrating $CD3^+$ T cells; inhibiting Siglec-7 binding to one or more Siglec-7 ligands; decreasing cellular levels of Siglec-7 in peripheral immune cells; reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in blood; reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in the tumor; reducing PD-L1 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); reducing PD-L2 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); reducing CD11b levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); reducing B7-H3 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); reducing CD200R levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); reducing CD163 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); reducing CD206 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); decreasing tumor growth rate of solid tumors; reducing tumor volume; increasing efficacy of one or more PD-1 inhibitors; increasing efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, optionally wherein the one or more checkpoint inhibitor therapies and/or immune-modulating therapies target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, LAG3, or any combination thereof; inhibiting differentiation, survival, and/or one or more functions of non-tumorigenic myeloid-derived suppressor cells (MDSC); inducing cell death of one or more myeloid-derived suppressor cells (MDSC); and increasing proliferation of T cells in the presence of non-tumorigenic myeloid-derived suppressor cells (MDSC).

[0171] In some embodiments, the anti-Siglec-7 antibodies inhibit interaction (*e.g.*, binding) between a Siglec-7 protein of the present disclosure and one or more Siglec-7 ligands including, without limitation, Siglec-7 ligands expressed on red blood cells,Siglec-7 ligands expressed on bacterial cells, Siglec-7 ligands expressed on apoptotic cells, Siglec-7 ligands expressed on nerve cells, Siglec-7 ligands expressed on glial cells, Siglec-7 ligands expressed on microglia, Siglec-7 ligands expressed on astrocytes, Siglec-7 ligands expressed on tumor cells, Siglec-7 ligands expressed on viruses, Siglec-7 ligands expressed on dendritic cells, Siglec-7 ligands bound to beta amyloid plaques, Siglec-7 ligands bound to Tau tangles, Siglec-7 ligands on disease-causing proteins,

Siglec-7 ligands on disease-causing peptides, Siglec-7 ligands expressed on macrophages, Siglec-7 ligands expressed on neutrophils, Siglec-7 ligands expressed on monocytes, Siglec-7 ligands expressed on natural killer cells, Siglec-7 ligands expressed on T cells, Siglec-7 ligands expressed on T helper cells, Siglec-7 ligands expressed on cytotoxic T cells, Siglec-7 ligands expressed on B cells, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor dendritic cells, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor macrophages, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor neutrophils, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor NK cells, Siglec-7 ligands expressed on myeloid-derived suppressor cells, and Siglec-7 ligands expressed on regulatory T cells. In some embodiments, Siglec-7 ligands of the present disclosure are gangliosides (e.g., disialogangliosides).

[0172] In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to a Siglec-7 protein of the present disclosure expressed on the surface of cell and the naked antibodies inhibit interaction (*e.g.*, binding) between the Siglec-7 protein and one or more Siglec-7 ligands. In some embodiments, anti-Siglec-7 antibodies of the present disclosure that bind to a Siglec-7 protein of the present disclosure inhibit interaction (*e.g.*, binding) between the Siglec-7 protein and one or more Siglec-7 ligands by reducing the effective levels of Siglec-7 that is available to interact with these proteins either on the cell surface or inside the cell. In some embodiments, anti-Siglec-7 antibodies of the present disclosure that bind to a Siglec-7 protein of the present disclosure inhibit interaction (*e.g.*, binding) between the Siglec-7 protein and one or more Siglec-7 ligands by inducing degradation of Siglec-7.

[0173] Other aspects of the present disclosure relate to anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction between Siglec-7 and one or more Siglec-7 ligands.

[0174] As used herein, an anti-Siglec-7 antibody does not significantly decrease cell surface levels of Siglec-7 if it decreases cell surface levels of Siglec-7 by less than 20% as compared to cellular levels of Siglec-7 in the absence of the anti-Siglec-7 antibody utilizing any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art. In some embodiments, anti-Siglec-7 antibodies of the present disclosure decrease cell surface levels of Siglec-7 by less than 20%, less than 19%, less than 18%, less than 17%, less than 16%, less than 15%, less than 14%, less than 13%, less than 12%, less than 11%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% as compared to cellular levels of Siglec-7 in the absence of the anti-Siglec-7 antibody.

[0175] As used herein, an anti-Siglec-7 antibody does not inhibit the interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands if it decreases ligand binding to Siglec-7 by less than 20% at saturating antibody concentrations (*e.g.*, 67 nM) utilizing any *in vitro* assay or cell-based

culture assay described herein or known in the art. In some embodiments, anti-Siglec-7 antibodies of the present disclosure inhibit interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands by less than 20%, less than 19%, less than 18%, less than 17%, less than 16%, less than 15%, less than 14%, less than 13%, less than 12%, less than 11%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% at saturating antibody concentrations (*e.g.*, 67 nM) utilizing any *in vitro* assay or cell-based culture assay described herein or known in the art.

[0176] As used herein, levels of Siglec-7 may refer to expression levels of the gene encoding Siglec-7; to expression levels of one or more transcripts encoding Siglec-7; to expression levels of Siglec-7 protein; and/or to the amount of Siglec-7 protein present within cells and/or on the cell surface. Any methods known in the art for measuring levels of gene expression, transcription, translation, and/or protein abundance or localization may be used to determine the levels of Siglec-7.

[0177] Additionally, anti-Siglec-7 antibodies of the present disclosure can be used to prevent, reduce risk of, or treat 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and/or Haemophilus influenza. In some embodiments, anti-Siglec-7 antibodies of the present disclosure can be used for

inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof; or for decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, and/or chronic myeloid leukemia (CML) cell in an individual in need thereof. In some embodiments, anti-Siglec-7 antibodies of the present disclosure are monoclonal antibodies.

[0178] In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure decreases cellular levels of Siglec-7 (*e.g.*, cell surface levels, intracellular levels, and/or total levels). In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure induces downregulation of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure induces cleavage of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure induces internalization of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure induces shedding of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure induces degradation of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure induces desensitization of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure acts as a ligand mimetic to transiently activate Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure acts as a ligand mimetic and transiently activates Siglec-7 before inducing a decrease in cellular levels of Siglec-7 and/or inhibition of interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure acts as a ligand mimetic and transiently activates Siglec-7 before inducing degradation of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure acts as a ligand mimetic and transiently activates Siglec-7 before inducing cleavage of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure acts as a ligand mimetic and transiently activates Siglec-7 before inducing internalization of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure acts as a ligand mimetic and transiently activates Siglec-7 before inducing shedding of Siglec-7. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure acts as a ligand mimetic and transiently activates Siglec-7 before inducing downregulation of Siglec-7 expression. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure acts as a ligand mimetic and transiently activates Siglec-7 before inducing desensitization of Siglec-7.

[0179] In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure is a murine antibody. In some embodiments, an isolated anti-Siglec-7 antibody of the present disclosure is a human antibody, a humanized antibody, a bispecific antibody, a monoclonal antibody, a

multivalent antibody, or a chimeric antibody. Exemplary descriptions of such antibodies are found throughout the present disclosure.

[0180] In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to a human Siglec-7, or a homolog thereof, including without limitation, a mammalian Siglec-7 protein, chimpanzee Siglec-7 protein (NCBI Accession No. XP_009434417.1),pygmy chimpanzee Siglec-7 protein (XP_008964443.1), orangutan Siglec-7 protein (NCBI Accession No. XP_009231247), gorilla Siglec-7 protein (NCBI Accession No. XP_004061321.1), or gibbon Siglec-7 protein (NCBI Accession No. XP_003269883.1). In some embodiments, anti-Siglec-7 antibodies of the present disclosure specifically bind to human Siglec-7. In some embodiments, anti-Siglec-7 antibodies of the present disclosure specifically bind to primate Siglec-7. In some embodiments, anti-Siglec-7 antibodies of the present disclosure specifically bind to both human Siglec-7 and primate Siglec-7.

[0181] In some embodiments, anti-Siglec-7 antibodies of the present disclosure are agonist antibodies or antagonist antibodies that bind to a Siglec-7 protein of the present disclosure expressed on the surface of a cell and modulate (e.g., induce or inhibit) one or more Siglec-7 activities of the present disclosure after binding to the surface-expressed Siglec-7 protein. In some embodiments, anti-Siglec-7 antibodies of the present disclosure are inert antibodies.

[0182] In some embodiments, anti-Siglec-7 antibodies of the present disclosure do not significantly reduce TREM2 expression, including, without limitation, cell surface levels of TREM2, intracellular levels of TREM2, and/or total levels of TREM2. In some embodiments, an anti-Siglec-7 antibody does not reduce cellular levels of TREM2 *in vivo*. In some embodiments, the cellular levels of TREM2 are measured on primary cells selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, and NK cells, or on cell lines, and wherein the cellular levels of TREM2 are measured utilizing an *in vitro* cell assay. As used herein, an anti-Siglec-7 antibody does not significantly reduce cTREM2 expression if it reduced TREM2 by less than 20% as compared toTREM2 expression in the absence of the anti-Siglec-7 antibody utilizing any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art. In some embodiments, anti-Siglec-7 antibodies of the present disclosure decrease TREM2 expression by less than 20%, less than 19%, less than 18%, less than 17%, less than 16%, less than 15%, less than 14%, less than 13%, less than 12%, less than 11%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% as compared to TREM2 expression in the absence of the anti-Siglec-7 antibody.

Anti-Siglec-7 antibody-binding regions

[0183] Certain aspects of the preset disclosure provide anti-Siglec-7 antibodies that bind to one or more amino acids within amino acid residues 9-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of human Siglec-7 (SEQ ID NO: 1), or

within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 9-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 60-69 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 60-69 and 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 and 84-95 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 60-69 and 117-127 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 68-78 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 68-78 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 84-95 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 111-122 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 111-122 and 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122 and 282-291 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 113-123 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-123 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 113-125 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-125 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 117-127 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 117-127 of SEQ ID NO: 1. In some embodiments, the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 282-29 of SEQ ID NO: 1.

[0184] In some embodiments, an anti-Siglec-7 antibody of the present disclosure binds to one or more amino acid residues selected from M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian Siglec-7 protein corresponding to an amino acid residue selected from M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1. In some embodiments, an anti-Siglec-7 antibody of the present disclosure binds to one or more, two or more, three or more, or all four amino acid residues selected from I72, W74, N81, and R124 of SEQ ID NO: 1, or one or more, two or more, three or more, or all four amino acid residues on a mammalian Siglec-7 protein corresponding to an amino acid residue selected from I72, W74, N81, and R124 of SEQ ID NO: 1. In some embodiments, an anti-Siglec-7 antibody of the present disclosure binds to one or more, two or more, three or more, four or more, or all five amino acid residues selected from R45, S47, T103, K104, and T107 of SEQ ID NO: 1, or one or more, two or more, three or more, four or more, or all five amino acid residues on a mammalian Siglec-7 protein corresponding to an amino acid residue selected from R45, S47, T103, K104, and T107 of SEQ ID NO: 1. In some embodiments, an anti-Siglec-7 antibody of the present disclosure binds to one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or all ten amino acid residues selected from M30, Q31, V44, R45, S47, F48, Y50, T103, K104, and T107 of SEQ ID NO: 1, or one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or all ten amino acid residues on a mammalian Siglec-7 protein corresponding to an amino acid residue selected from M30, Q31, V44, R45, S47, F48, Y50, T103, K104, and T107 of SEQ ID NO: 1.

[0185] As indicated in **Table 7B**, the critical Siglec-7 residues involved in binding by antibody 4E3 corresponded to amino acid residues I_{72}, W_{74}, N_{81}, and R_{124} of SEQ ID NO: 1. The critical Siglec-7 residues involved in binding by antibody 10B5 corresponded to amino acid residues R_{45}, S_{47}, T_{103}, K_{104}, and T_{107} of SEQ ID NO: 1; and the secondary residues involved in binding by antibody 10B5 corresponded to amino acid residues M_{30}, Q_{31}, V_{44}, F_{48}, and Y_{50} of SEQ ID NO: 1.

[0186] Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 60-69 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 60-69 and 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69

and 84-95 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 60-69 and 117-127 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 68-78 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 68-78 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 84-95 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 111-122 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 111-122 and 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122 and 282-291 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 113-123 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-123 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 113-125 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-125 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 117-127 of human Siglec-7

(SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 117-127 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that decrease cellular levels of Siglec-7 and/or inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 282-29 of SEQ ID NO: 1.

[0187] Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 60-69 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 60-69 and 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 and 84-95 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 60-69 and 117-127 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 68-78 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 68-78 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 84-95 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 84-95 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 111-122 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122

of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 111-122 and 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 111-122 and 282-291 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 113-123 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-123 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 113-125 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 113-125 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 117-127 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 117-127 of SEQ ID NO: 1. Other aspects of the preset disclosure provide anti-Siglec-7 antibodies that do not significantly decrease cell surface levels of Siglec-7 and/or do not inhibit interaction (e.g., binding) between Siglec-7 and one or more Siglec-7 ligands, and that bind to one or more amino acids within amino acid residues 282-291 of human Siglec-7 (SEQ ID NO: 1), or within amino acid residues on a Siglec-7 homolog or ortholog corresponding to amino acid residues 282-29 of SEQ ID NO: 1.

[0188] In some embodiments, anti-Siglec-7 antibodies of the present disclosure may bind a conformational epitope. In some embodiments, anti-Siglec-7 antibodies of the present disclosure may bind a discontinuous Siglec-7 epitope. In some embodiments, the discontinuous Siglec-7 epitope may have two or more peptides, three or more peptides, four or more peptides, five or more peptides, six or more peptides, seven or more peptide, eight or more peptides, nine or more peptides, or 10 or more peptides. As disclosed herein, Siglec-7 epitopes may comprise one or more peptides comprising five or more, six or more, seven or more, eight or more, nine or more, 10 or more, 11 or more, 12 or more, 13 or more 14 or more, 15 or more, 16 or more, 17 or more, 18 or more, 19 or more, or 20 or more amino acid residues of the amino acid sequence of SEQ ID NO: 1, or five or more, six or more, seven or more, eight or more, nine or more, 10 or more, 11 or more, 12 or more, 13 or more 14 or more, 15

or more, 16 or more, 17 or more, 18 or more, 19 or more, or 20 or more amino acid residues on a mammalian Siglec-7 protein corresponding to the amino acid sequence of SEQ ID NO: 1.

[0189] In some embodiments, anti-Siglec-7 antibodies of the present disclosure competitively inhibit binding of at least one antibody selected from any of the antibodies listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**. In some embodiments, anti-Siglec-7 antibodies of the present disclosure competitively inhibit binding of at least one antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8.

[0190] In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to an epitope of human Siglec-7 that is the same as or overlaps with the Siglec-7 epitope bound by at least one antibody selected from any of the antibodies listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind to an epitope of human Siglec-7 that is the same as or overlaps with the Siglec-7 epitope bound by at least one antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8.

[0191] In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind essentially the same Siglec-7 epitope bound by at least one antibody selected from any of the antibodies listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**. In some embodiments, anti-Siglec-7 antibodies of the present disclosure bind essentially the same Siglec-7 epitope bound by at least one antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ).

[0192] In some embodiments, anti-Siglec-7 antibodies of the present disclosure compete with one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof for binding to Siglec-7.

[0193] In some embodiments, an anti-Siglec-7 antibody of the present disclosure competes with one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof, for binding to Siglec-7 when the anti-Siglec-7 antibody reduces the binding of one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof to Siglec-7 by an amount the ranges from about 50% to 100%, as compared to binding to Siglec-7 in the absence of the anti-Siglec-7 antibody. In some embodiments, an anti-Siglec-7 antibody of the present disclosure competes with one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11,

7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof for binding to Siglec-7 when the anti-Siglec-7 antibody reduces the binding of one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof to Siglec-7 by at least 50%, at least 55%, by at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100%, as compared to binding to Siglec-7 in the absence of the anti-Siglec-7 antibody. In some embodiments, an anti-Siglec-7 antibody of the present disclosure that reduces the binding of one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof to Siglec-7 by 100% indicates that the anti-Siglec-7 antibody essential completely blocks the binding of one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof to Siglec-7. In some embodiments, the anti-Siglec-7 antibody and the one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof are present in an amount that corresponds to a 10:1 ratio, 9:1 ratio, 8:1 ratio, 7:1 ratio, 6:1 ratio, 5:1 ratio, 4:1 ratio, 3:1 ratio, 2:1 ratio, 1:1 ratio, 0.75:1 ratio, 0.5:1 ratio, 0.25:1 ratio, 0.1:1 ratio, 0.075:1 ratio, 0.050:1 ratio, 0.025:1 ratio, 0.01:1 ratio, 0.0075: ratio, 0.0050:1 ratio, 0.0025:1 ratio, 0.001: ratio, 0.00075:1 ratio, 0.00050:1 ratio, 0.00025:1 ratio, 0.0001: ratio, 1:10 ratio, 1:9 ratio, 1:8 ratio, 1:7 ratio, 1:6 ratio, 1:5 ratio, 1:4 ratio, 1:3 ratio, 1:2 ratio, 1:0.75 ratio, 1:0.5 ratio, 1:0.25 ratio, 1:0.1 ratio, 1:0.075 ratio, 1:0.050 ratio, 1:0.025 ratio, 1:0.01 ratio, 1:0.0075 ratio, 1:0.0050 ratio, 1:0.0025 ratio, 1:0.001 ratio, 1:0.00075 ratio, 1:0.00050 ratio, 1:0.00025 ratio, or 1:0.0001ratio of anti-Siglec-7 antibody to one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof. In some embodiments, the anti-Siglec-7 antibody is present in excess by an amount that ranges from about 1.5-fold to 100-fold, or greater than 100-fold compared to the amount of the one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof. In some embodiments, the anti-Siglec-7 antibody is present in an amount that is about a 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 15-fold, 20-fold, 25-fold, 30-fold, 35-fold, 40-fold, 45-fold, 50-fold, 55-fold, 60-fold, 65-fold, 70-fold, 75-fold, 80-fold, 85-fold, 90-fold, 95-fold, or 100-fold excess compared to the amount of the one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof.

[0194] Any suitable competition assay or Siglec-7 binding assay known in the art, such as BIAcore analysis, ELISA assays, or flow cytometry, may be utilized to determine whether an anti-Siglec-7 antibody competes with one or more antibodies selected from 1A12, 1E8, 2G1, 2G4, 3E11,

4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof for binding to Siglec-7. In an exemplary competition assay, immobilized Siglec-7 or cells expressing Siglec-7 on the cell surface are incubated in a solution comprising a first labeled antibody that binds to Siglec-7 (e.g., human or non-human primate) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to Siglec-7. The second antibody may be present in a hybridoma supernatant. As a control, immobilized Siglec-7 or cells expressing Siglec-7 is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to Siglec-7, excess unbound antibody is removed, and the amount of label associated with immobilized Siglec-7 or cells expressing Siglec-7 is measured. If the amount of label associated with immobilized Siglec-7 or cells expressing Siglec-7 is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to Siglec-7. *See*, Harlow and Lane (1988) *Antibodies: A Laboratory Manual* ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

Anti-Siglec-7 antibody light chain and heavy chain variable regions

[0195] In some embodiments, anti-Siglec-7 antibodies of the present disclosure comprise (a) a light chain variable region comprising at least one, two, or three HVRs selected from HVR-L1, HVR-L2, and HVR-L3 of any one of the antibodies listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof; and/or (b) a heavy chain variable region comprising at least one, two, or three HVRs selected from HVR-H1, HVR-H2, and HVR-H3 of any one of the antibodies listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof. In some embodiments, the HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 comprise EU or Kabat CDR, Chothia CDR, or Contact CDR sequences as shown in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or from an antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof.

[0196] In some embodiments, anti-Siglec-7 antibodies of the present disclosure comprise at least one, two, three, four, five, or six HVRs selected from (i) HVR-L1 comprising the amino acid sequence of any of the HVR-L1 sequences listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or from an antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8; (ii) HVR-L2 comprising the amino acid sequence of any of the HVR-L2 sequences listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or from an antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1,

10B5H1, and 10G8; (iii) HVR-L3 comprising the amino acid sequence of any of the HVR-L3 sequences listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or from an antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8; (iv) HVR-H1 comprising the amino acid sequence of any of the HVR-H1 sequences listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or from an antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8; (v) HVR-H2 comprising the amino acid sequence of any of the HVR-H2 sequences listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or from an antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8; and (vi) HVR-H3 comprising the amino acid sequence of any of the HVR-H3 sequences listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or from an antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8. In some embodiments, anti-Siglec-7 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein (a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 7, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 59, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 72; (b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 60, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 73; (c) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 22, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 48, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 61, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74; (d) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 62, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 75; (e) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 37, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 50, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 63, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 76; (f) the HVR-L1 comprises

the amino acid sequence of SEQ ID NO: 12, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 25, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 38, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 64, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 77; (g) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 13, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 39, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 52, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 65, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 78; (h) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79; (i) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 480, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74; (j) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 481 and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79; (k) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 41, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 67, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 80; (l) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 42, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 68, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 81; (m) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 82; (n) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ

ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83; (n) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 476, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 477, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 478, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83; (o) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 479, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 482, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 483; or (p) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 84.

[0197] In some embodiments, anti-Siglec-7 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises one or more of: (a) an HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 7-19 and 476, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 7-19 and 476; (b) an HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 20-32 and 477, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 20-32 and 477; and (c) an HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 33-45 and 478, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 33-45 and 478; and/or wherein the heavy chain variable domain comprises one or more of: (a) a an HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 46-58 and 479, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 46-58 and 479; (b) an HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 59-71 and 480-482; and (c) an HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 72-84 and 483, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from SEQ ID NOs: 72-84 and 483.

[0198] In some embodiments, anti-Siglec-7 antibodies of the present disclosure comprise a light chain variable region of any one of the antibodies listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or

selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8; and/or a heavy chain variable region of any one of the antibodies listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8. In some embodiments, anti-Siglec-7 antibodies of the present disclosure comprise a light chain variable region comprising an amino acid sequence selected from any of SEQ ID NOs: 189-318, 449-461, and 484-489; and/or a heavy chain variable domain comprising an amino acid sequence selected from any of SEQ ID NOs: 319-448, 462-474, and 490-496.

[0199] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 1A12. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 1A12. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 1A12. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 1A12. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 1A12.

[0200] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 1E8. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 1E8. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 1E8. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 1E8. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 1E8.

[0201] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 2G1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 2G1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 2G1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 2G1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody

comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 2G1.

[0202] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 2G4. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 2G4. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 2G4. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 2G4. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 2G4.

[0203] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 3E11. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 3E11. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 3E11. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 3E11. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 3E11.

[0204] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 4A1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 4A1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4A1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4A1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4A1.

[0205] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 4D7. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 4D7. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4D7. In some embodiments, the anti-Siglec-7 antibody is an isolated

antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4D7. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4D7.

[0206] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 4E3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 4E3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3H1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3H2. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3H3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3L1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3L2. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3L3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3H1 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3H2 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3H1 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3L1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable

domain of monoclonal antibody 4E3H2and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3L2. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3H2 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3L3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3H3 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3L2. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 4E3H3 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 4E3L3.

[0207] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 7A3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 7A3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 7A3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 7A3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 7A3.

[0208] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 7E11. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 7E11. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 7E11. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 7E11. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 7E11.

[0209] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 7F12. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 7F12. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 7F12. In some embodiments, the anti-Siglec-7 antibody is an

isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 7F12. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 7F12.

[0210] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 10B5. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 10B5. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H2. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H4. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5L1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5L2. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5L3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H1 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H2 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-

H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5L1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H1 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5L1. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H2 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5L2. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H3 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5L2. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H2 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5L3. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10B5H4 and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10B5L3.

[0211] In some embodiments, the anti-Siglec-7 antibody is anti-Siglec-7 monoclonal antibody 10G8. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody which binds essentially the same TREM2 epitope as 10G8. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody 10G8. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10G8. In some embodiments, the anti-Siglec-7 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody 10G8.

[0212] Any of the antibodies of the present disclosure may be produced by a cell line. In some embodiments, the cell line may be a mammalian cell line. In certain embodiments, the cell line may be a hybridoma cell line. In other embodiments, the cell line may be a yeast cell line. Any cell line known in the art suitable for antibody production may be used to produce an antibody of the present disclosure. Exemplary cell lines for antibody production are described throughout the present disclosure.

[0213] In some embodiments, the anti-Siglec-7 antibody is an anti-Siglec-7 monoclonal antibody selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8. In certain embodiments, the anti-Siglec-7 antibody is an antagonist antibody. In certain embodiments, the anti-Siglec-7 antibody is an agonist antibody or an inert antibody.

Anti-Siglec-7 antibody binding affinity

[0214] The dissociation constants (K_D) of anti-Siglec-7 antibodies for human Siglec-7, mammalian Siglec-7, or both, may be less than 100nM, less than 90 nM, less than 80 nM, less than 70 nM, less than 60 nM, less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, less than 10 nM, less than 9.5 nM, less than 9 nM, less than 8.5 nM, less than 8 nM, less than 7.5 nM, less than 7 nM, less than 6.5 nM, less than 6 nM, less than 5.5 nM, less than 5 nM, less than 4.5 nM, less than 4 nM, less than 3.5 nM, less than 3 nM, less than 2.5 nM, less than 2 nM, less than 1.5 nM, less than 1 nM, less than 0.5 nM, less than 0.4 nM, less than 0.3 nM, less than 0.2 nM, less than 0.1 nM, less than 0.05 nM (i.e., 50 pM), less than 40 pM, less than 30 pM, less than 20 pM, less than 19 pM, less than 18 pM, less than 17 pM, less than 16 pM, less than 15 pM, less than 14 pM, less than 13 pM, less than 12 pM, less than 11 pM, less than 10 pM, or less than 5 pM. In some embodiments, the antibody has a dissociation constant (K_D) for human Siglec-7, mammalian Siglec-7, or both, that ranges from about 10 nM to about 10 pM (i.e., 0.01 nM), or less than 10 pM. In some embodiments, the antibody has a dissociation constant (K_D) for human Siglec-7 that ranges from about 9.5 nM to about 17 pM, or less than 17 pM. In some embodiments, the antibody has a dissociation constant (K_D) for human Siglec-7 that ranges from about 2 nM to about 100 pM. Dissociation constants may be determined through any analytical technique, including any biochemical or biophysical technique such as ELISA, surface plasmon resonance (SPR), bio-layer interferometry (*see*, *e.g.*, Octet System by ForteBio), isothermal titration calorimetry (ITC), differential scanning calorimetry (DSC), circular dichroism (CD), stopped-flow analysis, and colorimetric or fluorescent protein melting analyses. In some embodiments, the dissociation constant (K_D) for Siglec-7 is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (e.g., a Fab) or a full-length antibody. In some embodiments, the K_D is determined using a full-length antibody in a monovalent form. In some embodiments, the K_D is determined utilizing, for example, a surface plasmon resonance assay as described herein (see, *e.g.,* **Example 1**).

[0215] Additional anti-Siglec-7 antibodies, *e.g.*, antibodies that specifically bind to a Siglec-7 protein of the present disclosure, may be identified, screened, and/or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

Anti-Siglec-7 antibodies capable of binding Fc gamma receptors

[0216] In some embodiments, anti-Siglec-7 antibodies of the present disclosure retain the ability to bind Fc gamma receptors. In some embodiments, such antibodies when they have the correct epitope specificity that is compatible with receptor activation may have features that enable them to cluster and transiently stimulate, for example, the Siglec-7 receptor. In some embodiments, such antibodies may subsequently act as longer-term inhibitors of Siglec-7 expression and/or one or more activities of a Siglec-7 protein by inducing Siglec-7 degradation, Siglec-7 desensitization, Siglec-7 cleavage, Siglec-7 internalization, Siglec-7 shedding, downregulation of Siglec-7 expression, and/or lysosomal degradation of Siglec-7.

[0217] *In vivo*, anti-Siglec-7 antibodies of the present disclosure may cluster receptors and transiently activate Siglec-7 by any one or more of multiple potential mechanisms. Some isotypes of human antibodies such as IgG2 have, due to their unique structure, an intrinsic ability to cluster receptors, or retain receptors in a clustered configuration, thereby transiently activating receptors such as Siglec-7 without binding to an Fc receptor (*e.g.*, White et al., (2015) Cancer Cell 27, 138–148).

[0218] In some embodiments, other antibodies may cluster receptors (*e.g.,* Siglec-7) by binding to Fcg receptors on adjacent cells. In some embodiments, binding of the constant IgG Fc region of the antibody to Fcg receptors may lead to aggregation of the antibodies, and the antibodies in turn may aggregate the receptors to which they bind through their variable region (Chu et al (2008) Mol Immunol , 45:3926-3933; and Wilson et al., (2011) Cancer Cell 19, 101–113). In some embodiments, binding to the inhibitory Fcg receptor FcgR (FcgRIIB) that does not elicit cytokine secretion, oxidative burst, increased phagocytosis, and enhanced antibody-dependent, cell-mediated cytotoxicity (ADCC) is a preferred way to cluster antibodies *in vivo*, since binding to FcgRIIB is not associated with adverse immune response effects.

[0219] There are other mechanisms by which anti-Siglec-7 antibodies of the present disclosure can cluster receptors. For example, antibody fragments (*e.g.,* Fab fragments) that are cross-linked together may be used to cluster receptors (*e.g.,* Siglec-7) in a manner similar to antibodies with Fc regions that bind Fcg receptors, as described above. In some embodiments, cross-linked antibody fragments (*e.g.,* Fab fragments) may transiently function as agonist antibodies if they induce receptor clustering on the cell surface and bind an appropriate epitope on the target (*e.g.,* Siglec-7).

[0220] Therefore, in some embodiments, antibodies of the present disclosure that bind a Siglec-7 protein may include agonist antibodies that due to their epitope specificity bind Siglec-7 and transiently activate one or more Siglec-7 activities before they, for example, decrease cellular levels of Siglec-7, inhibit one or more Siglec-7 activities, and/or inhibit interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands. In some embodiments, such antibodies may bind to the

ligand-binding site on Siglec-7 and transiently mimic the action of a natural ligand, or stimulate the target antigen to transduce signal by binding to one or more domains that are not the ligand-binding sites. In some embodiments, such antibodies would not interfere with ligand binding. In some embodiments, regardless of whether antibodies bind or do not bind to the ligand-binding site on Siglec-7, the antibodies may subsequently act as longer term inhibitors of Siglec-7 expression and/or one or more activities of a Siglec-7 protein by inducing Siglec-7 degradation, Siglec-7 desensitization, Siglec-7 cleavage, Siglec-7 internalization, Siglec-7 shedding, downregulation of Siglec-7 expression, and/or lysosomal degradation of Siglec-7.

[0221] In some embodiments, an anti-Siglec-7 antibody of the present disclosure is a transient agonist antibody that transiently induces one or more activities of a Siglec-7 protein. In some embodiments, the antibody transiently induces the one or more activities after binding to a Siglec-7 protein that is expressed in a cell. In some embodiments, the Siglec-7 protein is expressed on a cell surface. In some embodiments, the one or more activities of a Siglec-7 protein that are transiently induced by transient agonist anti-Siglec-7 antibodies of the present disclosure may include, without limitation, phosphorylation of Tyr-437 and Tyr-460 by a Src family tyrosine kinase, such as Syk, LCK, FYM, and/or ZAP70; recruitment of and binding to the tyrosine-specific protein phosphatases SHP1 and SHP2; recruitment of and binding to PLC-gamma1, which acts as a guanine nucleotide exchange factor for Dynamini-1; recruitment of and binding to SH2-domain containing protein (*e.g.*, Crkl); recruitment of and binding to the spleen tyrosine kinase Syk; recruitment of and binding to SH3-SH2-SH3 growth factor receptor-bound protein 2 (Grb2); recruitment of and binding to multiple SH2-containing proteins; modulated expression of one or more pro-inflammatory cytokines, such as IFN-a4, IFN-beta, IL-1â, IL-1alpha, TNF-á, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, CRP, MCP-1, and MIP-1-beta; modulated expression of one or more pro-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; increased expression of one or more anti-inflammatory cytokines, such as IL-4, IL-10, IL-13, IL-35, IL-16, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, or IL-6; modulated expression of one or more anti-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; modulate expression of one or more proteins selected from C1qa, C1qB, C1qC, C1s, C1R, C4, C2, C3, ITGB2, HMOX1, LAT2, CASP1, CSTA, VSIG4, MS4A4A, C3AR1, GPX1, TyroBP, ALOX5AP, ITGAM, SLC7A7, CD4, ITGAX, and PYCARD; inhibition of extracellular signal-regulated kinase (ERK) phosphorylation; decreasing tyrosine phosphorylation on one or more cellular proteins, optionally,

wherein the one or more cellular proteins comprise ZAP-70 and the tyrosine phosphorylation occurs on Tyr-319 of ZAP-70; modulated expression of C-C chemokine receptor 7 (CCR7); inhibition of microglial cell chemotaxis toward CCL19-expressing and CCL21-expressing cells; decreasing T cell proliferation induced by one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, M1 microglia, activated M1 microglia, M2 microglia, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, and M2 NK cells; inhibition of osteoclast production, decreased rate of osteoclastogenesis, or both; decreasing survival of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; decreasing proliferation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibiting migration of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibiting one or more functions of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibiting maturation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; inhibition of one or more types of clearance selected from apoptotic neuron clearance, nerve tissue debris clearance, dysfunctional synapse clearance, non-nerve tissue debris clearance,

bacteria clearance, other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, and tumor cell clearance; optionally wherein the disease-causing protein is selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides and the tumor cell is from a cancer selected from 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, and thyroid cancer; inhibition of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, dysfunctional synapses, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, disease-causing nucleic acids, or tumor cells; optionally wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and the tumor cells are from a cancer selected from 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, or thyroid cancer; binding to Siglec-7 ligand on tumor cells; binding to Siglec-7 ligand on cells selected from neutrophils, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, and NK cells; inhibition of tumor cell killing by one or more of microglia, macrophages, neutrophils,

NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; inhibiting anti-tumor cell proliferation activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; inhibition of anti-tumor cell metastasis activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; inhibition of one or more ITAM motif containing receptors, optionally wherein the one or more ITAM motif containing receptors are selected from TREM1, TREM2, Sirp beta, FcgR, DAP10, and DAP12; inhibition of signaling by one or more pattern recognition receptors (PRRs), optionally wherein the one or more PRRs are selected from receptors that identify pathogen-associated molecular patterns (PAMPs), receptors that identify damage-associated molecular patterns (DAMPs), and any combination thereof; inhibition of one or more receptors comprising the motif $D/Ex_{0-2}YxxL/IX_{6-8}YxxL/I$ (SEQ ID NO: 537); inhibition of signaling by one or more Toll-like receptors; inhibition of the JAK-STAT signaling pathway; inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NFêB); de-phosphorylation of an ITAM motif containing receptor; modulated expression of one or more inflammatory receptors, optionally wherein the one or more inflammatory receptors comprise CD86 and the one or more inflammatory receptors are expressed on one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; increasing expression of one or more Siglec-7-dependent genes; normalization of disrupted Siglec-7-dependent gene expression; decreasing expression of one or more ITAM-dependent genes, optionally wherein the one more ITAM-dependent genes are activated by nuclear factor of activated T cells (NFAT) transcription factors; promoting or rescuing functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells; increasing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells into tumors-; increasing the number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; enhancing tumor-promoting activity of myeloid-derived suppressor cells; increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; increasing tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes; enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); decreasing activation of tumor-specific T lymphocytes with tumor killing

potential; decreasing infiltration of tumor-specific NK cells with tumor killing potential; decreasing the tumor killing potential of NK cells; decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; increasing tumor volume; increasing tumor growth rate; increasing metastasis; increasing rate of tumor recurrence; decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more target proteins selected from PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines; inhibition of PLCã/PKC/calcium mobilization; and inhibition of PI3K/Akt, Ras/MAPK signaling. Anti-Siglec-7 antibodies of the present disclosure may be tested for their ability to transiently induce one or more activities of a Siglec-7 protein utilizing any suitable technique or assay known in the art and disclosed herein. Regardless of the activities that such antibodies transiently induce, such antibodies may subsequently act as longer-term inhibitors of Siglec-7 expression and/or one or more activities of a Siglec-7 protein by inducing Siglec-7 degradation, Siglec-7 desensitization, Siglec-7 cleavage, Siglec-7 internalization, Siglec-7 shedding, downregulation of Siglec-7 expression, and/or lysosomal degradation of Siglec-7. In some embodiments, the Siglec-7 antibody transiently induces one or more activities of a Siglec-7 protein independently of binding to an Fc receptor.

[0222] Exemplary antibody Fc isotypes and modifications are provided in Table C below. In some embodiments, an anti-Siglec-7 antibody of the present disclosure that is capable of binding an Fc gamma receptor has an Fc isotype listed in Table C below.

Table C: Exemplary anti-Siglec-7 antibody Fc isotypes that are capable of binding Fc gamma receptor

Fc Isotype	Mutation (EU numbering scheme)
IgG1	N297A
IgG1	D265A and N297A
IgG1	D270A
IgG1	L234A and L235A L234A and G237A L234A and L235A and G237A
IgG1	D270A, and/or P238D, and/or L328E, and/or S267E/L328F, and/or E233, and or/ G237D, and/or H268D, and/or P271G, and/or A330R
IgG1	P238D and L328E and E233D and G237D and H268D and P271G and A330R
IgG1	P238D and L328E and G237D and H268D and P271G and A330R
IgG1	P238D and S267E and L328F and E233D and G237D and H268D and P271G and A330R

Fc Isotype	Mutation (EU numbering scheme)
IgG1	P238D and S267E and L328F and G237D and H268D and P271G and A330R
IgG2	V234A and G237A
IgG4	L235A and G237A and E318A
IgG4	S228P and L236E
IgG2/4 hybrid	IgG2 aa 118 to 260 and IgG4 aa 261 to 447
	H268Q and V309L; and A330S and P331S
IgG1	C226S and C229S and E233P and L234V and L235A
IgG1	L234F and L235E and P331S
IgG2	C232S or C233S
IgG2	A330S and P331S
IgG1	S267E, and L328F S267E alone
IgG2	S267E and L328F
IgG4	S267E and L328F
IgG2	WT HC with Kappa (light chain) LC HC C127S with Kappa LC Kappa LC C214S Kappa LC C214S and HC C233S Kappa LC C214S and HC C232S Any of the above listed mutations together with P330S and P331S mutations F(ab')2 fragment of WT IgG1 and any of the above listed mutations
IgG1	Substitute the Constant Heavy 1 (CH1) and hinge region of IgG1 With CH1 and hinge region of IGg2 ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP (SEQ ID NO: 475) With a Kappa LC
IgG1	Any of the above listed mutations together with A330L and/ or L234F and/or L235E and/or P331S
IgG1, IgG2, or IgG4	Any of the above listed mutations together with M252Y and/or S254T and/or T256E
Mouse IgG1	For mouse disease models
IgG4	WT

[0223] In addition to the isotypes described in Table C, and without wishing to be bound to theory, it is thought that antibodies with human IgG1 or IgG3 isotypes and mutants thereof (e.g. Strohl (2009) Current Opinion in Biotechnology 2009, 20:685–691) that bind the Fcg Receptors I, IIA, IIC, IIIA, IIIB in human and/or Fcg Receptors I, III and IV in mouse, may also act as transient agonist antibodies.

[0224] In some embodiments, the Fc gamma receptor-binding antibody is of the IgG class, the IgM class, or the IgA class. In some embodiments, the Fc gamma receptor-binding antibody has an IgG1, IgG2, IgG3, or IgG4 isotype.

[0225] In certain embodiments, the Fc gamma receptor-binding antibody has an IgG2 isotype. In some embodiments, the Fc gamma receptor-binding antibody contains a human IgG2 constant region. In some embodiments, the human IgG2 constant region includes an Fc region. In some embodiments, the Fc gamma receptor-binding antibody binds an inhibitory Fc receptor. In certain embodiments, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In some embodiments, the Fc region contains one or more modifications. For example, in some embodiments, the Fc region contains one or more amino acid substitutions (*e.g.,* relative to a wild-type Fc region of the same isotype). In some embodiments, the one or more amino acid substitutions are selected from V234A (Alegre et al., (1994) *Transplantation* 57:1537-1543. 31; Xu et al., (2000) *Cell Immunol*, 200:16-26), G237A (Cole et al. (1999) *Transplantation*, 68:563-571), H268Q, V309L, A330S, P331S (US 2007/0148167; Armour et al. (1999) *Eur J Immunol* 29: 2613-2624; Armour et al. (2000) *The Haematology Journal* 1(Suppl.1):27; Armour et al. (2000) *The Haematology Journal* 1(Suppl.1):27), C232S, and/or C233S (White et al.(2015) *Cancer Cell* 27, 138–148), S267E, L328F (Chu et al., (2008) *Mol Immunol*, 45:3926-3933), M252Y, S254T, and/or T256E, where the amino acid position is according to the EU or Kabat numbering convention.

[0226] In some embodiments, the Fc gamma receptor-binding antibody has an IgG2 isotype with a heavy chain constant domain that contains a C127S amino acid substitution, where the amino acid position is according to the EU or Kabat numbering convention (White et al.,(2015) *Cancer Cell* 27, 138-148; Lightle et al., (2010) *PROTEIN SCIENCE* 19:753-762; and WO2008079246).

[0227] In some embodiments, the Fc gamma receptor-binding antibody has an IgG2 isotype with a Kappa light chain constant domain that contains a C214S amino acid substitution, where the amino acid position is according to the EU or Kabat numbering convention (White et al.,(2015) *Cancer Cell* 27, 138-148; Lightle et al., (2010) *PROTEIN SCIENCE* 19:753-762; and WO2008079246).

[0228] In certain embodiments, the Fc gamma receptor-binding antibody has an IgG1 isotype. In some embodiments, the Fc gamma receptor-binding antibody contains a mouse IgG1 constant region. In some embodiments, the Fc gamma receptor-binding antibody contains a human IgG1 constant region. In some embodiments, the human IgG1 constant region includes an Fc region. In some embodiments, the Fc gamma receptor-binding antibody binds an inhibitory Fc receptor. In certain embodiments, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In some embodiments, the Fc region contains one or more modifications. For example, in some embodiments, the Fc region contains one or more amino acid substitutions (*e.g.,* relative to a wild-type Fc region of the same isotype). In some embodiments, the one or more amino acid substitutions are selected from

N297A (Bolt S et al. (1993) *Eur J Immunol* 23:403-411), D265A (Shields et al. (2001) *R. J. Biol. Chem.* 276, 6591–6604), D270A, L234A, L235A (Hutchins et al. (1995) *Proc Natl Acad Sci* USA, 92:11980-11984; Alegre et al., (1994) *Transplantation* 57:1537-1543. 31; Xu et al., (2000) *Cell Immunol*, 200:16-26), G237A (Alegre et al. (1994) *Transplantation* 57:1537-1543. 31; Xu et al. (2000) *Cell Immunol*, 200:16-26), P238D, L328E, E233D, G237D, H268D, P271G, A330R, C226S, C229S, E233P, L234V, L234F, L235E (McEarchern et al., (2007) *Blood*, 109:1185-1192), P331S (Sazinsky et al., (2008) *Proc Natl Acad Sci USA* 2008, 105:20167-20172), S267E, L328F, A330L, M252Y, S254T, T256E, N297Q, P238S, P238A, A327Q, A327G, P329A, K322A, and/or T394D where the amino acid position is according to the EU or Kabat numbering convention.

[0229] In some embodiments, the antibody includes an IgG2 isotype heavy chain constant domain 1(CH1) and hinge region (White et al., (2015) Cancer Cell 27, 138–148). In certain embodiments, the IgG2 isotype CH1 and hinge region contain the amino acid sequence of ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP (SEQ ID NO: 475). In some embodiments, the antibody Fc region contains a S267E amino acid substitution, a L328F amino acid substitution, or both, and/or a N297A or N297Q amino acid substitution, where the amino acid position is according to the EU or Kabat numbering convention.

[0230] In certain embodiments, the Fc gamma receptor-binding antibody has an IgG4 isotype. In some embodiments, the Fc gamma receptor-binding antibody contains a human IgG4 constant region. In some embodiments, the human IgG4 constant region includes an Fc region. In some embodiments, the Fc gamma receptor-binding antibody binds an inhibitory Fc receptor. In certain embodiments, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In some embodiments, the Fc region contains one or more modifications. For example, in some embodiments, the Fc region contains one or more amino acid substitutions (*e.g.,* relative to a wild-type Fc region of the same isotype). In some embodiments, the one or more amino acid substitutions are selected from L235A, G237A, S228P, L236E (Reddy et al., (2000) *J Immunol*,164:1925-1933), S267E, E318A, L328F, M252Y, S254T, and/or T256E, where the amino acid position is according to the EU or Kabat numbering convention.

[0231] In certain embodiments, the Fc gamma receptor-binding antibody has a hybrid IgG2/4 isotype. In some embodiments, the Fc gamma receptor-binding antibody includes an amino acid sequence containing amino acids 118 to 260 according to EU or, Kabat numbering of human IgG2 and amino acids 261-447 according to EU or, Kabat numbering of human IgG4 (WO 1997/11971; WO 2007/106585).

[0232] In certain embodiments, the antibody contains a mouse IgG4 constant region (Bartholomaeus, et al. (2014). J. Immunol. 192, 2091–2098).

[0233] In some embodiments, the Fc region further contains one or more additional amino acid substitutions selected from A330L, L234F; L235E, or P331S according to EU or, Kabat numbering; and any combination thereof.

Inert antibodies

[0234] Another class of anti-Siglec-7 antibodies of the present disclosure includes inert antibodies. As used herein, "inert" antibodies refer to antibodies that specifically bind their target antigen (*e.g.*, Siglec-7) but do not modulate (*e.g.*, decrease/inhibit or activate/induce) antigen function. For example, in the case of Siglec-7, inert antibodies do not modulate cellular levels of Siglec-7, do not modulate interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands, or do not modulate one or more activities of a Siglec-7 protein. In some embodiments, antibodies that do not have the ability to cluster Siglec-7 on the cell surface may be inert antibodies even if they have an epitope specificity that is compatible with receptor activation.

[0235] In some embodiments, antibodies that bind a Siglec-7 protein may include antibodies that bind Siglec-7 but, due to their epitope specificity, or characteristics, do not decrease cellular levels of Siglec-7 and/or inhibit interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands. In some embodiments, such antibodies can be used as cargo to, for example, transport toxins (*e.g.*, chemotherapeutics) into tumor cells. Such antibodies may be superior to current commercially available anti-Siglec-7 antibodies, such as antibody Mab1138 (R&D Systems; Cat. No. MAB 1138). In some embodiments, inert anti-Siglec-7 antibodies of the present disclosure may be superior to commercial antibodies, such as antibody Mab1138, because antibodies that do not decrease cellular levels of Siglec-7 will leave Siglec-7 intact on the surface of tumor cells for targeting by additional toxin-conjugated antibodies. In contrast, antibodies that decrease cellular levels of Siglec-7 will remove Siglec-7 from the cell surface and will lead to protection of the tumor cells from further targeting by toxin-conjugated antibodies. Therefore, in some embodiments, antibodies of the present disclosure are inert antibodies that bind Siglec-7 but are incapable of decreasing cellular levels of Siglec-7, inhibiting interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands, or inducing one or more activities of a Siglec-7 protein.

[0236] Antibodies that either decrease or do not decrease cellular levels of Siglec-7 on cells can be combined with an inert Fc region that displays reduced binding to one or more Fcg Receptor. Examples of such Fc regions and modifications are provided in Table D below. In some embodiments, the antibody with an inert Fc region has an Fc isotype listed in Table D below.

Antagonist anti-Siglec-7 antibodies

[0237] A third class of anti-Siglec-7 antibodies of the present disclosure includes antagonist antibodies. In some embodiments, antibodies that bind a Siglec-7 protein may include antagonist antibodies that reduce cellular levels of Siglec-7, inhibit interaction (*e.g.*, binding) between Siglec-7

and/or one or more Siglec-7 ligands, and inhibit one or more activities of a Siglec-7 protein. Such antibodies inhibit one or more activities of a Siglec-7 protein either by preventing interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands or by preventing signal transduction from the extracellular domain of Siglec-7 into the cell cytoplasm in the presence of one or more Siglec-7 ligands. Antagonist antibodies also can inhibit one or more activities of a Siglec-7 protein by decreasing cell surface levels of Siglec-7 by inducing Siglec-7 degradation, Siglec-7 desensitization, Siglec-7 cleavage, Siglec-7 internalization, Siglec-7 shedding, downregulation of Siglec-7 expression, and/or lysosomal degradation of Siglec-7. In some embodiments, such antagonist anti-Siglec-7 antibodies may not transiently activate Siglec-7.

[0238] In some embodiments, antagonist anti-Siglec-7 antibodies of the present disclosure may have the epitope specificity of a transient agonist anti-Siglec-7 antibody of the present disclosure, but have an Fc domain that is not capable of binding Fcg receptors and thus is unable to, for example, transiently clustering and activating Siglec-7.

[0239] In some embodiments, antagonist anti-Siglec-7 antibodies of the present disclosure have, without limitation, one or more of the following activities: the ability to decrease binding of a Siglec-7 protein to one or more Siglec-7 ligands, such as sialic acid-containing glycolipids or sialic acid-containing glycoproteins, the ability to decrease the binding of a suppressor of cytokine signaling (SOCS) protein (*e.g.,* SOCS3 protein) to a Siglec-7 protein, the ability to increase the proteasomal degradation of a Siglec-7 protein, the ability to reduce functional expression of Siglec-7 on the surface of circulating dendritic cells, macrophages, monocytes, T cells, and/or microglia, the ability to decrease or inhibit phosphorylation of Tyr-437 and Tyr-460 by a Src family tyrosine kinase, such as Syk, LCK, FYM, and/orZAP70; the ability to inhibit recruitment of and binding to the tyrosine-specific protein phosphatases SHP1 and SHP2; the ability to inhibit recruitment of and binding to PLC-gamma1, which acts as a guanine nucleotide exchange factor for Dynamini-1; the ability to inhibit recruitment of and binding to SH2-domain containing protein (*e.g.*, Crkl); the ability to inhibit recruitment of and binding to the spleen tyrosine kinase Syk; the ability to inhibit recruitment of and binding to SH3-SH2-SH3 growth factor receptor-bound protein 2 (Grb2); the ability to inhibit recruitment of and binding to multiple SH2-containing proteins; the ability to modulate expression of one or more pro-inflammatory cytokines, optionally wherein the one or more anti-inflammatory cytokines are selected from IFN-a4, IFN-beta, IL-1β, IL-1alpha, TNF-α, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-33, MCP-1, and MIP-1-beta; the ability to modulate expression of one or more pro-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; the ability to modulate expression of one or more anti-inflammatory cytokines,

optionally wherein the one or more anti-inflammatory cytokines are selected from IL-4, IL-10, IL-13, IL-35, IL-16, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, or IL-6; the ability to modulate expression of one or more anti-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; the ability to modulate expression of one or more proteins selected from C1qa, C1qB, C1qC, C1s, C1R, C4, C2, C3, ITGB2, HMOX1, LAT2, CASP1, CSTA, VSIG4, MS4A4A, C3AR1, GPX1, TyroBP, ALOX5AP, ITGAM, SLC7A7, CD4, ITGAX, and PYCARD; the ability to counteract inhibition of extracellular signal-regulated kinase (ERK) phosphorylation; the ability to prevent decreased tyrosine phosphorylation on one or more cellular proteins, optionally, wherein the one or more cellular proteins comprise ZAP-70 and the tyrosine phosphorylation occurs on Tyr-319 of ZAP-70; the ability to modulate expression of C-C chemokine receptor 7 (CCR7); the ability to prevent inhibition of microglial cell chemotaxis toward CCL19-expressing and CCL21-expressing cells; the ability to prevent decreasing T cell proliferation induced by one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, M1 microglia, activated M1 microglia, M2 microglia, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, and M2 NK cells; the ability to prevent inhibition of osteoclast production, the ability to prevent decreased rate of osteoclastogenesis, or both; the ability to prevent decreased survival of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; the ability to prevent decreased proliferation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; the ability to enhance migration of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; the ability to prevent a decrease in one or more functions of one or more cells selected

from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; the ability to enhance maturation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; the ability to enhance one or more types of clearance selected from apoptotic neuron clearance, nerve tissue debris clearance, dysfunctional synapse clearance, non-nerve tissue debris clearance, bacteria clearance, other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, and tumor cell clearance; optionally wherein the disease-causing protein is selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides and the tumor cell is from a cancer selected from 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, and thyroid cancer; inhibition of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, dysfunctional synapses, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, disease-causing nucleic acids, or tumor cells; optionally wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin,

apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and the tumor cells are from a cancer selected from 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, or thyroid cancer; binding to Siglec-7 ligand on tumor cells; binding to Siglec-7 ligand on cells selected from neutrophils, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, and NK cells; inhibition of tumor cell killing by one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; activating anti-tumor cell proliferation activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; the ability to enhance anti-tumor cell metastasis activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; the ability to enhance the activity of one or more ITAM motif containing receptors, optionally wherein the one or more ITAM motif containing receptors are selected from TREM1, TREM2, SIRP beta, FcgR, DAP10, and DAP12; the ability to enhance signaling by one or more pattern recognition receptors (PRRs), optionally wherein the one or more PRRs are selected from receptors that identify pathogen-associated molecular patterns (PAMPs), receptors that identify damage-associated molecular patterns (DAMPs), and any combination thereof; the ability to enhance activity of one or more receptors comprising the motif $D/Ex_{0-2}YxxL/IX_{6-8}YxxL/I$ (SEQ ID NO: 537); the ability to enhance signaling by one or more Toll-like receptors; the ability to enhance the JAK-STAT signaling pathway; the ability to enhance the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NFêB); the ability to increase phosphorylation of an ITAM motif containing receptor; the ability to increase expression of one or more inflammatory receptors, optionally wherein the one or more inflammatory receptors comprise CD86 and the one or more inflammatory receptors are expressed on one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; the ability to decrease expression of one or more Siglec-7-dependent genes; the ability to enhance expression of one or more ITAM-dependent genes, optionally wherein the one more ITAM-dependent genes are activated by nuclear factor of activated T cells (NFAT) transcription factors; the ability to decrease or otherwise inhibit differentiation of one or more of

immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells; the ability to decrease or otherwise inhibit functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells; the ability to decrease or otherwise inhibit infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells into tumors; the ability to decrease or otherwise inhibit the number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; the ability to decrease or otherwise inhibit tumor-promoting activity of myeloid-derived suppressor cells; the ability to decrease or otherwise inhibit expression of tumor-promoting cytokines, such as TGF-beta or IL-10, in a tumor or in peripheral blood; the ability to decrease or otherwise inhibit tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes; the ability to decrease or otherwise inhibit tumor-promoting activity of myeloid-derived suppressor cells (MDSC); the ability to increase or otherwise enhance tumor-specific T lymphocytes with tumor killing potential; the ability to increase or otherwise enhance infiltration of tumor-specific NK cells with tumor killing potential; the ability to increase or otherwise enhance the tumor killing potential of NK cells; the ability to increase or otherwise enhance infiltration of tumor-specific B lymphocytes with potential to enhance immune response; the ability to increase or otherwise enhance infiltration of tumor-specific T lymphocytes with tumor killing potential; the ability to decrease tumor volume; the ability to decrease tumor growth rate; the ability to decrease or otherwise inhibit metastasis; the ability to decrease rate of tumor recurrence; the ability to increase or otherwise enhance efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more target proteins selected from PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines; the ability to increase or otherwise enhance PLCã/PKC/calcium mobilization; and the ability to increase or otherwise enhance PI3K/Akt, Ras/MAPK signaling.

[0240] In some embodiments, antagonist anti-Siglec-7 antibodies of the present disclosure have an Fc region that displays reduced binding to one or more Fcg Receptor. Examples of such Fc regions

and modifications are provided in Table D below. In some embodiments, the antibody has an Fc isotype listed in Table D below.

Antibody Fc isotypes with reduced binding to Fc gamma receptors

[0241] In some embodiments, anti-Siglec-7 antibodies with reduced binding to Fc gamma receptors have an Fc isotype listed in **Table D** below.

Table D: Exemplary anti-Siglec-7 antibody Fc isotypes with reduced binding to Fc gamma receptor

Fc Isotype	**Mutation (EU numbering scheme)**
IgG1	N297Aor N297Q
IgG1	D265A, D270A, and N297A
IgG1	L234A and L235A
IgG2	V234A and G237A
IgG4	F235A and G237A and E318A E233P and/or F234V N297Aor N297Q
IgG4	S228P and L236E S241P S241P and L248E S228P and F234A and L235A
IgG2	H268Q and V309L and A330S and P331S
IgG1	C220S and C226S and C229S and P238S
IgG1	C226S and C229S and E233P and L234V, and L235A
IgG1	E233P and L234V and L235A and G236-deleted P238A D265A N297A A327Q or A327G P329A
IgG1	K322A and L234A and L235A
IgG1	L234Fand L235E and P331S
IgG1 or IgG4	T394D
IgG2	C232S or C233S N297Aor N297Q
IgG2	V234A and G237A and P238S and H268A and V309L and A330S and P331S
IgG1, IgG2, or IgG4	delta a,b , c, ab, ac, g modifications
IgG1	Any of the above listed mutations together with A330L or L234F and/or L235E and/or P331S
IgG1, IgG2, or IgG4	Any of the above listed mutations together with M252Y and/or S254T and/or T256E

[0242] In certain embodiments, the anti-Siglec-7antibody has an IgG1 isotype. In some embodiments, the antibody contains a mouse IgG1 constant region. In some embodiments, the antibody contains a human IgG1 constant region. In some embodiments, the human IgG1 constant region includes an Fc region. In some embodiments, the Fc region contains one or more

modifications. For example, in some embodiments, the Fc region contains one or more amino acid substitutions (*e.g.,* relative to a wild-type Fc region of the same isotype).

[0243] In some embodiments, the one or more amino acid substitutions are selected from N297A, N297Q (Bolt S et al. (1993) *Eur J Immunol* 23:403-411), D270A, D265A, L234A, L235A (McEarchern et al., (2007) *Blood*, 109:1185-1192), C226S, C229S (McEarchern et al., (2007) *Blood*, 109:1185-1192), P238S (Davis et al., (2007) *J Rheumatol*, 34:2204-2210), E233P, L234V (McEarchern et al., (2007) *Blood*, 109:1185-1192), P238A, A327Q, A327G, P329A (Shields RL. et al., (2001) *J Biol Chem.* 276(9):6591-604), K322A, L234F, L235E (Hezareh,et al., (2001) J Virol *75*, 12161–12168; Oganesyan et al., (2008). *Acta Crystallographica 64*, 700–704), P331S (Oganesyan et al., (2008) *Acta Crystallographica 64*, 700–704), T394D (Wilkinson et al. (2013) *MAbs* 5(3): 406–417), A330L, M252Y, S254T, and/or T256E, where the amino acid position is according to the EU or Kabat numbering convention. In certain embodiments, the Fc region further includes an amino acid deletion at a position corresponding to glycine 236 according to the EU or Kabat numbering convention.

[0244] In some embodiments, the anti-Siglec-7 antibody has an IgG1 isotype with a heavy chain constant region that contains a C220S amino acid substitution according to the EU or Kabat numbering convention. In some embodiments, the Fc region further contains one or more additional amino acid substitutions selected from t A330L, L234F; L235E, and/or P331S according to EU or Kabat numbering convention. In certain embodiments, the anti-Siglec-7 antibody has an IgG2 isotype. In some embodiments, the anti-Siglec-7 antibody contains a human IgG2 constant region. In some embodiments, the human IgG2 constant region includes an Fc region. In some embodiments, the Fc region contains one or more modifications. For example, in some embodiments, the Fc region contains one or more amino acid substitutions (*e.g.,* relative to a wild-type Fc region of the same isotype). In some embodiments, the one or more amino acid substitutions are selected from P238S, V234A, G237A, H268A, H268Q, H268E, V309L, N297A, N297Q, V309L, A330S, P331S, C232S, C233S, M252Y, S254T, and/or T256E, where the amino acid position is according to the EU or Kabat numbering convention (Vafa O. et al., (2014) Methods 65:114–126).

[0245] In certain embodiments, the anti-Siglec-7 antibody has an IgG4 isotype. In some embodiments, the anti-Siglec-7 antibody contains a human IgG4 constant region. In some embodiments, the human IgG4 constant region includes an Fc region. In some embodiments, the Fc region contains one or more modifications. For example, in some embodiments, the Fc region contains one or more amino acid substitutions (*e.g.,* relative to a wild-type Fc region of the same isotype). In some embodiments, the one or more amino acid substitutions are selected from E233P, F234V, L235A, G237A, E318A (Hutchins et al. (1995) *Proc Natl Acad Sci* USA, 92:11980-11984), S228P, L234A/F234A,, L236E, S241P, L248E (Reddy et al., (2000) *J Immunol*,164:1925-1933;

Angal et al., (1993) *Mol Immunol.* 30(1):105-8; US 8614299 B2; Vafa O. et al., (2014) Methods 65:114–126), T394D, M252Y, S254T, T256E, N297A, and/or N297Q, where the amino acid position is according to the EU or Kabat numbering convention.

[0246] In some embodiments, the Fc region further contains one or more additional amino acid substitutions selected from a M252Y, S254T, and/or T256E, where the amino acid position is according to the EU or Kabat numbering convention.

Further IgG mutations

[0247] In some embodiments, one or more of the IgG1 variants described herein may be combined with an A330L mutation (Lazar et al., (2006) Proc Natl Acad Sci USA, 103:4005-4010), or one or more of L234F, L235E, and/or P331S mutations (Sazinsky et al., (2008) Proc Natl Acad Sci USA, 105:20167-20172), where the amino acid position is according to the EU or Kabat numbering convention, to eliminate complement activation. In some embodiments, the IgG variants described herein may be combined with one or more mutations to enhance the anti-Siglec-7 antibody half-life in human serum (e.g. M252Y, S254T, T256E mutations according to the EU or Kabat numbering convention) (Dall'Acqua et al., (2006) J Biol Chem, 281:23514-23524; and Strohl e al., (2009) Current Opinion in Biotechnology, 20:685–691).

[0248] In some embodiments, an IgG4 variant of the present disclosure may be combined with an S228P mutation according to the EU or Kabat numbering convention (Angal et al., (1993) Mol Immunol, 30:105-108), an F234A mutation, an L235A mutation, and/or with one or more mutations described in Peters et al., (2012) J Biol Chem. 13;287(29):24525-33) to enhance antibody stabilization.

[0249] In some embodiments, anti-Siglec-7 antibodies of the present disclosure have an IgG4 isotype. In some embodiments, the antibody Fc region contains an S228P amino acid substitution at residue position 228, an F234A amino acid substitution at residue position 234, and an L235A amino acid substitution at residue position 235, according to EU numbering.

Bispecific antibodies

[0250] Certain aspects of the present disclosure relate to bispecific antibodies that bind to one or more domains on a Siglec-7 protein of the present disclosure and a second antigen. Methods of generating bispecific antibodies are well known in the art and described herein. In some embodiments, bispecific antibodies of the present disclosure bind to one or more amino acid residues of a Siglec-7 protein of the present disclosure, such as one or more amino acid residues of human Siglec-7 (SEQ ID NO: 1), or amino acid residues on a Siglec-7 protein corresponding to amino acid residues of SEQ ID NO: 1. In some embodiments, bispecific antibodies of the present disclosure recognize a first antigen and a second antigen. In some embodiments, the first antigen is a Siglec-7 protein or a naturally occurring variant thereof. In some embodiments, the second antigen is also a

Siglec-7 protein, or a naturally occurring variant thereof. In some embodiments, the second antigen is an antigen facilitating transport across the blood-brain-barrier (*see, e.g.*, Gabathuler R., *Neurobiol. Dis.* 37 (2010) 48-57). Such second antigens include, without limitation, transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, Angiopep peptides such as ANG1005 (*see, e.g.*, Gabathuler, 2010), and other cell surface proteins that are enriched on blood-brain barrier endothelial cells (*see, e.g.*, Daneman et al., PLoS One. 2010 Oct 29;5(10):e13741). In some embodiments, the second antigen is a disease-causing protein including, without limitation, amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides. In some embodiments, the second antigen is one or more ligands and/or proteins expressed on immune cells, including without limitation, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, CD3, and phosphatidylserine. In some embodiments, the second antigen is a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells.

Antibody fragments

[0251] Certain aspects of the present disclosure relate to antibody fragments that bind to one or more of a Siglec-7 protein of the present disclosure, a naturally occurring variant of a Siglec-7 protein, and a disease variant of a Siglec-7 protein. In some embodiments, the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv or scFv fragment.

[0252] In some embodiments, the antibody fragment is used in combination with a second Siglec-7 antibody and/or with one or more antibodies that specifically bind a disease-causing protein selected from: amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body,

atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and any combination thereof; or with one or more antibodies that bind an immunomodulatory protein selected from: CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, CD33, Siglec-5, Siglec-9, Siglec-11, phosphatidylserine, and any combination thereof.

[0253] In some embodiments, antibody fragments of the present disclosure may be functional fragments that bind the same epitope as any of the anti-Siglec-7 antibodies of the present disclosure. In some embodiments, the antibody fragments are miniaturized versions of the anti-Siglec-7 antibodies or antibody fragments of the present disclosure that have the same epitope of the corresponding full-length antibody, but have much smaller molecule weight. Such miniaturized anti-Siglec-7 antibody fragments may have better brain penetration ability and a shorter half-life, which is advantageous for imaging and diagnostic utilities (*see e.g.*, Lütje S et al., *Bioconjug Chem.* 2014 Feb 19;25(2):335-41; Tavaré R et al., *Proc Natl Acad Sci U S A*. 2014 Jan 21;111(3):1108-13; and Wiehr S et al., *Prostate*. 2014 May;74(7):743-55). Accordingly, in some embodiments, anti-Siglec-7 antibody fragments of the present disclosure have better brain penetration as compared to their corresponding full-length antibodies and/or have a shorter half-life as compared to their corresponding full-length antibodies.

Antibody frameworks

[0254] Any of the antibodies described herein further include a framework. In some embodiments, the framework is a human immunoglobulin framework. For example, in some embodiments, an antibody (*e.g.,* an anti-Siglec-7 antibody) comprises HVRs as in any of the above embodiments and further comprises an acceptor human framework, *e.g.*, a human immunoglobulin framework or a human consensus framework. Human immunoglobulin frameworks may be part of the human antibody, or a non-human antibody may be humanized by replacing one or more endogenous frameworks with human framework region(s). Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the "best-fit" method (see, e.g., Sims et al. *J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, e.g., Carter et al. *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); and Presta et al. *J. Immunol.*, 151:2623 (1993)); human mature (somatically mutated) framework regions or human

germline framework regions (see, e.g., Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, e.g., Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997) and Rosok et al., *J. Biol. Chem.* 271:22611-22618 (1996)).

[0255] In some embodiments, an antibody comprises a light chain variable region comprising an HVR-L1, an HVR-L2, and an HVR-L3 of the present disclosure and one, two, three or four of the light chain framework regions as shown in **Table 3A**. In some embodiments, an antibody comprises a heavy chain variable region comprising an HVR-H1, an HVR-H2, and an HVR-H3 of the present disclosure and one, two, three or four of the heavy chain framework regions as shown in **Table 3B**. In some embodiments, an antibody comprises a light chain variable region comprising an HVR-L1, an HVR-L2, and an HVR-L3 of the present disclosure and one, two, three or four of the light chain framework regions as shown in **Table 3A,** and further comprises a heavy chain variable region comprising an HVR-H1, an HVR-H2, and an HVR-H3 of the present disclosure and one, two, three or four of the heavy chain framework regions as shown in **Table 3B**.

Antibody preparation

[0256] Anti-Siglec-7 antibodies of the present disclosure can encompass polyclonal antibodies, monoclonal antibodies, humanized and chimeric antibodies, human antibodies, antibody fragments (*e.g.*, Fab, Fab'-SH, Fv, scFv, and $F(ab')_2$), bispecific and polyspecific antibodies, multivalent antibodies, heteroconjugate antibodies, conjugated antibodies, library derived antibodies, antibodies having modified effector functions, fusion proteins containing an antibody portion, and any other modified configuration of the immunoglobulin molecule that includes an antigen recognition site, such as an epitope having amino acid residues of a Siglec-7 protein of the present disclosure, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies. The anti-Siglec-7 antibodies may be human, murine, rat, or of any other origin (including chimeric or humanized antibodies).

(1) Polyclonal antibodies

[0257] Polyclonal antibodies, such as polyclonal anti-Siglec-7 antibodies, are generally raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen (*e.g.*, a purified or recombinant Siglec-7 protein of the present disclosure) to a protein that is immunogenic in the species to be immunized, *e.g.*, keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor, using a bifunctional or derivatizing agent, *e.g.*, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, $SOCl_2$, or $R^1N=C=NR$, where R and R^1 are independently lower alkyl groups. Examples of adjuvants which may be employed include Freund's complete adjuvant

and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

[0258] The animals are immunized against the desired antigen, immunogenic conjugates, or derivatives by combining, *e.g.*, 100 μg (for rabbits) or 5 μg (for mice) of the protein or conjugate with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later, the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to fourteen days later, the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitable to enhance the immune response.

(2) Monoclonal antibodies

[0259] Monoclonal antibodies, such as monoclonal anti-Siglec-7 antibodies, are obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translational modifications (*e.g.*, isomerizations, amidations) that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies.

[0260] For example, the monoclonal anti-Siglec-7 antibodies may be made using the hybridoma method first described by Kohler et al., *Nature,* 256:495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

[0261] In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization (*e.g.*, a purified or recombinant Siglec-7 protein of the present disclosure). Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)).

[0262] The immunizing agent will typically include the antigenic protein (*e.g.*, a purified or recombinant Siglec-7 protein of the present disclosure) or a fusion variant thereof. Generally peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, while spleen or lymph node cells are used if non-human mammalian sources are desired. The lymphoctyes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell. Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press (1986), pp. 59-103.

[0263] Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine or human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which are substances that prevent the growth of HGPRT-deficient cells.

[0264] Preferred immortalized myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, preferred are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors (available from the Salk Institute Cell Distribution Center, San Diego, California USA), as well as SP-2 cells and derivatives thereof (*e.g.*, X63-Ag8-653) (available from the American Type Culture Collection, Manassas, Virginia USA). Human myeloma and mouse-human heteromyeloma cell lines have also been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

[0265] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen (*e.g.*, a Siglec-7 protein of the present disclosure). Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA).

[0266] The culture medium in which the hybridoma cells are cultured can be assayed for the presence of monoclonal antibodies directed against the desired antigen (*e.g.*, a Siglec-7 protein of the present disclosure). Preferably, the binding affinity and specificity of the monoclonal antibody can be determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked assay (ELISA). Such techniques and assays are known in the in art. For example, binding affinity may be determined by the Scatchard analysis of Munson et al., *Anal. Biochem.*, 107:220 (1980).

[0267] After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, *supra*). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as tumors in a mammal.

[0268] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, affinity chromatography, and other methods as described above.

[0269] Anti-Siglec-7 monoclonal antibodies may also be made by recombinant DNA methods, such as those disclosed in U.S. Patent No. 4,816,567, and as described above. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that specifically bind to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, in order to synthesize monoclonal antibodies in such recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., *Curr. Opin. Immunol.*, 5:256-262 (1993) and Plückthun, *Immunol. Rev.* 130:151-188 (1992).

[0270] In certain embodiments, anti-Siglec-7 antibodies can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., *Nature*, 348:552-554 (1990). Clackson et al., *Nature*, 352:624-628 (1991) and Marks et al., *J. Mol. Biol.*, 222:581-597 (1991) described the isolation of murine and human antibodies, respectively, from phage libraries. Subsequent publications describe the production of high affinity (nanomolar ("nM") range) human antibodies by chain shuffling (Marks et al., *Bio/Technology*, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse et al., *Nucl. Acids Res.*, 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies of desired specificity (*e.g.*, those that bind a Siglec-7 protein of the present disclosure).

[0271] The DNA encoding antibodies or fragments thereof may also be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, et al., *Proc. Natl Acad. Sci. USA*, 81:6851 (1984)), or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Typically such non-immunoglobulin polypeptides are substituted for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

[0272] The monoclonal antibodies described herein (*e.g.*, anti-Siglec-7 antibodies of the present disclosure or fragments thereof) may by monovalent, the preparation of which is well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and a modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues may be substituted with another amino acid residue or are deleted so as to prevent crosslinking. *In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly Fab fragments, can be accomplished using routine techniques known in the art.

[0273] Chimeric or hybrid anti-Siglec-7 antibodies also may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide-exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate.

(3) Humanized antibodies

[0274] Anti-Siglec-7 antibodies of the present disclosure or antibody fragments thereof may further include humanized or human antibodies. Humanized forms of non-human (*e.g.*, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fab, Fab'-SH, Fv, scFv, $F(ab')_2$ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally will also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Jones et al., *Nature* 321: 522-525 (1986); Riechmann et al., *Nature* 332: 323-329 (1988) and Presta, *Curr. Opin. Struct. Biol.* 2: 593-596 (1992).

[0275] Methods for humanizing non-human anti-Siglec-7 antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import"

residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers, Jones et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-327 (1988); Verhoeyen et al., *Science* 239:1534-1536 (1988), or through substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[0276] The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework (FR) for the humanized antibody. Sims et al., *J. Immunol.*, 151:2296 (1993); Chothia et al., *J. Mol. Biol.*, 196:901 (1987). Another method uses a particular framework derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies. Carter et al., *Proc. Nat'l Acad. Sci. USA* 89:4285 (1992); Presta et al., *J. Immunol.* 151:2623 (1993).

[0277] Furthermore, it is important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analyzing the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, *i.e.*, the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen or antigens (*e.g.*, Siglec-7 proteins of the present disclosure), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding.

[0278] Various forms of the humanized anti-Siglec-7 antibody are contemplated. For example, the humanized anti-Siglec-7 antibody may be an antibody fragment, such as an Fab, which is

optionally conjugated with one or more cytotoxic agent(s) in order to generate an immunoconjugate. Alternatively, the humanized anti-Siglec-7 antibody may be an intact antibody, such as an intact IgG1 antibody.

(4) Human antibodies

[0279] Alternatively, human anti-Siglec-7 antibodies can be generated. For example, it is now possible to produce transgenic animals (*e.g.*, mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. The homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. *See, e.g.*, Jakobovits et al., *Proc. Nat'l Acad. Sci. USA*, 90:2551 (1993); Jakobovits et al., *Nature*, 362:255-258 (1993); Bruggermann et al., *Year in Immunol.*, 7:33 (1993); U.S. Patent Nos. 5,591,669 and WO 97/17852.

[0280] Alternatively, phage display technology can be used to produce human anti-Siglec-7 antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. McCafferty et al., *Nature* 348:552-553 (1990); Hoogenboom and Winter, *J. Mol. Biol.* 227: 381 (1991). According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B-cell. Phage display can be performed in a variety of formats, reviewed in, *e.g.*, Johnson, Kevin S. and Chiswell, David J., *Curr. Opin Struct. Biol.* 3:564-571 (1993). Several sources of V-gene segments can be used for phage display. Clackson et al., Nature 352:624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., J. Mol. Biol. 222:581-597 (1991), or Griffith et al., EMBO J. 12:725-734 (1993). *See also* U.S. Patent. Nos. 5,565,332 and 5,573,905. Additionally, yeast display technology can be used to produce human anti-Siglec-7 antibodies and antibody fragments *in vitro* (*e.g.*, WO 2009/036379; WO 2010/105256; WO 2012/009568; US 2009/0181855; US 2010/0056386; and Feldhaus and Siegel (2004) J. Immunological Methods 290:69-80). In other embodiments, ribosome display technology can be used to produce human anti-Siglec-7 antibodies and antibody fragments *in vitro* (*e.g.*, Roberts and

Szostak (1997) Proc Natl Acad Sci 94:12297-12302; Schaffitzel et al. (1999) J. Immunolical Methods 231:119-135; Lipovsek and Plückthun (2004) J. Immunological Methods 290:51-67).

[0281] The techniques of Cole et al., and Boerner et al., are also available for the preparation of human anti-Siglec-7 monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner et al., *J. Immunol.* 147(1): 86-95 (1991). Similarly, human anti-Siglec-7 antibodies can be made by introducing human immunoglobulin loci into transgenic animals, *e.g.*, mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806, 5,569,825, 5,625,126, 5,633,425, 5,661,016 and in the following scientific publications: Marks et al., *Bio/Technology* 10: 779-783 (1992); Lonberg et al., *Nature* 368: 856-859 (1994); Morrison, *Nature* 368: 812-13 (1994), Fishwild et al., *Nature Biotechnology* 14: 845-51 (1996), Neuberger, *Nature Biotechnology* 14: 826 (1996) and Lonberg and Huszar, *Intern. Rev. Immunol.* 13: 65-93 (1995).

[0282] Finally, human anti-Siglec-7 antibodies may also be generated in vitro by activated B-cells (see U.S. Patent Nos 5,567,610 and 5,229,275).

(5) Antibody fragments

[0283] In certain embodiments there are advantages to using anti-Siglec-7 antibody fragments, rather than whole anti-Siglec-7 antibodies. Smaller fragment sizes allow for rapid clearance and better brain penetration.

[0284] Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (*see, e.g.*, Morimoto et al., *J. Biochem. Biophys. Method.* 24:107-117 (1992); and Brennan et al., *Science* 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells, for example, using nucleic acids encoding anti-Siglec-7 antibodies of the present disclosure. Fab, Fv and scFv antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the straightforward production of large amounts of these fragments. A anti-Siglec-7 antibody fragments can also be isolated from the antibody phage libraries as discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form $F(ab')_2$ fragments (Carter et al., *Bio/Technology* 10:163-167 (1992)). According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. Production of Fab and $F(ab')_2$ antibody fragments with increased *in vivo* half-lives are described in U.S. Patent No. 5,869,046. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185; U.S. Patent No. 5,571,894 and U.S. Patent No. 5,587,458. The anti-Siglec-7 antibody fragment may also

be a "linear antibody," *e.g.*, as described in U.S. Patent 5,641,870. Such linear antibody fragments may be monospecific or bispecific.

(6) Bispecific and polyspecific antibodies

[0285] Bispecific antibodies (BsAbs) are antibodies that have binding specificities for at least two different epitopes, including those on the same or another protein (*e.g.*, one or more Siglec-7 proteins of the present disclosure). Alternatively, one part of a BsAb can be armed to bind to the target Siglec-7 antigen, and another can be combined with an arm that binds to a second protein. Such antibodies can be derived from full length antibodies or antibody fragments (*e.g.*, $F(ab')_2$ bispecific antibodies).

[0286] Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the coexpression of two immunoglobulin heavy-chain/light chain pairs, where the two chains have different specificities. Millstein et al., *Nature*, 305:537-539 (1983). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829 and in Traunecker et al., *EMBO J.*, 10:3655-3659 (1991).

[0287] According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, C_H2, and C_H3 regions. It is preferred to have the first heavy-chain constant region (C_H1) containing the site necessary for light chain binding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide chains in one expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

[0288] In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific

compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only half of the bispecific molecules provides for an easy way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies, see, for example, Suresh et al., *Methods in Enzymology* 121: 210 (1986).

[0289] According to another approach described in WO 96/27011 or U.S. Patent No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the C_H3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (*e.g.*, tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chains(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (*e.g.*, alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

[0290] Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., *Science* 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

[0291] Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.* 175: 217-225 (1992) describes the production of fully humanized bispecific antibody $F(ab')_2$ molecules. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

[0292] Various techniques for making and isolating bivalent antibody fragments directly from recombinant cell culture have also been described. For example, bivalent heterodimers have been produced using leucine zippers. Kostelny et al., *J. Immunol.*, 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. The "diabody" technology

described by Hollinger et al., *Proc. Nat'l Acad. Sci. USA*, 90: 6444-6448 (1993) has provided an alternative mechanism for making bispecific/bivalent antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific/bivalent antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. *See* Gruber et al., *J. Immunol.*, 152:5368 (1994).

[0293] Antibodies with more than two valencies are also contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

[0294] Exemplary bispecific antibodies may bind to two different epitopes on a given molecule (*e.g.*, a Siglec-7 protein of the present disclosure). Alternatively, an arm targeting a Siglec-7 signaling component may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T cell receptor molecule (*e.g.*, CD2, CD3, CD28 or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular protein. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express a particular protein. Such antibodies possess a protein-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA or TETA. Another bispecific antibody of interest binds the protein of interest and further binds tissue factor (TF).

(7) Multivalent antibodies

[0295] A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind. The anti-Siglec-7 antibodies of the present disclosure or antibody fragments thereof can be multivalent antibodies (which are other than of the IgM class) with three or more antigen binding sites (*e.g.*, tetravalent antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or more antigen binding sites. The preferred dimerization domain comprises an Fc region or a hinge region. In this scenario, the antibody will comprise an Fc region and three or more antigen binding sites amino-terminal to the Fc region. The preferred multivalent antibody herein contains three to about eight, but preferably four, antigen binding sites. The multivalent antibody contains at least one polypeptide chain (and preferably two polypeptide chains), wherein the polypeptide chain or chains comprise two or more variable domains. For instance, the polypeptide chain or chains may comprise VD1-(X1)n-VD2-(X2)n-Fc, wherein VD1 is a first variable domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or

polypeptide, and n is 0 or 1. Similarly, the polypeptide chain or chains may comprise V_H-C_H1-flexible linker-V_H-C_H1-Fc region chain; or V_H-C_H1-V_H-C_H1-Fc region chain. The multivalent antibody herein preferably further comprises at least two (and preferably four) light chain variable domain polypeptides. The multivalent antibody herein may, for instance, comprise from about two to about eight light chain variable domain polypeptides. The light chain variable domain polypeptides contemplated here comprise a light chain variable domain and, optionally, further comprise a CL domain. The multivalent antibodies may recognize the Siglec-7 antigen as well as, without limitation, additional antigens A beta peptide, antigen or an alpha synuclain protein antigen or, Tau protein antigen or, TDP-43 protein antigen or, prion protein antigen or, huntingtin protein antigen, or RAN, translation Products antigen, including the DiPeptide Repeats,(DPRs peptides) composed of glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), proline-alanine (PA), or proline-arginine (PR), insulin receptor, insulin like growth factor receptor, transferrin receptor, or any other antigen that facilitates antibody transfer across the blood brain barrier.

(8) Heteroconjugate antibodies

[0296] Heteroconjugate antibodies are also within the scope of the present disclosure. Heteroconjugate antibodies are composed of two covalently joined antibodies (*e.g.*, anti-Siglec-7 antibodies of the present disclosure or antibody fragments thereof). For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells, U.S. Patent No. 4,676,980, and have been used to treat HIV infection. International Publication Nos. WO 91/00360, WO 92/200373 and EP 0308936. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980. Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Patent No. 4,676,980, along with a number of cross-linking techniques.

(9) Effector function engineering

[0297] It may also be desirable to modify an anti-Siglec-7 antibody of the present disclosure to modify effector function and/or to increase serum half-life of the antibody. For example, the Fc receptor binding site on the constant region may be modified or mutated to remove or reduce binding affinity to certain Fc receptors, such as FcγRI, FcγRII, and/or FcγRIII. In some embodiments, the effector function is impaired by removing N-glycosylation of the Fc region (*e.g.*, in the CH 2 domain of IgG) of the antibody. In some embodiments, the effector function is impaired by modifying

regions such as 233-236, 297, and/or 327-331 of human IgG as described in PCT WO 99/58572 and Armour et al., *Molecular Immunology* 40: 585-593 (2003); Reddy et al., *J. Immunology* 164:1925-1933 (2000).

[0298] To increase the serum half-life of the antibody, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment) as described in U.S. Patent 5,739,277, for example. As used herein, the term "*salvage receptor binding epitope*" refers to an epitope of the Fc region of an IgG molecule (*e.g.*, IgG_1, IgG_2, IgG_3, or IgG_4) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

(10) Other amino acid sequence modifications

[0299] Amino acid sequence modifications of anti-Siglec-7 antibodies of the present disclosure, or antibody fragments thereof, are also contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibodies or antibody fragments. Amino acid sequence variants of the antibodies or antibody fragments are prepared by introducing appropriate nucleotide changes into the nucleic acid encoding the antibodies or antibody fragments, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics (*i.e.*, the ability to bind or physically interact with a Siglec-7 protein of the present disclosure). The amino acid changes also may alter post-translational processes of the antibody, such as changing the number or position of glycosylation sites.

[0300] A useful method for identification of certain residues or regions of the anti-Siglec-7 antibody that are preferred locations for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells in *Science*, 244:1081-1085 (1989). Here, a residue or group of target residues are identified (*e.g.*, charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (most preferably alanine or polyalanine) to affect the interaction of the amino acids with the target antigen. Those amino acid locations demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation *per se* need not be predetermined. For example, to analyze the performance of a mutation at a given site, alanine scanning or random mutagenesis is conducted at the target codon or region and the expressed antibody variants are screened for the desired activity.

[0301] Amino acid sequence insertions include amino- ("N") and/or carboxy- ("C") terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as

well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue or the antibody fused to a cytotoxic polypeptide. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme or a polypeptide which increases the serum half-life of the antibody.

[0302] Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in the antibody molecule replaced by a different residue. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in the **Table E** below under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in **Table E**, or as further described below in reference to amino acid classes, may be introduced and the products screened.

Table E: Amino acid substitutions

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; asp, lys; arg	gln
Asp (D)	glu; asn	glu
Cys (C)	ser; ala	ser
Gln (Q)	asn; glu	asn
Glu (E)	asp; gln	asp
Gly (G)	ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	tyr
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	Ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

[0303] Substantial modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

(1) hydrophobic: norleucine, met, ala, val, leu, ile;

(2) neutral hydrophilic: cys, ser, thr;

(3) acidic: asp, glu;

(4) basic: asn, gln, his, lys, arg;

(5) residues that influence chain orientation: gly, pro; and

(6) aromatic: trp, tyr, phe.

[0304] Non-conservative substitutions entail exchanging a member of one of these classes for another class.

[0305] Any cysteine residue not involved in maintaining the proper conformation of the antibody also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment, such as an Fv fragment).

[0306] A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (*e.g.* a humanized or human anti-Siglec-7 antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (*e.g.*, 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (*e.g.*, binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and the antigen (*e.g.,* a Siglec-7 protein of the present disclosure). Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

[0307] Another type of amino acid variant of the antibody alters the original glycosylation pattern of the antibody. By altering is meant deleting one or more carbohydrate moieties found in the antibody, and/or adding one or more glycosylation sites that are not present in the antibody.

[0308] Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide

sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[0309] Addition of glycosylation sites to the antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites).

[0310] Nucleic acid molecules encoding amino acid sequence variants of the anti-IgE antibody are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the antibodies (*e.g.,* anti-Siglec-7 antibodies of the present disclosure) or antibody fragments.

(11) Antibody conjugates

[0311] Anti-Siglec-7 antibodies of the present disclosure, or antibody fragments thereof, can be conjugated to a detectable marker, a toxin, or a therapeutic agent. Any suitable method known in the art for conjugating molecules, such as a detectable marker, a toxin, or a therapeutic agent to antibodies may be used.

[0312] For example, drug conjugation involves coupling of a biological active cytotoxic (anticancer) payload or drug to an antibody that specifically targets a certain tumor marker (e.g. a protein that, ideally, is only to be found in or on tumor cells). Antibodies track these proteins down in the body and attach themselves to the surface of cancer cells. The biochemical reaction between the antibody and the target protein (antigen) triggers a signal in the tumor cell, which then absorbs or internalizes the antibody together with the cytotoxin. After the ADC is internalized, the cytotoxic drug is released and kills the cancer. Due to this targeting, ideally the drug has lower side effects and gives a wider therapeutic window than other chemotherapeutic agents. Technics to conjugate antibodies are disclosed are known in the art (*see, e.g.*, Jane de Lartigue, OncLive July 5, 2012; ADC Review on antibody-drug conjugates; and Ducry et al., (2010). *Bioconjugate Chemistry* 21 (1): 5–13).

[0313] In some embodiments, an anti-Siglec-7 antibody of the present disclosure may be conjugated to a toxin selected from ricin, ricin A-chain, doxorubicin, daunorubicin, a maytansinoid, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine,

dihydroxy anthracin dione, actinomycin, diphtheria toxin, *Pseudomonas* exotoxin (PE) A, PE40, abrin, abrin A chain, modeccin A chain, alpha-sarcin, gelonin, mitogellin, retstrictocin, phenomycin, enomycin, curicin, crotin, calicheamicin, *Saponaria officinalis* inhibitor, glucocorticoid, auristatin, auromycin, yttrium, bismuth, combrestatin, duocarmycins, dolastatin, cc1065, and a cisplatin.

(12) Other antibody modifications

[0314] Anti-Siglec-7 antibodies of the present disclosure, or antibody fragments thereof, can be further modified to contain additional non-proteinaceous moieties that are known in the art and readily available. Preferably, the moieties suitable for derivatization of the antibody are water-soluble polymers. Non-limiting examples of water-soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, polypropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (*e.g.*, glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer is attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, *etc.* Such techniques and other suitable formulations are disclosed in *Remington: The Science and Practice of Pharmacy*, 20th Ed., Alfonso Gennaro, Ed., Philadelphia College of Pharmacy and Science (2000).

Binding assays and other assays

[0315] Anti-Siglec-7 antibodies of the present disclosure may be tested for antigen binding activity, *e.g.*, by known methods such as ELISA, surface plasmon resonance (SPR), Western blot, *etc.*

[0316] In some embodiments, competition assays may be used to identify an antibody that competes with any of the antibodies listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8. In certain embodiments, such a competing antibody binds to the same epitope (e.g., a linear or a conformational epitope) that is bound by any of the antibodies listed in **Tables 2A, 2B, 3A, 3B, 6A, and 6B**, or selected from 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ).

[0317] In an exemplary competition assay, immobilized Siglec-7 or cells expressing Siglec-7 on a cell surface are incubated in a solution comprising a first labeled antibody that binds to Siglec-7 (*e.g.*, human or non-human primate) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to Siglec-7. The second antibody may be present in a hybridoma supernatant. As a control, immobilized Siglec-7 or cells expressing Siglec-7 is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to Siglec-7, excess unbound antibody is removed, and the amount of label associated with immobilized Siglec-7 or cells expressing Siglec-7 is measured. If the amount of label associated with immobilized Siglec-7 or cells expressing Siglec-7 is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to Siglec-7. *See*, Harlow and Lane (1988) *Antibodies: A Laboratory Manual* ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

Nucleic acids, vectors, and host cells

[0318] Anti-Siglec-7 antibodies of the present disclosure may be produced using recombinant methods and compositions, *e.g.*, as described in U.S. Patent No. 4,816,567. In some embodiments, isolated nucleic acids having a nucleotide sequence encoding any of the anti-Siglec-7 antibodies of the present disclosure are provided. Such nucleic acids may encode an amino acid sequence containing the VL and/or an amino acid sequence containing the VH of the anti-Siglec-7 antibody (*e.g.*, the light and/or heavy chains of the antibody). In some embodiments, one or more vectors (*e.g.*, expression vectors) containing such nucleic acids are provided. In some embodiments, a host cell containing such nucleic acid is also provided. In some embodiments, the host cell contains (*e.g.*, has been transduced with): (1) a vector containing a nucleic acid that encodes an amino acid sequence containing the VL of the antibody and an amino acid sequence containing the VH of the antibody, or (2) a first vector containing a nucleic acid that encodes an amino acid sequence containing the VL of the antibody and a second vector containing a nucleic acid that encodes an amino acid sequence containing the VH of the antibody. In some embodiments, the host cell is eukaryotic, *e.g.*, a Chinese Hamster Ovary (CHO) cell or lymphoid cell (*e.g.*, Y0, NS0, Sp20 cell).

[0319] Methods of making an anti-Siglec-7 antibody of the present disclosure are provided. In some embodiments, the method includes culturing a host cell of the present disclosure containing a nucleic acid encoding the anti-Siglec-7 antibody, under conditions suitable for expression of the antibody. In some embodiments, the antibody is subsequently recovered from the host cell (or host cell culture medium).

[0320] For recombinant production of an anti-Siglec-7 antibody of the present disclosure, a nucleic acid encoding the anti-Siglec-7 antibody is isolated and inserted into one or more vectors for

further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0321] Suitable vectors containing a nucleic acid sequence encoding any of the anti-Siglec-7 antibodies of the present disclosure, or fragments thereof polypeptides (including antibodies) described herein include, without limitation, cloning vectors and expression vectors. Suitable cloning vectors can be constructed according to standard techniques, or may be selected from a large number of cloning vectors available in the art. While the cloning vector selected may vary according to the host cell intended to be used, useful cloning vectors generally have the ability to self-replicate, may possess a single target for a particular restriction endonuclease, and/or may carry genes for a marker that can be used in selecting clones containing the vector. Suitable examples include plasmids and bacterial viruses, *e.g.*, pUC18, pUC19, Bluescript (*e.g.*, pBS SK+) and its derivatives, mpl8, mpl9, pBR322, pMB9, ColE1, pCR1, RP4, phage DNAs, and shuttle vectors such as pSA3 and pAT28. These and many other cloning vectors are available from commercial vendors such as BioRad, Strategene, and Invitrogen.

[0322] Expression vectors generally are replicable polynucleotide constructs that contain a nucleic acid of the present disclosure. The expression vector may replicable in the host cells either as episomes or as an integral part of the chromosomal DNA. Suitable expression vectors include but are not limited to plasmids, viral vectors, including adenoviruses, adeno-associated viruses, retroviruses, cosmids, and expression vector(s) disclosed in PCT Publication No. WO 87/04462. Vector components may generally include, but are not limited to, one or more of the following: a signal sequence; an origin of replication; one or more marker genes; suitable transcriptional controlling elements (such as promoters, enhancers and terminator). For expression (*i.e.*, translation), one or more translational controlling elements are also usually required, such as ribosome binding sites, translation initiation sites, and stop codons.

[0323] The vectors containing the nucleic acids of interest can be introduced into the host cell by any of a number of appropriate means, including electroporation, transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (*e.g.*, where the vector is an infectious agent such as vaccinia virus). The choice of introducing vectors or polynucleotides will often depend on features of the host cell. In some embodiments, the vector contains a nucleic acid containing one or more amino acid sequences encoding an anti-Siglec-7 antibody of the present disclosure.

[0324] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells. For example, anti-Siglec-7 antibodies of the present disclosure may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed.

For expression of antibody fragments and polypeptides in bacteria (*e.g.*, U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523; and Charlton, *Methods in Molecular Biology, Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.). After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0325] In addition to prokaryotes, eukaryotic microorganisms, such as filamentous fungi or yeast, are also suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern (*e.g.*, Gerngross, *Nat. Biotech.* 22:1409-1414 (2004); and Li et al., *Nat. Biotech.* 24:210-215 (2006)).

[0326] Suitable host cells for the expression of glycosylated antibody can also be derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells. Plant cell cultures can also be utilized as hosts (*e.g.*, U.S. Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429, describing PLANTIBODIES™ technology for producing antibodies in transgenic plants.).

[0327] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, *e.g.*, in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, *e.g.*, in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, *e.g.*, in Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR- CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, *e.g.*, Yazaki and Wu, *Methods in Molecular Biology, Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

Siglec-7 Activities

PI3K activation

[0328] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may induce PI3K activation after binding to a Siglec-7 protein expressed in a cell.

[0329] PI3Ks are a family of related intracellular signal transducer kinases capable of phosphorylating the 3-position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns). The PI3K family is divided into three different classes (Class I, Class II, and Class III) based on primary structure, regulation, and *in vitro* lipid substrate specificity.

[0330] Activated PI3K produces various 3-phosphorylated phosphoinositides, including without limitation, PtdIns3P, PtdIns(3,4)P2, PtdIns(3,5)P2, and PtdIns(3,4,5)P3. These 3-phosphorylated phosphoinositides function in a mechanism by which signaling proteins are recruited to various cellular membranes. These signaling proteins contain phosphoinositide-binding domains, including without limitation, PX domains, pleckstrin homology domains (PH domains), and FYVE domains. Any method known in the art for determining PI3K activation may be used.

[0331] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased levels of PI3K activity, including, without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas*

aeruginosa infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Modulated expression of cytokines

[0332] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may modulate (e.g., increase or decrease) pro-inflammatory mediators in the brain after binding to a Siglec-7 protein expressed on a cell surface. In certain embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, modulate the expression of cytokines (e.g., proinflammatory mediators) and/or reduce the expression of anti-inflammatory mediators after binding to a Siglec-7 protein expressed in a cell.

[0333] Inflammation is part of a complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, and irritants. The classical signs of acute inflammation are pain, heat, redness, and swelling. Inflammation is an immune response that protects an organism by limiting the site of injury or clearing an infection by recruiting and activating cells of the immune system. The inflammatory response is tightly regulated and restricted in its duration and severity to avoid causing damage to the organism. Inflammation can be classified as either acute or chronic. Acute inflammation is driven by the innate immune response, which initially recognizes harmful stimuli and recruits leukocytes from the blood into the injured tissues. A cascade of biochemical events, including cytokine and chemokine release, propagates the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Chronic inflammation is prolonged and persistent which leads to a progressive shift in the type of immune cells participating in the inflammatory response. Chronic inflammation is characterized by progressive destruction and fibrosis of the tissue as a result of the inflammatory process.

[0334] As used herein, anti-inflammatory mediators are proteins involved either directly or indirectly (*e.g.*, by way of an anti-inflammatory signaling pathway) in a mechanism that reduces, inhibits, or inactivates an inflammatory response. Any method known in the art for identifying and characterizing anti-inflammatory mediators may be used. Examples of anti-inflammatory mediators include, without limitation, cytokines, such as IL-4, IL-10, IL-13, IL-35, IL-16, IFN-alpha, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, or IL-6. Examples of pro-inflammatory mediators include, without limitation, cytokines, such as IFN-a4, IFN-beta, IL-1β, IL-1alpha, TNF-α, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, IL-33, MCP-1, and MIP-1-beta.

[0335] In some embodiments, the Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may modulate (e.g., increase or decrease) expression of

cytokines, such as IL-1b, IL-8, and TNF-a. In certain embodiments, modulated expression of the cytokines occurs in macrophages, neutrophils, natural killer (NK) cells, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, T cells, and/or microglial cells. Modulated expression may include, without limitation, an increase in gene expression, an increase in transcriptional expression, or an increase in protein expression. Any method known in the art for determining gene, transcript (*e.g.*, mRNA), and/or protein expression may be used. For example, Northern blot analysis may be used to determine cytokine gene expression levels, RT-PCR may be used to determine the level of cytokine transcription, and Western blot analysis may be used to determine cytokine protein levels.

[0336] As used herein, a cytokine may have modulated expression if its expression in one or more cells of a subject treated with an Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, is modulated as compared to the expression of the same cytokine expressed in one or more cells of a corresponding subject that is not treated with the Siglec-7 agent. In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may modulate cytokine expression in one or more cells of a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to cytokine expression in one or more cells of a corresponding subject that is not treated with the Siglec-7 agent. In other embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, modulate cytokine expression in one or more cells of a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to cytokine expression in one or more cells of a corresponding subject that is not treated with the Siglec-7 agent.

[0337] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are useful for preventing, lowering the risk of, or treating conditions and/or diseases associated with abnormal levels of one or more pro-inflammatory mediators, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Modulated expression of pro-inflammatory mediators

[0338] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may modulate (e.g., increase or decrease) the expression of pro-inflammatory mediators after binding to a Siglec-7 protein expressed in a cell.

[0339] As used herein, pro-inflammatory mediators are proteins involved either directly or indirectly (*e.g.*, by way of pro-inflammatory signaling pathways) in a mechanism that induces, activates, promotes, or otherwise increases an inflammatory response. Any method known in the art for identifying and characterizing pro-inflammatory mediators may be used.

[0340] Examples of pro-inflammatory mediators include, without limitation, cytokines, such as type I and II interferons, IFN-a4, IFN-beta, IL-1β, IL-1alpha, TNF-α, IL-6, IL-8, CRP, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, CRP, MCP-1, and MIP-1-beta.

[0341] In some embodiments, the anti-Siglec-7 antibodies of the present disclosure may modulate functional expression and/or secretion of pro-inflammatory mediators, such as type I and II interferons, IFN-a, IFN-b, IL-1β, TNF-α, IL-6, IL-8, CRP, IL-20 family members, IL-33, LIF, IFN-

gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, CRP. MCP-1, and MIP-1-beta. In certain embodiments, modulated expression of the pro-inflammatory mediators occurs in macrophages, neutrophils, NK cells, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, T cells, and/or microglial cells. Modulated expression may include, without limitation, a modulated gene expression, modulated transcriptional expression, or modulated protein expression. Any method known in the art for determining gene, transcript (*e.g.*, mRNA), and/or protein expression may be used. For example, Northern blot analysis may be used to determine pro-inflammatory mediator gene expression levels, RT-PCR may be used to determine the level of pro-inflammatory mediator transcription, and Western blot analysis may be used to determine pro-inflammatory mediator protein levels.

[0342] In certain embodiments, pro-inflammatory mediators include inflammatory cytokines. Accordingly, in certain embodiments, the Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may modulate secretion of one or more inflammatory cytokines. Examples of inflammatory cytokines whose secretion may be modulated by the anti-Siglec-7 antibodies of the present disclosure include, without limitation, such as type I and II interferons, IFN-a4, IFN-b, IL-1β, TNF-α, IL-6, IL-8, CRP, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, MCP-1, and MIP-1-beta.

[0343] In certain embodiments, pro-inflammatory mediators include inflammatory receptors. Accordingly, in certain embodiments, the Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may modulate expression of one or more inflammatory receptors. Examples of inflammatory receptors whose expression may be modulated by the Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, include, without limitation, CD86, CD80, CD83.

[0344] As used herein, a pro-inflammatory mediator may have modulated expression if its expression in one or more cells of a subject treated with a Siglec-7 agent, such as an agonist anti-Siglec-7 antibody of the present disclosure is modulated (e.g., increased or decreased) as compared to the expression of the same pro-inflammatory mediator expressed in one or more cells of a corresponding subject that is not treated with the agonist anti-Siglec-7 antibody. In some embodiments, the anti-Siglec-7 antibody of the present disclosure may modulate pro-inflammatory mediator expression in one or more cells of a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at

least 190%, or at least 200% for example, as compared to pro-inflammatory mediator expression in one or more cells of a corresponding subject that is not treated with the anti-Siglec-7 antibody. In other embodiments, the anti-Siglec-7 antibody may modulate pro-inflammatory mediator expression in one or more cells of a subject by at least at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to pro-inflammatory mediator expression in one or more cells of a corresponding subject that is not treated with the anti-Siglec-7 antibody.

[0345] In some embodiments, some Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may be useful for preventing, lowering the risk of, or treating conditions and/or diseases associated with abnormal levels of one or more pro-inflammatory mediators, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection,

Campylobacter jejuni infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

ERK phosphorylation

[0346] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may induce extracellular signal-regulated kinase (ERK) phosphorylation after binding to a Siglec-7 protein expressed in a cell.

[0347] Extracellular-signal-regulated kinases (ERKs) are widely expressed protein kinase intracellular signaling kinases that are involved in, for example, the regulation of meiosis, mitosis, and postmitotic functions in differentiated cells. Various stimuli, such as growth factors, cytokines, virus infection, ligands for heterotrimeric G protein-coupled receptors, transforming agents, and carcinogens, activate ERK pathways. Phosphorylation of ERKs leads to the activation of their kinase activity.

[0348] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased levels of ERK phosphorylation, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection,

Campylobacter jejuni infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Syk phosphorylation

[0349] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may induce spleen tyrosine kinase (Syk) phosphorylation after binding to a Siglec-7 protein expressed in a cell.

[0350] Spleen tyrosine kinase (Syk) is an intracellular signaling molecule that functions downstream of Siglec-7 by phosphorylating several substrates, thereby facilitating the formation of a signaling complex leading to cellular activation and inflammatory processes.

[0351] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased levels of Syk phosphorylation, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Siglec-7 phosphorylation

[0352] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may transiently induce Siglec-7 phosphorylation of Tyr-437 and Tyr-460 by a by Src family tyrosine kinase such as Src, Syk, Fyn, Fgr, Lck, Hck, Blk, Lyn, and Frk after binding to a Siglec-7 protein expressed in a cell.

[0353] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased levels of Siglec-7 phosphorylation, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Phosphorylation of ITAM motif containing receptors

[0354] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may induce phosphorylate ITAM motif-containing receptors, such as TREM1, TREM2, Sirp beta, FcgR, DAP10, and DAP12, after binding to a Siglec-7 protein expressed in a cell.

[0355] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased levels of phosphorylation of ITAM motif-containing receptors, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Modulated expression of C-C chemokine receptor 7

[0356] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may modulate expression of C-C chemokine receptor 7 (CCR7) after binding to a Siglec-7 protein expressed in a cell. Modulated (e.g., increased or decreased) expression may include, without limitation, modulation in gene expression, modulation in transcriptional expression, or modulation in protein expression. Any method known in the art for determining gene, transcript (*e.g.*, mRNA), and/or protein expression may be used. For example, Northern blot analysis may be used to determine anti-inflammatory mediator gene expression levels, RT-PCR may be used to determine the level of anti-inflammatory mediator transcription, and Western blot analysis may be used to determine anti-inflammatory mediator protein levels.

[0357] C-C chemokine receptor 7 (CCR7) is a member of the G protein-coupled receptor family. CCR7 is expressed in various lymphoid tissues and can activate B cells and T cells. In some embodiments, CCR7 may modulate the migration of memory T cells to secondary lymphoid organs, such as lymph nodes. In other embodiments, CCR7 may stimulate dendritic cell maturation. CCR7 is a receptor protein that can bind the chemokine (C-C motif) ligands CCL19/ELC and CCL21.

[0358] As used herein, CCR7 may have modulated expression if its expression in one or more cells of a subject treated with an Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, is modulated (e.g., increased or decreased) as compared to the expression of CCR7 expressed in one or more cells of a corresponding subject that is not treated with the Siglec-7 agent. In some embodiments, an Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, may modulate CCR7 expression in one or more cells of a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to CCR7 expression in one or more cells of a corresponding subject that is not treated with the Siglec-7 agent. In other embodiments, an Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, modulates CCR7 expression in one or more cells of a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to CCR7 expression in one or more cells of a corresponding subject that is not treated with the Siglec-7 agent.

[0359] In some embodiments, increased expression of CCR7 occurs in macrophages, neutrophils, NK cells, dendritic cells, and/or microglial cells. Increased expression of CCR7 may induce microglial cell chemotaxis toward cells expressing the chemokines CCL19 and CCL21. Accordingly, in certain embodiments, anti-Siglec-7 antibodies of the present disclosure may induce microglial cell chemotaxis toward CCL19 and CCL21 expressing cells.

[0360] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are useful for preventing, lowering the risk of, or treating conditions and/or diseases associated with abnormal levels of CCR7, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Modulated expression of immune-related proteins

[0361] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec7 antibodies of the present disclosure, may modulate expression of PD-L1, PD-L2, B7-H3, CD11b, CD200R, CD163 and/or CD206 after binding to a Siglec-7 protein expressed in a cell. Modulated (e.g., increased or decreased) expression may include, without limitation, modulation in gene expression, modulation in transcriptional expression, or modulation in protein expression. Any method known in the art for determining gene, transcript (*e.g.*, mRNA), and/or protein expression may be used. For example, Northern blot analysis may be used to determine anti-inflammatory mediator gene expression levels, RT-PCR may be used to determine the level of anti-inflammatory mediator transcription, and Western blot analysis may be used to determine anti-inflammatory mediator protein levels.

[0362] As used herein, PD-L1, PD-L2, B7-H3, CD11b, CD200R, CD163 and/or CD206 may have modulated expression if its expression in one or more cells of a subject treated with a Siglec-7 agent of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, is

modulated (e.g., increased or decreased) as compared to the expression of PD-L1, PD-L2, B7-H3, CD11b, CD200R, CD163 and/or CD206 expressed in one or more cells of a corresponding subject that is not treated with the Siglec-7 agent. In some embodiments, a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, may modulate PD-L1, PD-L2, B7-H3, CD11b, CD200R, CD163 and/or CD206 expression in one or more cells of a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to PD-L1, PD-L2, B7-H3, CD11b, CD200R, CD163 and/or CD206 expression in one or more cells of a corresponding subject that is not treated with the Siglec-7 agent. In other embodiments, a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, modulates PD-L1, PD-L2, B7-H3, CD11b, CD200R, CD163 and/or CD206 expression in one or more cells of a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to PD-L1, PD-L2, B7-H3, CD11b, CD200R, CD163 and/or CD206 expression in one or more cells of a corresponding subject that is not treated with the Siglec-7 agent.

[0363] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are useful for preventing, lowering the risk of, or treating conditions and/or diseases associated with abnormal levels of PD-L1, PD-L2, B7-H2, B7-H3, CD11b, CD200R, CD163 and/or CD206, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Enhancement or normalization of the ability of bone marrow-derived dendritic cells to induce antigen-specific T cell proliferation

[0364] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may enhance and/or normalize the ability of bone marrow-derived dendritic cells to induce antigen-specific T cell proliferation after binding to a Siglec-7 protein expressed in a cell.

[0365] In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, may enhance and/or normalize the ability of bone marrow-derived dendritic cells to induce antigen-specific T cell proliferation in one or more bone marrow-derived dendritic cells of a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to the ability of bone marrow-derived dendritic cells to induce antigen-specific T cell proliferation in one or more bone marrow-derived dendritic cells of a corresponding subject that is not treated with the agent. In other embodiments, the Siglec-7 agent, such as an antagonist anti-Siglec-7 antibody, may enhance and/or normalize the ability of bone marrow-derived dendritic cells to induce antigen-specific T cell proliferation in one or more bone marrow-derived dendritic cells of a subject by at least at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least

5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to the ability of bone marrow-derived dendritic cells to induce antigen-specific T cell proliferation in one or more bone marrow-derived dendritic cells of a corresponding subject that is not treated with the Siglec-7 agent.

[0366] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased or dysregulated ability of bone marrow-derived dendritic cells to induce antigen-specific T cell proliferation, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Osteoclast production

[0367] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may induce osteoclast production and/or increase the rate of osteoclastogenesis after binding to a Siglec-7 protein expressed in a cell.

[0368] As used herein, an osteoclast is a type of bone cell that can remove bone tissue by removing its mineralized matrix and breaking up the organic bone (*e.g.*, bone resorption). Osteoclasts can be formed by the fusion of cells of the myeloid lineage. In some embodiments, osteoclasts may be characterized by high expression of tartrate resistant acid phosphatase (TRAP) and cathepsin K.

[0369] As used herein, the rate of osteoclastogenesis may be increased if the rate of osteoclastogenesis in a subject treated with a Siglec-7 agent of the present disclosure, such as antagonist anti-Siglec-7 antibody, is greater than the rate of osteoclastogenesis in a corresponding subject that is not treated with the Siglec-7 agent. In some embodiments, a Siglec-7 agent, such as an antagonist anti-Siglec-7 antibody of the present disclosure, may increase the rate of osteoclastogenesis in a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to rate of osteoclastogenesis in a corresponding subject that is not treated with the Siglec-7 agent. In other embodiments, a Siglec-7 agent, such as an antagonist anti-Siglec-7 antibody of the present disclosure, may increase the rate of osteoclastogenesis in a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to rate of osteoclastogenesis in a corresponding subject that is not treated with the Siglec-7 agent.

[0370] As used herein, the rate of osteoclastogenesis may be decreased if the rate of osteoclastogenesis in a subject treated with a Siglec-7 agent, such as an agonist anti-Siglec-7 antibody of the present disclosure, is smaller than the rate of osteoclastogenesis in a corresponding subject that is not treated with the Siglec-7 agent. In some embodiments, a Siglec-7 agent, such as an agonist anti-Siglec-7 antibody of the present disclosure, may decrease the rate of osteoclastogenesis in a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to rate of osteoclastogenesis in a corresponding subject that is not treated with the Siglec-7 agent. In

other embodiments, a Siglec-7 agent, such as an agonist anti-Siglec-7 antibody of the present disclosure, may decrease the rate of osteoclastogenesis in a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to rate of osteoclastogenesis in a corresponding subject that is not treated with the Siglec-7 agent.

[0371] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with abnormal bone formation and maintenance including osteoporosis, which is associated with pathological decrease in bone density and osteoporotic diseases which are associated with pathological increase in bone density.

Proliferation and survival of Siglec-7-expressing cells

[0372] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may increase the proliferation, survival, and/or function of dendritic cells, macrophages, neutrophils, NK cells, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, T cells, and microglial cells after binding to Siglec-7 protein expressed on a cell.

[0373] As used herein, macrophages of the present disclosure include, without limitation, M1 macrophages, activated M1 macrophages, and M2 macrophages. As used herein, neutrophils of the present disclosure include, without limitation, M1 neutrophils, activated M1 neutrophils, and M2 neutrophils. As used herein, natural killer (NK) cells of the present disclosure include, without limitation, M1 NK cells, activated M1 NK cells, and M2 NK cells. As used herein, microglial cells of the present disclosure include, without limitation, M1 microglial cells, activated M1 microglial cells, and M2 microglial cells.

[0374] Microglial cells are a type of glial cell that are the resident macrophages of the brain and spinal cord, and thus act as the first and main form of active immune defense in the central nervous system (CNS). Microglial cells constitute 20% of the total glial cell population within the brain. Microglial cells are constantly scavenging the CNS for plaques, damaged neurons and infectious agents. The brain and spinal cord are considered "immune privileged" organs in that they are separated from the rest of the body by a series of endothelial cells known as the blood–brain barrier, which prevents most pathogens from reaching the vulnerable nervous tissue. In the case where infectious agents are directly introduced to the brain or cross the blood–brain barrier, microglial cells

must react quickly to limit inflammation and destroy the infectious agents before they damage the sensitive neural tissue. Due to the unavailability of antibodies from the rest of the body (few antibodies are small enough to cross the blood brain barrier), microglia must be able to recognize foreign bodies, swallow them, and act as antigen-presenting cells activating T cells. Since this process must be done quickly to prevent potentially fatal damage, microglial cells are extremely sensitive to even small pathological changes in the CNS. They achieve this sensitivity in part by having unique potassium channels that respond to even small changes in extracellular potassium.

[0375] In some embodiments, anti-Siglec-7 antibodies of the present disclosure may increase the expression of CD80, CD83 and/or CD86 on dendritic cells, monocytes, macrophages, neutrophils, NK cells, and/or microglia.

[0376] As used herein, the rate of proliferation, survival, and/or function of macrophages, neutrophils, NK cells, dendritic cells, monocytes, T cells, and/or microglia may include increased expression if the rate of proliferation, survival, and/or function of dendritic cells, macrophages, neutrophils, NK cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglia in a subject treated with a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, is greater than the rate of proliferation, survival, and/or function of dendritic cells, macrophages, neutrophils, NK cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, T cells, and/or microglia in a corresponding subject that is not treated with the Siglec-7 agent. In some embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase the rate of proliferation, survival, and/or function of dendritic cells, macrophages, neutrophils, NK cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, T cells, and/or microglia in a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to the rate of proliferation, survival, and/or function of dendritic cells, macrophages, neutrophils, NK cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, T cells, and/or microglia in a corresponding subject that is not treated with the Siglec-7 agent. In other embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase the rate of proliferation, survival, and/or function of dendritic cells, macrophages, neutrophils, NK cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, T cells, and/or microglia in a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold,

at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to the rate of proliferation, survival, and/or function of dendritic cells, macrophages, neutrophils, NK cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, T cells, and/or microglia in a corresponding subject that is not treated with the Siglec-7 agent.

[0377] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with a reduction in proliferation, survival, increased apoptosis and/or function of dendritic cells, neutrophils, macrophages, neutrophils, NK cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, T cells, and/or microglia including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Clearance and phagocytosis

[0378] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may induce clearance and/or phagocytosis after binding to a Siglec-7 protein expressed in a cell of one or more of apoptotic neurons, nerve tissue debris of the nervous system, dysfunctional synapses, non-nerve tissue debris of the nervous system, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, disease-causing nucleic acid, or tumor cells. In certain embodiments, disease-causing proteins include, without limitation, amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides. In certain embodiments, disease-causing nucleic acids include, without limitation, antisense GGCCCC (G2C4) repeat-expansion RNA.

[0379] In some embodiments, the Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may induce of one or more types of clearance, including without limitation, apoptotic neuron clearance, nerve tissue debris clearance, dysfunctional synapse clearance, non- nerve tissue debris clearance, bacteria or other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, disease-causing nucleic acid clearance, and tumor cell clearance.

[0380] In some embodiments, the Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may induce phagocytosis of one or more of apoptotic neurons, nerve tissue debris, dysfunctional synapses, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, disease-causing nucleic acid, and/or tumor cells.

[0381] In some embodiments, the Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may increase phagocytosis by neutrophils, macrophages, neutrophils, NK cells, dendritic cells, monocytes, and/or microglia under conditions of reduced levels of macrophage colony-stimulating factor (M-CSF).

[0382] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with apoptotic neurons, nerve tissue debris of the nervous

system, non-nerve tissue debris of the nervous system, bacteria, other foreign bodies, disease-causing proteins, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Siglec-7-dependent gene expression

[0383] In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, may decrease the activity and/or expression of Siglec-7-dependent genes, and by that increase gene expression associated with signaling cascade that activate the immune system such as gene expression associated with ITAM containing receptors, pattern recognition receptors, of Toll-like receptors, of damage-associated molecular pattern (DAMP) receptors such as one or more transcription factors of the nuclear factor of activated T cells (NFAT) family of transcription factors.

[0384] In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with high levels of Siglec-7-dependent genes, including without limitation, 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Siglec-7-dependent activation of T cells

[0385] In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, may increase the activity of cytotoxic T cells helper T cells or both. In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased activity of cytotoxic T cells helper T cells or both, including without limitation, tumors, including solid tumors such as 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, and thyroid cancer.

[0386] In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, may induce an increase in proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells (*e.g.,* tumor infiltrating $CD3^+$ T cells, etc.), helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts,

Langerhans cells of skin, Kupffer cells, and/or microglial cells. In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, induce an increase in proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in the presence of myeloid-derived suppressor cells (MDSC).

[0387] As used herein, the rate of proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells (*e.g.,* tumor infiltrating $CD3^+$ T cells, etc.), helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells may include an increased rate if the rate of proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in a subject treated with a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, is greater than the rate of proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in a corresponding subject that is not treated with the Siglec-7 agent. In some embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to the level of proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in a corresponding subject that is not treated with the Siglec-7 agent. In other embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at

least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to the level of proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in a corresponding subject that is not treated with the Siglec-7 agent.

[0388] In some embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in the presence of myeloid-derived suppressor cells (MDSC) by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to the level of proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in the presence of myeloid-derived suppressor cells (MDSC) that are not treated with the Siglec-7 agent. In other embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in the presence of myeloid-derived suppressor cells (MDSC) by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to the level of proliferation, survival, activity, and/or number of T cells, cytotoxic T cells, $CD3^+$ T cells, helper T cells, dendritic cells, macrophages, monocytes, neutrophils, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells in the presence of myeloid-derived suppressor cells (MDSC) that are not treated with the Siglec-7 agent.

Siglec-7-dependent inhibition of neutrophils

[0389] In some embodiments, Siglec-7 agents of the present disclosure, such as agonist anti-Siglec-7 antibodies of the present disclosure, may decrease the activity of neutrophils. In some embodiments, Siglec-7 agents of the present disclosure, such as agonist anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased activity of the activity of natural killer cells, neutrophils or both, including without limitation, tumors, including solid tumors such as 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, and thyroid cancer.

Siglec-7-dependent enhanced cell killing by natural killer (NK) cells

[0390] In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, may increase the killing activity of NK cells. In some embodiments, Siglec-7 agents of the present disclosure, such as antagonistic anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased activity of natural killer cells, neutrophils or both, including without limitation, tumors, including solid tumors such as 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, and thyroid cancer.

Siglec-7-dependent inhibition of tumor-associated immune cells

[0391] In some embodiments, Siglec-7 agents of the present disclosure, such as agonist anti-Siglec-7 antibodies of the present disclosure, may decrease the activity, decrease the proliferation, decrease the survival, decrease the functionality, decrease infiltration to tumors or lymphoid organs (e.g., the spleen and lymph nodes), and/or promote apoptosis of T-regulatory cells or inhibitory tumor-imbedded immunosuppressor dendritic cells or, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, or, myeloid-derived suppressor cells. In some embodiments, Siglec-7 agents of the present disclosure, such as agonist anti-Siglec-7 antibodies of the present disclosure, are beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with the activity of one or more type of immune suppressor cells, including without limitation, tumors, including solid tumors that do not express Siglec-7 such as bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, thyroid cancer, and blood tumors that express Siglec-7, such as leukemia cells.

[0392] In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, may decrease the number of $CD14^+$ myeloid cells (*e.g.,* the number of tumor-infiltrating $CD14^+$ myeloid cells, the number of peripheral blood $CD14^+$ myeloid cells, etc.), decrease tumor growth rate, reduce tumor volume, or reduce or inhibit differentiation, survival, and/or one or more functions of myeloid-derived suppressor cells (MDSC).

[0393] In some embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may decrease the number of $CD14^+$ myeloid cells(*e.g.,* the number of tumor-infiltrating $CD14^+$ myeloid cells, the number of peripheral blood $CD14^+$ myeloid cells, etc.), decrease tumor growth rate, reduce tumor volume, or reduce or inhibit differentiation, survival, and/or one or more functions of myeloid-derived suppressor cells (MDSC) in a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to the number of $CD14^+$ myeloid cells, tumor growth rate, tumor volume, or level of differentiation, survival, and/or one or more functions of myeloid-derived suppressor cells (MDSC) in a corresponding subject that is not treated with the Siglec-7 agent. In other embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may decrease the number of $CD14^+$ myeloid cells(*e.g.,* the number of tumor-infiltrating $CD14^+$ myeloid cells, the number of peripheral blood $CD14^+$ myeloid cells, etc.), decrease tumor growth rate, reduce tumor volume, or reduce or inhibit differentiation, survival, and/or one or more functions of myeloid-derived suppressor cells (MDSC) in a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to the number of $CD14^+$ myeloid cells, tumor growth rate, tumor volume, or level of differentiation, survival, and/or one or more functions of myeloid-derived suppressor cells (MDSC) in a corresponding subject that is not treated with the Siglec-7 agent.

Increased efficacy of checkpoint inhibitor therapies

[0394] In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, may increase the efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, such as PD-1 inhibitors or therapies that target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, and/or LAG3.

[0395] In some embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase the efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, such as PD-1 inhibitors or therapies that target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, and/or LAG3 in a subject receiving such one or more therapies by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to the level of effectiveness of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, such as PD-1 inhibitors or therapies that target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, and/or LAG3 in a corresponding subject receiving such one or more therapies that is not treated with the Siglec-7 agent. In other embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase the efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, such as PD-1 inhibitors or therapies that target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, and/or LAG3 in a subject receiving such one or more therapies by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to the level of effectiveness of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, such as PD-1 inhibitors or therapies that target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, and/or LAG3 in a corresponding subject receiving such one or more therapies that is not treated with the Siglec-7 agent.

Increased efficacy of chemotherapeutic agents

[0396] In some embodiments, Siglec-7 agents of the present disclosure, such as antagonist anti-Siglec-7 antibodies of the present disclosure, may increase the efficacy of one or more chemotherapy agents, such as gemcitabine, capecitabine, anthracyclines, doxorubicin (Adriamycin®), epirubicin (Ellence®), taxanes, paclitaxel (Taxol®), docetaxel (Taxotere®), 5-fluorouracil (5-FU), cyclophosphamide (Cytoxan®), and/orcarboplatin (Paraplatin®).

[0397] In some embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase the efficacy of one or more chemotherapy agents in a subject receiving such

one or more therapies by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to the level of effectiveness of one or more chemotherapy agents in a corresponding subject receiving such one or more therapies that is not treated with the Siglec-7 agent. In other embodiments, a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, may increase the efficacy of one or more chemotherapy agents in a subject receiving such one or more therapies by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to the level of effectiveness of one or more chemotherapy agents in a corresponding subject receiving such one or more therapies that is not treated with the Siglec-7 agent.

Pharmaceutical compositions

[0398] Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, can be incorporated into a variety of formulations for therapeutic administration by combining the agents, such as anti-Siglec-7 antibodies, with appropriate pharmaceutically acceptable carriers or diluents, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms. Examples of such formulations include, without limitation, tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Pharmaceutical compositions can include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers of diluents, which are vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents include, without limitation, distilled water, buffered water, physiological saline, PBS, Ringer's solution, dextrose solution, and Hank's solution. A pharmaceutical composition or formulation of the present disclosure can further include other carriers, adjuvants, or non-toxic, nontherapeutic, nonimmunogenic stabilizers, excipients and the like. The compositions can also include additional substances to approximate physiological conditions, such as pH adjusting and buffering agents, toxicity adjusting agents, wetting agents and detergents.

[0399] A pharmaceutical composition of the present disclosure can also include any of a variety of stabilizing agents, such as an antioxidant for example. When the pharmaceutical composition includes a polypeptide, the polypeptide can be complexed with various well-known compounds that enhance the *in vivo* stability of the polypeptide, or otherwise enhance its pharmacological properties (*e.g.*, increase the half-life of the polypeptide, reduce its toxicity, and enhance solubility or uptake). Examples of such modifications or complexing agents include, without limitation, sulfate, gluconate, citrate and phosphate. The polypeptides of a composition can also be complexed with molecules that enhance their *in vivo* attributes. Such molecules include, without limitation, carbohydrates, polyamines, amino acids, other peptides, ions (*e.g.*, sodium, potassium, calcium, magnesium, manganese), and lipids.

[0400] Further examples of formulations that are suitable for various types of administration can be found in Remington's *Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985). For a brief review of methods for drug delivery, see, Langer, *Science* 249:1527-1533 (1990).

[0401] For oral administration, the active ingredient can be administered in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. The active component(s) can be encapsulated in gelatin capsules together with inactive ingredients and powdered carriers, such as glucose, lactose, sucrose, mannitol, starch, cellulose or cellulose derivatives, magnesium stearate, stearic acid, sodium saccharin, talcum, magnesium carbonate. Examples of additional inactive ingredients that may be added to provide desirable color, taste, stability, buffering capacity, dispersion or other known desirable features are red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric-coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[0402] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

[0403] The components used to formulate the pharmaceutical compositions are preferably of high purity and are substantially free of potentially harmful contaminants (*e.g.*, at least National Food (NF) grade, generally at least analytical grade, and more typically at least pharmaceutical grade).

Moreover, compositions intended for *in vivo* use are usually sterile. To the extent that a given compound must be synthesized prior to use, the resulting product is typically substantially free of any potentially toxic agents, particularly any endotoxins, which may be present during the synthesis or purification process. Compositions for parental administration are also sterile, substantially isotonic and made under GMP conditions.

[0404] Formulations may be optimized for retention and stabilization in the brain or central nervous system. When the agent is administered into the cranial compartment, it is desirable for the agent to be retained in the compartment, and not to diffuse or otherwise cross the blood brain barrier. Stabilization techniques include cross-linking, multimerizing, or linking to groups such as polyethylene glycol, polyacrylamide, neutral protein carriers, *etc.* in order to achieve an increase in molecular weight.

[0405] Other strategies for increasing retention include the entrapment of an agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, in a biodegradable or bioerodible implant. The rate of release of the therapeutically active agent is controlled by the rate of transport through the polymeric matrix, and the biodegradation of the implant. The transport of drug through the polymer barrier will also be affected by compound solubility, polymer hydrophilicity, extent of polymer cross-linking, expansion of the polymer upon water absorption so as to make the polymer barrier more permeable to the drug, geometry of the implant, and the like. The implants are of dimensions commensurate with the size and shape of the region selected as the site of implantation. Implants may be particles, sheets, patches, plaques, fibers, microcapsules and the like and may be of any size or shape compatible with the selected site of insertion.

[0406] The implants may be monolithic, *i.e.* having the active agent homogenously distributed through the polymeric matrix, or encapsulated, where a reservoir of active agent is encapsulated by the polymeric matrix. The selection of the polymeric composition to be employed will vary with the site of administration, the desired period of treatment, patient tolerance, the nature of the disease to be treated and the like. Characteristics of the polymers will include biodegradability at the site of implantation, compatibility with the agent of interest, ease of encapsulation, a half-life in the physiological environment.

[0407] Biodegradable polymeric compositions which may be employed may be organic esters or ethers, which when degraded result in physiologically acceptable degradation products, including the monomers. Anhydrides, amides, orthoesters or the like, by themselves or in combination with other monomers, may find use. The polymers will be condensation polymers. The polymers may be cross-linked or non-cross-linked. Of particular interest are polymers of hydroxyaliphatic carboxylic acids, either homo- or copolymers, and polysaccharides. Included among the polyesters of interest are polymers of D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, polycaprolactone, and

combinations thereof. By employing the L-lactate or D-lactate, a slowly biodegrading polymer is achieved, while degradation is substantially enhanced with the racemate. Copolymers of glycolic and lactic acid are of particular interest, where the rate of biodegradation is controlled by the ratio of glycolic to lactic acid. The most rapidly degraded copolymer has roughly equal amounts of glycolic and lactic acid, where either homopolymer is more resistant to degradation. The ratio of glycolic acid to lactic acid will also affect the brittleness of in the implant, where a more flexible implant is desirable for larger geometries. Among the polysaccharides of interest are calcium alginate, and functionalized celluloses, particularly carboxymethylcellulose esters characterized by being water insoluble, a molecular weight of about 5 kD to 500 kD, *etc.* Biodegradable hydrogels may also be employed in the implants of the present disclosure. Hydrogels are typically a copolymer material, characterized by the ability to imbibe a liquid. Exemplary biodegradable hydrogels which may be employed are described in Heller in: Hydrogels in Medicine and Pharmacy, N. A. Peppes ed., Vol. III, CRC Press, Boca Raton, Fla., 1987, pp 137-149.

Pharmaceutical dosages

[0408] Pharmaceutical compositions of the present disclosure containing a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, may be administered to an individual in need of treatment with the Siglec-7 agent, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, intracranial, intraspinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

[0409] Dosages and desired drug concentration of pharmaceutical compositions of the present disclosure may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary artisan. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles described in Mordenti, J. and Chappell, W. "The Use of Interspecies Scaling in Toxicokinetics," In *Toxicokinetics and New Drug Development*, Yacobi et al., Eds, Pergamon Press, New York 1989, pp.42-46.

[0410] For *in vivo* administration of any of the Siglec-7 agents of the present disclosure, such as any of the anti-Siglec-7 antibodies of the present disclosure, normal dosage amounts may vary from about 10 ng/kg up to about 100 mg/kg of an individual's body weight or more per day, preferably about 1 mg/kg/day to 10 mg/kg/day, depending upon the route of administration. For repeated administrations over several days or longer, depending on the severity of the disease, disorder, or condition to be treated, the treatment is sustained until a desired suppression of symptoms is achieved.

[0411] An exemplary dosing regimen may include administering an initial dose of a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody, of about 2 mg/kg, followed by a weekly maintenance dose of about 1 mg/kg every other week. Other dosage regimens may be useful, depending on the pattern of pharmacokinetic decay that the physician wishes to achieve. For example, dosing an individual from one to twenty-one times a week is contemplated herein. In certain embodiments, dosing ranging from about 3 μg/kg to about 2 mg/kg (such as about 3 μg/kg, about 10 μg/kg, about 30 μg/kg, about 100 μg/kg, about 300 μg/kg, about 1 mg/kg, and about 2/mg/kg) may be used. In certain embodiments, dosing frequency is three times per day, twice per day, once per day, once every other day, once weekly, once every two weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every nine weeks, once every ten weeks, or once monthly, once every two months, once every three months, or longer. Progress of the therapy is easily monitored by conventional techniques and assays. The dosing regimen, including the Siglec-7 agent, such as the anti-Siglec-7 antibody administered, can vary over time independently of the dose used.

[0412] Dosages for a particular Siglec-7 agent, such as a particular anti-Siglec-7 antibody, may be determined empirically in individuals who have been given one or more administrations of the Siglec-7agent, such as the anti-Siglec-7 antibody. Individuals are given incremental doses of a Siglec-7 agent, such as an anti-Siglec-7 antibody. To assess efficacy of a Siglec-7 agent, such as an anti-Siglec-7 antibody, a clinical symptom of any of the diseases, disorders, or conditions of the present disclosure (*e.g.*, frontotemporal dementia, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, a traumatic brain injury, a spinal cord injury, long-term depression, atherosclerotic vascular diseases, and undesirable symptoms of normal aging) can be monitored.

[0413] Administration of a Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure, can be continuous or intermittent, depending, for example, on the recipient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to skilled practitioners. The administration of a Siglec-7 agent, such as an anti-Siglec-7 antibody, may be essentially continuous over a preselected period of time or may be in a series of spaced doses.

[0414] Guidance regarding particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Patent Nos. 4,657,760; 5,206,344; or 5,225,212. It is within the scope of the present disclosure that different formulations will be effective for different treatments and different disorders, and that administration intended to treat a specific organ or tissue may necessitate delivery in a manner different from that to another organ or tissue. Moreover, dosages may be administered by one or more separate administrations, or by continuous infusion. For repeated administrations over several days or longer, depending on the condition, the treatment is

sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

Therapeutic uses

[0415] Further aspects of the present disclosure provide methods of modulating (*e.g.*, activating or inhibiting) one or more Siglec-7 activities, including with limitation, modulating (*e.g.*, activating or inhibiting) a Siglec-7 protein of the present disclosure, counteracting one or more phosphorylation of Tyr-437 and Tyr-460 by a Src family tyrosine kinase, such as Syk, LCK, FYM, and/or ZAP70; recruitment of and binding to the tyrosine-specific protein phosphatases SHP1 and SHP2; recruitment of and binding to PLC-gamma1, which acts as a guanine nucleotide exchange factor for Dynamini-1; recruitment of and binding to SH2-domain containing protein (*e.g.*, Crkl); recruitment of and binding to the spleen tyrosine kinase Syk; recruitment of and binding to SH3-SH2-SH3 growth factor receptor-bound protein 2 (Grb2); recruitment of and binding to multiple SH2-containing proteins; modulating (e.g., activating or inhibiting) expression of one or more pro-inflammatory cytokines, optionally wherein the one or more anti-inflammatory cytokines are selected from IFN-a4, IFN-beta, IL-1β, IL-1alpha, TNF-α, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-33, MCP-1, and MIP-1-beta; modulating (*e.g.*, activating or inhibiting) expression of one or more pro-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; modulating (*e.g.*, activating or inhibiting) expression of one or more anti-inflammatory cytokines, optionally wherein the one or more anti-inflammatory cytokines are selected from IL-4, IL-10, IL-13, IL-35, IL-16, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, or IL-6; modulating (*e.g.*, activating or inhibiting) expression of one or more anti-inflammatory cytokines in one or more cells selected from macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, and microglial cells; modulating (*e.g.*, activating or inhibiting) expression of one or more proteins selected from C1qa, C1qB, C1qC, C1s, C1R, C4, C2, C3, ITGB2, HMOX1, LAT2, CASP1, CSTA, VSIG4, MS4A4A, C3AR1, GPX1, TyroBP, ALOX5AP, ITGAM, SLC7A7, CD4, ITGAX, and PYCARD; activation of extracellular signal-regulated kinase (ERK) phosphorylation; modulating (e.g., activating or inhibiting) tyrosine phosphorylation on one or more cellular proteins, optionally, wherein the one or more cellular proteins comprise ZAP-70 and the tyrosine phosphorylation occurs on Tyr-319 of ZAP-70; modulating (e.g., activating or inhibiting) expression of C-C chemokine receptor 7 (CCR7); activation of microglial cell chemotaxis toward CCL19-expressing and CCL21-expressing cells; modulating (e.g., activating or inhibiting) T cell proliferation induced by one or

more cells selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, M1 microglia, activated M1 microglia, M2 microglia, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, and M2 NK cells; modulating (*e.g.*, activating or inhibiting) osteoclast production, modulating (*e.g.*, activating or inhibiting) rate of osteoclastogenesis, or both; modulating (*e.g.*, activating or inhibiting) survival of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; modulating (e.g., activating or inhibiting) proliferation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; modulating (e.g., activating or inhibiting) migration of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; modulating (e.g., activating or inhibiting) one or more functions of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; modulating (e.g., activating or inhibiting) maturation of one or more cells selected from dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia; activation of one or more types of clearance selected from apoptotic neuron clearance, nerve tissue debris clearance, dysfunctional synapse clearance, non-nerve tissue debris clearance, bacteria clearance, other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, and tumor cell

clearance; optionally wherein the disease-causing protein is selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides and the tumor cell is from a cancer selected from 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, and thyroid cancer; activation of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, dysfunctional synapses, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, disease-causing nucleic acids, or tumor cells; optionally wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and the tumor cells are from a cancer selected from 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, or thyroid cancer; inhibiting binding to Siglec-7 ligand on tumor cells; modulating (e.g., activating or inhibiting) binding to Siglec-7 ligand on cells selected from neutrophils, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, and NK cells; activation of tumor cell killing by one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils,

T cells, T helper cells, or cytotoxic T cells; activating anti-tumor cell proliferation activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; activation of anti-tumor cell metastasis activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; modulating (e.g., activating or inhibiting) of one or more ITAM motif containing receptors, optionally wherein the one or more ITAM motif containing receptors are selected from TREM1, TREM2, Sirp beta, FcgR, DAP10, and DAP12; modulating (e.g., activating or inhibiting) of signaling by one or more pattern recognition receptors (PRRs), optionally wherein the one or more PRRs are selected from receptors that identify pathogen-associated molecular patterns (PAMPs), receptors that identify damage-associated molecular patterns (DAMPs), and any combination thereof; modulating (e.g., activating or inhibiting) of one or more receptors comprising the motif $D/Ex_{0-2}YxxL/IX_{6-8}YxxL/I$ (SEQ ID NO: 537); modulating (e.g., activating or inhibiting) of signaling by one or more Toll-like receptors; modulating (e.g., activating or inhibiting) of the JAK-STAT signaling pathway; modulating (e.g., activating or inhibiting) of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB); phosphorylation of an ITAM motif containing receptor; modulating (e.g., activating or inhibiting) expression of one or more inflammatory receptors, optionally wherein the one or more inflammatory receptors comprise CD86 and the one or more inflammatory receptors are expressed on one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; modulating (e.g., activating or inhibiting) expression of one or more Siglec-7-dependent genes; normalization of disrupted Siglec-7-dependent gene expression; modulating (e.g., activating or inhibiting) expression of one or more ITAM-dependent genes, optionally wherein the one more ITAM-dependent genes are activated by nuclear factor of activated T cells (NFAT) transcription factors; rescuing functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells; and/or reducing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells into tumors; increasing the number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; enhancing tumor-promoting activity of myeloid-derived suppressor cells; increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; increasing tumor infiltration of tumor-promoting

FoxP3+ regulatory T lymphocytes; enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); decreasing activation of tumor-specific T lymphocytes with tumor killing potential; decreasing infiltration of tumor-specific NK cells with tumor killing potential; decreasing the tumor killing potential of NK cells; decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; increasing tumor volume; increasing tumor growth rate; increasing metastasis; increasing rate of tumor recurrence; decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more target proteins selected from PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines; inhibition of PLCã/PKC/calcium mobilization; and/or inhibition of PI3K/Akt, Ras/MAPK signaling in an individual in need thereof, by administering to the individual a therapeutically effective amount of a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, to modulate (e.g., activate or inhibit) one or more of the Siglec-7 activities in the individual.

[0416] As disclosed herein, Siglec-7 agents of the present disclosure that decrease cellular levels of Siglec-7 and/or inhibit interaction between Siglec-7 and one or more Siglec-7 ligands, such as anti-Siglec-7 antibodies of the present disclosure, may be used for preventing, reducing risk, or treating 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and/or Haemophilus influenza. In some embodiments, the agents are selected from antibodies, soluble Siglec-7 receptors, Siglec-7-Fc fusion proteins, Siglec-7 immunoadhesins, soluble Siglec receptors that binds one or more Siglec-7 ligands, Siglec-Fc fusion proteins, Siglec immunoadhesins, antisense molecules, siRNAs, small molecule inhibitors, proteins, and peptides. In some embodiments, the Siglec-7 agents are agonist antibodies. In some embodiments, the Siglec-7 agents are inert antibodies. In some embodiments, the Siglec-7 agents are antagonist antibodies.

[0417] In some embodiments, the present disclosure provides methods of preventing, reducing risk, or treating 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, and 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and/or Haemophilus influenza, by administering to an individual in need thereof a therapeutically effective amount of an agent of the present disclosure that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and

one or more Siglec-7 ligands, or both. In some embodiments, the agent is selected from an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, a soluble Siglec receptor that binds one or more Siglec-7 ligands, a Siglec-Fc fusion protein, a Siglec immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In some embodiments, the agent is an anti-Siglec-7 antibody of the present disclosure.

[0418] In some embodiments, the present disclosure provides methods of preventing, reducing risk, or treating cancer, by administering to an individual in need thereof, a therapeutically effective amount of an agent of the present disclosure that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both. In some embodiments, the agent is selected from an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, a soluble Siglec receptor that binds one or more Siglec-7 ligands, a Siglec-Fc fusion protein, a Siglec immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In certain embodiments, the agent is an anti-Siglec-7 antibody of the present disclosure. In some embodiments, the cancer expresses Siglec-7 or one or more Siglec-7 ligands. In some embodiments, the cancer is 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), and/or multiple myeloma. In some embodiments, the anti-Siglec-7 antibody inhibits one or more Siglec-7 activities selected from: (a) promoting proliferation, maturation, migration, differentiation, and/or functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated suppressor neutrophils, tumor-associated suppressor NK cells, and regulatory T cells; (b) enhancing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated suppressor neutrophils, tumor-associated suppressor NK cells, and regulatory T cells into tumors; (c) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; (d) enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); (e) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; (f) increasing tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes; (g) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (h) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (i) decreasing infiltration of tumor-

specific NK cells with tumor killing potential; (j) decreasing the tumor killing potential of NK cells; (k) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (l) increasing tumor volume; (m) increasing tumor growth rate; (n) increasing metastasis; (o) increasing rate of tumor recurrence; (p) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, such as one or more immune-therapies are immune-therapies that target one or more target proteins selected from PD1/PDL1, CTLA4, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, and any combination thereof, or cancer vaccines; (q) inhibition of PLCγ/PKC/calcium mobilization; and (r) inhibition of PI3K/Akt, Ras/MAPK signaling. In some embodiments, the agent exhibits one or more activities selected from: (a) increasing the number of tumor infiltrating $CD3^+$ T cells; (b) inhibiting Siglec-7 binding to one or more Siglec-7 ligands; (c) decreasing cellular levels of Siglec-7 in peripheral immune cells; (d) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in blood; (e) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in the tumor; (f) reducing PD-L1 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (g) reducing PD-L2 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (h) reducing CD11b levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (i) reducing B7-H3 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (j) reducing CD200R levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (k) reducing CD163 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (l) reducing CD206 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (m) decreasing tumor growth rate of solid tumors; (n) reducing tumor volume; (o) increasing efficacy of one or more PD-1 inhibitors; (p) increasing efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, optionally wherein the one or more checkpoint inhibitor therapies and/or immune-modulating therapies target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, LAG3, or any combination thereof; (q) inhibiting differentiation, survival, and/or one or more functions of non-tumorigenic myeloid-derived suppressor cells (MDSC); (r) inducing cell death of one or more myeloid-derived suppressor cells

(MDSC); and (s) increasing proliferation of T cells in the presence of non-tumorigenic myeloid-derived suppressor cells (MDSC).

[0419] As disclosed herein, agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may also be used for inducing and/or promoting the survival maturation, functionality, migration, or proliferation of one or more immune cells (*e.g.*, innate immune cells or adaptive immune cells). In some embodiments, the present disclosure provides methods of inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof, by administering to the individual a therapeutically effective amount of an agent of the present disclosure that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both. In some embodiments, the agent is selected from an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, a soluble Siglec receptor that binds one or more Siglec-7 ligands, a Siglec-Fc fusion protein, a Siglec immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In some embodiments, the agent is an isolated anti-Siglec-7 antibody of the present disclosure. In some embodiments, the one or more immune cells are selected from dendritic cells, macrophages, neutrophils, NK cells, microglia, T cells, T helper cells, cytotoxic T cells, and any combination thereof.

[0420] In some embodiments, the agent is an agonist anti-Siglec-7 antibody. In some embodiments, the agent is a transient agonist anti-Siglec-7 antibody of the present disclosure that initially acts as an agonist and then acts as a long-term antagonist antibody. In some embodiments, the agent is an inert anti-Siglec-7 antibody. In some embodiments, the agent is an antagonist anti-Siglec-7 antibody. In some embodiments, the anti-Siglec-7 antibody reduces cellular (*e.g.*, cell surface, intracellular, or total) levels of Siglec-7. In some embodiments, the anti-Siglec-7 antibody induces degradation of Siglec-7. In some embodiments, the anti-Siglec-7 antibody induces cleavage of Siglec-7. In some embodiments, the anti-Siglec-7 antibody induces internalization of Siglec-7. In some embodiments, the anti-Siglec-7 antibody induces shedding of Siglec-7. In some embodiments, the anti-Siglec-7 antibody induces downregulation of Siglec-7 expression. In some embodiments, the anti-Siglec-7 antibody inhibits interaction (*e.g.*, binding) between Siglec-7 and one or more Siglec-7 ligands. In some embodiments, the anti-Siglec-7 antibody transiently activates and then induces degradation of Siglec-7. In some embodiments, the anti-Siglec-7 antibody transiently activates and then induces cleavage of Siglec-7. In some embodiments, the anti-Siglec-7 antibody transiently activates and then induces internalization of Siglec-7. In some embodiments, the anti-Siglec-7 antibody transiently activates and then induces shedding of Siglec-7. In some embodiments, the anti-Siglec-7 antibody transiently activates and then induces downregulation of Siglec-7 expression. In

some embodiments, the anti-Siglec-7 antibody transiently activates and then induces decreased expression of Siglec-7. In certain embodiments, the individual has a Siglec-7 variant allele.

[0421] As disclosed herein, agents of the present disclosure that bind or interact with Siglec-7, such as anti-Siglec-7 antibodies of the present disclosure, may further be used for decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, tumor-imbedded immunosuppressor neutrophils, tumor-imbedded immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, and/or chronic myeloid leukemia (CML) cells. In some embodiments, the present disclosure provides methods of decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, tumor-imbedded immunosuppressor neutrophils, tumor-imbedded immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual in need thereof, by administering to the individual a therapeutically effective amount of an agent that binds or interacts with Siglec-7. In some embodiments, the agent is selected from an antibody, an antagonist antibody, an inert antibody, an agonist antibody, a Siglec-7 ligand, a Siglec-7 ligand agonist fragment, a Siglec-7 immunoadhesin, a Siglec-7 ligand mimetic, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a soluble Siglec receptor that binds one or more Siglec-7 ligands, a Siglec-Fc fusion protein that binds one or more Siglec-7 ligands, and a small molecule compound. In some embodiments, the agent is an isolated anti-Siglec-7 antibody or anti-Siglec-7 antibody conjugate of the present disclosure. In some embodiments, the anti-Siglec-7 antibody conjugate comprises an anti-Siglec-7 antibody conjugated to a detectable marker, a toxin, or a therapeutic agent.

[0422] As disclosed herein, agents of the present disclosure that bind or interact with Siglec-7, such as anti-Siglec-7 antibodies of the present disclosure, may be used for decreasing cellular levels of Siglec-7 on one or more cells *in vitro* or *in vivo*, including without limitation, red blood cells, bacterial cells, apoptotic cells, nerve cells, glia cells, microglia, astrocytes, tumor cells, viruses, dendritic cells, Siglec-7 ligands bound to beta amyloid plaques, Siglec-7 ligands bound to Tau tangles, Siglec-7 ligands on disease-causing proteins, Siglec-7 ligands on disease-causing peptides, macrophages, neutrophils, natural killer cells, monocytes, T cells, T helper cells, cytotoxic T cells, B cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, and/or regulatory T cells. In some embodiments, the present disclosure provides methods of decreasing cellular levels of Siglec-7 on one or more cells in

an individual in need thereof, by administering to the individual a therapeutically effective amount of an agent that binds or interacts with Siglec-7. In some embodiments, the agent is selected from an antibody, an antagonist antibody, an inert antibody, an agonist antibody, a Siglec-7 ligand, a Siglec-7 ligand agonist fragment, a Siglec-7 immunoadhesin, a Siglec-7 ligand mimetic, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a soluble Siglec receptor that binds one or more Siglec-7 ligands, a Siglec-Fc fusion protein that binds one or more Siglec-7 ligands, and a small molecule compound. In some embodiments, the agent is an isolated anti-Siglec-7 antibody or anti-Siglec-7 antibody conjugate of the present disclosure. In some embodiments, the anti-Siglec-7 antibody conjugate comprises an anti-Siglec-7 antibody conjugated to a detectable marker, a toxin, or a therapeutic agent. In some embodiments, the one or more cells are selected from red blood cells, bacterial cells, apoptotic cells, nerve cells, glia cells, microglia, astrocytes, tumor cells, viruses, dendritic cells, Siglec-7 ligands bound to beta amyloid plaques, Siglec-7 ligands bound to Tau tangles, Siglec-7 ligands on disease-causing proteins, Siglec-7 ligands on disease-causing peptides, macrophages, neutrophils, natural killer cells, monocytes, T cells, T helper cells, cytotoxic T cells, B cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, regulatory T cells, and any combination thereof.

[0423] Cellular levels of Siglec-7 may refer to, without limitation, cell surface levels of Siglec-7, intracellular levels of Siglec-7, and total levels of Siglec-7. In some embodiments, a decrease in cellular levels of Siglec-7 comprises decrease in cell surface levels of Siglec-7. As used herein, an anti-Siglec-7 antibody decreases cell surface levels of Siglec-7 if it induces a decrease of 21% or more in cell surface levels of Siglec-7 as measured by any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art. In some embodiments, a decrease in cellular levels of Siglec-7 comprises a decrease in intracellular levels of Siglec-7. As used herein, an anti-Siglec-7 antibody decreases intracellular levels of Siglec-7 if it induces a decrease of 21% or more in intracellular levels of Siglec-7 as measured by any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art. In some embodiments, a decrease in cellular levels of Siglec-7 comprises a decrease in total levels of Siglec-7. As used herein, an anti-Siglec-7 antibody decreases total levels of Siglec-7 if it induces a decrease of 21% or more in total levels of Siglec-7 as measured by any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art. In some embodiments, the anti-Siglec-7 antibodies induce Siglec-7 degradation, Siglec-7 cleavage, Siglec-7 internalization, Siglec-7 shedding, and/or downregulation of Siglec-7 expression. In some embodiments, cellular levels of Siglec-7 are measured on primary cells (*e.g.*, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, and macrophages) or on cell lines utilizing an *in vitro* cell assay. In some embodiments, the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 with an EC_{50} that ranges from 500 pM to 18 pM. In some embodiments, the anti-Siglec-7

antibody decreases cellular levels of Siglec-7 with an EC_{50} that ranges from 350 pM to 33 pM. In some embodiments, the EC_{50} is determined at a temperature of approximately 37°C. In some embodiments, the anti-Siglec-7 antibody has a dissociation constant (K_D) for human Siglec-7 that ranges from about 10 nM to 10 pM, or less than 10 pM. In some embodiments that may be combined with any of the preceding embodiments, the anti-Siglec-7 antibody has a dissociation constant (K_D) for human Siglec-7 that ranges from about 9.5 nM to about 17 pM, or less than 17 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments, the anti-Siglec-7 antibody binds to human dendritic cells with an EC_{50} that ranges from 2 nM to 100 pM. In some embodiments, the anti-Siglec-7 antibody binds to human dendritic cells with an EC_{50} that ranges from 1.4 nM to 300 pM. In some embodiments, the EC_{50} for binding to human dendritic cells is determined at a temperature of approximately 4°C.

[0424] In some embodiments the individual has a heterozygous variant of Siglec-7.

[0425] In some embodiments, the methods of the present disclosure may further involve the coadministration of Siglec-7 agents, such as anti-Siglec-7 antibodies or bispecific anti-Siglec-7 antibodies, with antibodies that bind to pattern recognition receptors, antibodies that bind to Toll-like receptors, antibodies that bind to damage-associated molecular pattern (DAMP) receptors, and/or antibodies that bind to cytokine or antibodies to interleukins).

[0426] In some embodiments, the methods of the present disclosure may further include administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or one or more standard or investigational anti-cancer therapies. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the anti-Siglec-7 antibody. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti- B- and T-lymphocyte attenuator (BTLA) antibody, an anti-Killer inhibitory receptor (KIR) antibody, an anti-GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, an anti-TNFa antibody, an anti-CD33 antibody, an anti-Siglec-5 antibody, an anti-Siglec-9 antibody, an anti-Siglec-11 antibody, an antagonistic anti-TREM1 antibody, an antagonistic anti-TREM2 antibody, and any combination thereof. In some embodiments, the one or more standard or investigational anti-cancer therapies are selected from radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib therapy, trastuzumab therapy, etanercept therapy, adoptive cell transfer (ACT) therapy, chimeric antigen receptor T cell transfer (CAR-T) therapy, vaccine therapy, and cytokine therapy.

[0427] In some embodiments, the methods of the present disclosure may further include administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the Siglec-7 agent, such as an anti-Siglec-7 antibody. In some embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is selected from an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof.

[0428] In some embodiments, the methods of the present disclosure may further include administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In some embodiments, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the Siglec-7 agent, such as an anti-Siglec-7 antibody. In some embodiments, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonistic anti-TREM1 antibody, an agonistic anti-TREM2 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, and any combination thereof.

[0429] In some embodiments, the methods of the present disclosure may further include administering to the individual at least one stimulatory cytokine. In some embodiments, the at least one stimulatory cytokine is administered in combination with the Siglec-7 agent, such as an anti-Siglec-7 antibody. In some embodiments, the at least one stimulatory cytokine is selected from IFN-a4, IFN-b, IL-1β, TNF-α, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, IL-33, MCP-1, MIP-1-beta, and any combination thereof.

Dementia

[0430] Dementia is a non-specific syndrome (*i.e.*, a set of signs and symptoms) that presents as a serious loss of global cognitive ability in a previously unimpaired person, beyond what might be expected from normal ageing. Dementia may be static as the result of a unique global brain injury. Alternatively, dementia may be progressive, resulting in long-term decline due to damage or disease in the body. While dementia is much more common in the geriatric population, it can also occur before the age of 65. Cognitive areas affected by dementia include, without limitation, memory, attention span, language, and problem solving. Generally, symptoms must be present for at least six months to before an individual is diagnosed with dementia.

[0431] Exemplary forms of dementia include, without limitation, frontotemporal dementia, Alzheimer's disease, vascular dementia, semantic dementia, and dementia with Lewy bodies.

[0432] In some embodiments, administering a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, can prevent, reduce the risk, and/or treat dementia. In some embodiments, administering a Siglec-7 agent, such as an anti-Siglec-7 antibody, may modulate one or more Siglec-7 activities in an individual having dementia.

Frontotemporal dementia

[0433] Frontotemporal dementia (FTD) is a condition resulting from the progressive deterioration of the frontal lobe of the brain. Over time, the degeneration may advance to the temporal lobe. Second only to Alzheimer's disease (AD) in prevalence, FTD accounts for 20% of pre-senile dementia cases. The clinical features of FTD include memory deficits, behavioral abnormalities, personality changes, and language impairments (Cruts, M. & Van Broeckhoven, C., Trends Genet. 24:186-194 (2008); Neary, D., et al., Neurology 51:1546-1554 (1998); Ratnavalli, E., Brayne, C., Dawson, K. & Hodges, J. R., Neurology 58:1615-1621 (2002)).

[0434] A substantial portion of FTD cases are inherited in an autosomal dominant fashion, but even in one family, symptoms can span a spectrum from FTD with behavioral disturbances, to Primary Progressive Aphasia, to Cortico-Basal Ganglionic Degeneration. FTD, like most neurodegenerative diseases, can be characterized by the pathological presence of specific protein aggregates in the diseased brain. Historically, the first descriptions of FTD recognized the presence of intraneuronal accumulations of hyperphosphorylated Tau protein in neurofibrillary tangles or Pick bodies. A causal role for the microtubule associated protein Tau was supported by the identification of mutations in the gene encoding the Tau protein in several families (Hutton, M., et al., Nature 393:702-705 (1998). However, the majority of FTD brains show no accumulation of hyperphosphorylated Tau but do exhibit immunoreactivity to ubiquitin (Ub) and TAR DNA binding protein (TDP43) (Neumann, M., et al., Arch. Neurol. 64:1388-1394 (2007)). A majority of those FTD cases with Ub inclusions (FTD-U) were shown to carry mutations in the Progranulin gene.

[0435] In some embodiments, administering a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, can prevent, reduce the risk, and/or treat FTD. In some embodiments, administering a Siglec-7 agent, such as an anti-Siglec-7 antibody, may modulate one or more Siglec-7 activities in an individual having FTD.

Alzheimer's disease

[0436] Alzheimer's disease (AD), is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. Most often, AD is diagnosed in people over 65 years of age. However, the less-prevalent early-onset Alzheimer's can occur much earlier.

[0437] Common symptoms of Alzheimer's disease include, behavioral symptoms, such as difficulty in remembering recent events; cognitive symptoms, confusion, irritability and aggression,

mood swings, trouble with language, and long-term memory loss. As the disease progresses bodily functions are lost, ultimately leading to death. Alzheimer's disease develops for an unknown and variable amount of time before becoming fully apparent, and it can progress undiagnosed for years.

[0438] In some embodiments, administering a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, can prevent, reduce the risk, and/or treat Alzheimer's disease. In some embodiments, administering a Siglec-7 agent, such as an anti-Siglec-7 antibody, may modulate one or more Siglec-7 activities in an individual having Alzheimer's disease.

Parkinson's disease

[0439] Parkinson's disease, which may be referred to as idiopathic or primary parkinsonism, hypokinetic rigid syndrome (HRS), or paralysis agitans, is a neurodegenerative brain disorder that affects motor system control. The progressive death of dopamine-producing cells in the brain leads to the major symptoms of Parkinson's. Most often, Parkinson's disease is diagnosed in people over 50 years of age. Parkinson's disease is idiopathic (having no known cause) in most people. However, genetic factors also play a role in the disease.

[0440] Symptoms of Parkinson's disease include, without limitation, tremors of the hands, arms, legs, jaw, and face, muscle rigidity in the limbs and trunk, slowness of movement (bradykinesia), postural instability, difficulty walking, neuropsychiatric problems, changes in speech or behavior, depression, anxiety, pain, psychosis, dementia, hallucinations, and sleep problems.

[0441] In some embodiments, administering a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, can prevent, reduce the risk, and/or treat Parkinson's disease. In some embodiments, administering a Siglec-7 agent, such as an anti-Siglec-7 antibody, may modulate one or more Siglec-7 activities in an individual having Parkinson's disease.

Amyotrophic lateral sclerosis (ALS)

[0442] As used herein, amyotrophic lateral sclerosis (ALS) or, motor neuron disease or, Lou Gehrig's disease are used interchangeably and refer to a debilitating disease with varied etiology characterized by rapidly progressive weakness, muscle atrophy and fasciculations, muscle spasticity, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), and difficulty breathing (dyspnea).

[0443] It has been shown that Progranulin plays a role in ALS (Schymick, JC et al., (2007) J Neurol Neurosurg Psychiatry.;78:754-6) and protects again the damage caused by ALS causing proteins such as TDP-43 (Laird, AS et al., (2010). PLoS ONE 5: e13368). It was also demonstrated that pro-NGF induces p75 mediated death of oligodendrocytes and corticospinal neurons following spinal cord injury (Beatty et al., Neuron (2002),36, pp. 375-386; Giehl et al, Proc. Natl. Acad. Sci USA (2004), 101, pp 6226-30).

[0444] In some embodiments, administering a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, can prevent, reduce the risk, and/or treat ALS. In some embodiments, administering a Siglec-7 agent, such as an anti-Siglec-7 antibody, may modulate one or more Siglec-7 activities in an individual having amyotrophic lateral sclerosis.

Huntington's disease

[0445] Huntington's disease (HD) is an inherited neurodegenerative disease caused by an autosomal dominant mutation in the Huntingtin gene (HTT). Expansion of a cytokine-adenine-guanine (CAG) triplet repeat within the Huntingtin gene results in production of a mutant form of the Huntingtin protein (Htt) encoded by the gene. This mutant Huntingtin protein (mHtt) is toxic and contributes to neuronal death. Symptoms of Huntington's disease most commonly appear between the ages of 35 and 44, although they can appear at any age.

[0446] Symptoms of Huntington's disease, include, without limitation, motor control problems, jerky, random movements (chorea), abnormal eye movements, impaired balance, seizures, difficulty chewing, difficulty swallowing, cognitive problems, altered speech, memory deficits, thinking difficulties, insomnia, fatigue, dementia, changes in personality, depression, anxiety, and compulsive behavior.

[0447] In some embodiments, administering a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, can prevent, reduce the risk, and/or treat Huntington's disease (HD). In some embodiments, administering a Siglec-7 agent, such as an anti-Siglec-7 antibody, may modulate one or more Siglec-7 activities in an individual having Huntington's disease.

Taupathy disease

[0448] Taupathy diseases, or Tauopathies, are a class of neurodegenerative disease caused by aggregation of the microtubule-associated protein tau within the brain. Alzheimer's disease (AD) is the most well-known taupathy disease, and involves an accumulation of tau protein within neurons in the form of insoluble neurofibrillary tangles (NFTs). Other taupathy diseases and disorders include progressive supranuclear palsy, dementia pugilistica (chromic traumatic encephalopathy), frontotemporal dementia and parkinsonism linked to chromosome 17, Lytico-Bodig disease (Parkinson-dementia complex of Guam), Tangle-predominant dementia, Ganglioglioma and gangliocytoma, Meningioangiomatosis, Subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, Pick's disease, corticobasal degeneration, Argyrophilic grain disease (AGD), Huntington's disease, and frontotemporal lobar degeneration.

[0449] In some embodiments, administering a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, can prevent, reduce the risk, and/or treat taupathy

disease. In some embodiments, administering a Siglec-7 agent, such as an anti-Siglec-7 antibody, may modulate one or more Siglec-7 activities in an individual having a taupathy disease.

Multiple sclerosis

[0450] Multiple sclerosis (MS) can also be referred to as disseminated sclerosis or encephalomyelitis disseminata. MS is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms. MS affects the ability of nerve cells in the brain and spinal cord to communicate with each other effectively. Nerve cells communicate by sending electrical signals called action potentials down long fibers called axons, which are contained within an insulating substance called myelin. In MS, the body's own immune system attacks and damages the myelin. When myelin is lost, the axons can no longer effectively conduct signals. MS onset usually occurs in young adults, and is more common in women.

[0451] Symptoms of MS include, without limitation, changes in sensation, such as loss of sensitivity or tingling; pricking or numbness, such as hypoesthesia and paresthesia; muscle weakness; clonus; muscle spasms; difficulty in moving; difficulties with coordination and balance, such as ataxia; problems in speech, such as dysarthria, or in swallowing, such as dysphagia; visual problems, such as nystagmus, optic neuritis including phosphenes, and diplopia; fatigue; acute or chronic pain; and bladder and bowel difficulties; cognitive impairment of varying degrees; emotional symptoms of depression or unstable mood; Uhthoff's phenomenon, which is an exacerbation of extant symptoms due to an exposure to higher than usual ambient temperatures; and Lhermitte's sign, which is an electrical sensation that runs down the back when bending the neck.

[0452] In some embodiments, administering a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure, can prevent, reduce the risk, and/or treat multiple sclerosis. In some embodiments, administering a Siglec-7 agent, such as an anti-Siglec-7 antibody, may modulate one or more Siglec-7 activities in an individual having multiple sclerosis.

Cancer

[0453] Further aspects of the present disclosure provide methods for preventing, reducing risk, or treating cancer, by administering to an individual in need thereof a therapeutically effective amount of a Siglec-7 agent of the present disclosure, such as an isolated anti-Siglec-7 antibody of the present disclosure. Any of the isolated antibodies of the present disclosure may be used in these methods. In some embodiments, the isolated antibody is an agonist antibody of the present disclosure. In other embodiments, the isolated antibody is an antagonist antibody of the present disclosure. In other embodiments, the isolated antibody is an inert antibody of the present disclosure. In other embodiments, the isolated antibody is an antibody conjugate of the present disclosure.

[0454] As disclosed herein, the tumor microenvironment is known to contain a heterogeneous immune infiltrate, which includes T lymphocytes, macrophages, neutrophils, NK cells, and cells of myeloid/granulocytic lineage. The presence and activity of T-regulatory cells, tumor-imbedded immunosuppressor myeloid cells, and/or M2-macrophages, M2-neutrophils, and/or M2-NK cells in tumors is associated with poor prognosis. In contrast, the presence and activity of cytotoxic T cells is beneficial for cancer therapy. Therapies that directly or indirectly enhance the activity of cytotoxic T cells and reduce the number and activity of the various immunosuppressor cells, are expected to provide significant therapeutic benefit. A seminal preclinical study has shown synergies between drugs that target immunosuppressor cells (*e.g.,* CSF1/CSF1R blocking antibodies) and immune checkpoint blocking antibodies that activate cytotoxic T cells, indicating that manipulating both cell types shows efficacy in tumor models where individual therapies are poorly effective (Zhu Y; Cancer Res. 2014 Sep 15; 74(18):5057-69). Therefore, in some embodiments, blocking Siglec-7, which is expressed on myeloid cells, subset of T cells, and tumor-associated immune cells, may stimulate beneficial anti-tumor immune response, resulting in a therapeutic anti-tumor immune response.

[0455] In some embodiments, the methods for preventing, reducing risk, or treating an individual having cancer further include administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule. Examples of antibodies that specifically bind to an inhibitory checkpoint molecule include, without limitation, an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti-BTLA antibody, an anti- GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, and any combination thereof. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with a Siglec-7 agent of the present disclosure, such as an antagonist anti-Siglec-7 antibody of the present disclosure.

[0456] In some embodiments, a cancer to be prevented or treated by the methods of the present disclosure includes, without limitation, squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer and gastrointestinal stromal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, cancer of the urinary tract, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanomas, nodular melanomas, multiple myeloma and B cell lymphoma; chronic lymphocytic leukemia (CLL); acute lymphoblastic

leukemia (ALL); hairy cell leukemia; chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), Meigs' syndrome, brain, as well as head and neck cancer, and associated metastases. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is selected from 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), and multiple myeloma. In some embodiments, the cancer is selected from non-small cell lung cancer, glioblastoma, neuroblastoma, renal cell carcinoma, bladder cancer, ovarian cancer, melanoma, breast carcinoma, gastric cancer, and hepatocellular carcinoma. In some embodiments, the cancer is triple-negative breast carcinoma. In some embodiments, the cancer may be an early stage cancer or a late stage cancer. In some embodiments, the cancer may be a primary tumor. In some embodiments, the cancer may be a metastatic tumor at a second site derived from any of the above types of cancer.

[0457] In some embodiments, Siglec-7 agents of the present disclosure, such as anti-Siglec-7 antibodies of the present disclosure, may be used for preventing, reducing risk, or treating cancer, including, without limitation, bladder cancer breast cancer, colon and 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, and thyroid cancer.

[0458] In some embodiments, the present disclosure provides methods of preventing, reducing risk, or treating an individual having cancer, by administering to the individual a therapeutically effective amount of a Siglec-7 agent of the present disclosure, such as an anti-Siglec-7 antibody of the present disclosure.

[0459] In some embodiments, the method further includes administering to the individual at least one antibody that specifically binds to an inhibitory immune checkpoint molecule, and/or another standard or investigational anti-cancer therapy. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti- B- and T-lymphocyte attenuator (BTLA) antibody, an anti- Killer inhibitory receptor (KIR) antibody, an anti-GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-

phosphatidylserine antibody, an anti-CD27 antibody, and any combination thereof. In some embodiments, the standard or investigational anti-cancer therapy is one or more therapies selected from radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib (Gleevec®), trastuzumab (Herceptin®), adoptive cell transfer (ACT), chimeric antigen receptor T cell transfer (CAR-T), vaccine therapy, and cytokine therapy.

[0460] In some embodiments, the method further includes administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure. In some embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is selected from an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof.

[0461] In some embodiments, the method further includes administering to the individual at least one agonistic antibody that specifically binds to a stimulatory immune checkpoint protein. In some embodiments, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure. In some embodiments, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, and any combination thereof.

[0462] In some embodiments, the method further includes administering to the individual at least one stimulatory cytokine. In some embodiments, the at least one stimulatory cytokine is administered in combination with the Siglec-7 agent, such as an anti-Siglec-7 antibody of the present disclosure. In some embodiments, the at least one stimulatory cytokine is selected from IFN-a4, IFN-b, IL-1β, TNF-α, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, IL-33, MCP-1, MIP-1-beta, and any combination thereof.

Methods of Assessment

[0463] The present disclosure also provides methods of assessing responsiveness of an individual to an agent that binds or interacts with Siglec-7. In some embodiments, the method comprises: measuring the expression levels of one or more markers on non-tumorigenic myeloid cells in a blood sample obtained from the individual prior to administering to the individual an agent that binds or interacts with Siglec-7; administering to the individual a therapeutically effective amount of the agent; and measuring the expression levels of the one or more markers on non-tumorigenic myeloid cells in a blood sample obtained from the individual after administration of the agent. In some embodiments, a reduction in the levels of the one or more markers on non-tumorigenic myeloid cells

after administration of the agent that binds or interacts with Siglec-7 indicates the individual is responsive to the agent. In some embodiments, the one or more markers are one or more of CD45 and CD14. In some embodiments, the method further comprises administering one or more additional therapeutically effective amounts of the agent. In some embodiments, the agent is any Siglec-7 agent disclosed herein. In some embodiments, the agent is selected from the group consisting of an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and peptide. In some embodiments, the agent is an isolated anti-Siglec-7 antibody or anti-Siglec-7 antibody-conjugate. In some embodiments, the anti-Siglec-7 antibody is any of the anti-Siglec-7 antibodies disclosed herein.

[0464] The present disclosure also provides methods of assessing responsiveness of an individual to an agent that binds or interacts with Siglec-7. In some embodiments, the method comprises: measuring the expression levels of CD45 and CD14 on non-tumorigenic myeloid cells in a blood sample obtained from the individual prior to administering to the individual an agent that binds or interacts with Siglec-7; administering to the individual a therapeutically effective amount of the agent; and measuring the expression levels of CD45 and CD14 on non-tumorigenic myeloid cells in a blood sample obtained from the individual after administration of the agent. In some embodiments, a reduction in the levels of CD45 and CD14 on non-tumorigenic myeloid cells after administration of the agent that binds or interacts with Siglec-7 indicates the individual is responsive to the agent. In some embodiments, the method further comprises administering one or more additional therapeutically effective amounts of the agent. In some embodiments, the agent is any Siglec-7 agent disclosed herein. In some embodiments, the agent is selected from the group consisting of an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and peptide. In some embodiments, the agent is an isolated anti-Siglec-7 antibody or anti-Siglec-7 antibody-conjugate. In some embodiments, the anti-Siglec-7 antibody is any of the anti-Siglec-7 antibodies disclosed herein.

[0465] In some embodiments, a reduction of at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, 105%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 155%, at least 160%, at least 165%, at least 170%, at least 175%, at least 180%, at least 185%, at least 190%, at least 195%, at least 200%, at least 250%, or at least 500% in the levels of CD45 and CD14 on non-tumorigenic myeloid cells after administration of the agent that binds or interacts with Siglec-7 indicates the individual is responsive to the agent. In some embodiments, a reduction of at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at

least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold in the levels of CD45 and CD14 on non-tumorigenic myeloid cells after administration of the agent that binds or interacts with Siglec-7 indicates the individual is responsive to the agent.

Kits/Articles of Manufacture

[0466] The present disclosure also provides kits and/or articles of manufacture containing a Siglec-7 agent of the present disclosure (*e.g.,* an anti-Siglec-7 antibody described herein), or a functional fragment thereof. Kits and/or articles of manufacture of the present disclosure may include one or more containers comprising a purified antibody of the present disclosure. In some embodiments, the kits and/or articles of manufacture further include instructions for use in accordance with the methods of this disclosure. In some embodiments, these instructions comprise a description of administration of the Siglec-7 agent of the present disclosure (*e.g.,* an anti-Siglec-7 antibody described herein) to prevent, reduce risk, or treat an individual having a disease, disorder, or injury selected from 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, and cancer including 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 thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express Siglec-7, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection,

Campylobacter jejuni infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza, according to any methods of this disclosure.

[0467] In some embodiments, the instructions comprise a description of how to detect a Siglec-7 protein, for example in an individual, in a tissue sample, or in a cell. The kit and/or article of manufacture may further comprise a description of selecting an individual suitable for treatment based on identifying whether that individual has the disease and the stage of the disease.

[0468] In some embodiments, the kits and/or articles of manufacture may further include another antibody of the present disclosure (*e.g.,* at least one antibody that specifically binds to an inhibitory checkpoint molecule, at least one antibody that specifically binds to an inhibitory cytokine, and/or at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein) and/or at least one stimulatory cytokine. In some embodiments, the kits and/or articles of manufacture may further include instructions for using the antibody and/or stimulatory cytokine in combination with a Siglec-7 agent of the present disclosure (*e.g.,* an anti-Siglec-7 antibody described herein), instructions for using a Siglec-7 agent of the present disclosure (*e.g.,* an anti-Siglec-7 antibody described herein) in combination with an antibody and/or stimulatory cytokine, or instructions for using a Siglec-7 agent of the present disclosure (*e.g.,* an anti-Siglec-7 antibody described herein) and an antibody and/or stimulatory cytokine, according to any methods of this disclosure.

[0469] The instructions generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. Instructions supplied in the kits and/or articles of manufacture of the present disclosure are typically written instructions on a label or package insert (*e.g.*, a paper sheet included in the kit), but machine-readable instructions (*e.g.*, instructions carried on a magnetic or optical storage disk) are also acceptable.

[0470] The label or package insert indicates that the composition is used for treating, *e.g.*, a disease of the present disclosure. Instructions may be provided for practicing any of the methods described herein.

[0471] The kits and/or articles of manufacture of this disclosure are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging (*e.g.*, sealed Mylar or plastic bags), and the like. Also contemplated are packages for use in combination with a specific device, such as an inhaler, nasal administration device (*e.g.*, an atomizer) or an infusion device such as a minipump. A kit and/or article of manufacture may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container may also have a sterile access port (*e.g.*, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a Siglec-7 agent of the present disclosure

(*e.g.,* an anti-Siglec-7 antibody described herein). The container may further comprise a second pharmaceutically active agent.

[0472] Kits and/or articles of manufacture may optionally provide additional components such as buffers and interpretive information. Normally, the kit comprises a container and a label or package insert(s) on or associated with the container.

Diagnostic uses

[0473] The Siglec-7 agents of the present disclosure, such as the isolated antibodies of the present disclosure (*e.g.,* an anti-Siglec-7 antibody described herein) also have diagnostic utility. This disclosure therefore provides for methods of using the antibodies of this disclosure, or functional fragments thereof, for diagnostic purposes, such as the detection of a Siglec-7 protein in an individual or in tissue samples derived from an individual.

[0474] In some embodiments, the individual is a human. In some embodiments, the individual is a human patient suffering from, or at risk for developing a disease, disorder, or injury of the present disclosure. In some embodiments, the diagnostic methods involve detecting a Siglec-7 protein in a biological sample, such as a biopsy specimen, a tissue, or a cell. A Siglec-7 agent of the present disclosure (*e.g.,* an anti-Siglec-7 antibody described herein) is contacted with the biological sample and antigen-bound antibody is detected. For example, a biopsy specimen may be stained with an anti-Siglec-7 antibody described herein in order to detect and/or quantify disease-associated cells. The detection method may involve quantification of the antigen-bound antibody. Antibody detection in biological samples may occur with any method known in the art, including immunofluorescence microscopy, immunocytochemistry, immunohistochemistry, ELISA, FACS analysis, immunoprecipitation, or micro-positron emission tomography. In certain embodiments, the antibody is radiolabeled, for example with ^{18}F and subsequently detected utilizing micro-positron emission tomography analysis. Antibody-binding may also be quantified in a patient by non-invasive techniques such as positron emission tomography (PET), X-ray computed tomography, single-photon emission computed tomography (SPECT), computed tomography (CT), and computed axial tomography (CAT).

[0475] In other embodiments, an isolated antibody of the present disclosure (*e.g.,* an anti-Siglec-7 antibody described herein) may be used to detect and/or quantify, for example, microglia in a brain specimen taken from a preclinical disease model (*e.g.,* a non-human disease model). As such, an isolated antibody of the present disclosure (*e.g.,* an anti-Siglec-7 antibody described herein) may be useful in evaluating therapeutic response after treatment in a model for a nervous system disease or injury such as frontotemporal dementia, Alzheimer's disease, vascular dementia, seizures, retinal dystrophy, atherosclerotic vascular diseases, Nasu-Hakola disease, or multiple sclerosis, as compared to a control.

[0476] The present disclosure will be more fully understood by reference to the following Examples. They should not, however, be construed as limiting the scope of the present disclosure. All citations throughout the disclosure are hereby expressly incorporated by reference.

EXAMPLES

Example 1: Production, identification, and characterization of anti-Siglec-7 antibodies

Introduction

[0477] The amino acid sequence of human Siglec-7 is set forth below in SEQ ID NO: 1. Human Siglec-7 contains a signal sequence located at amino acid residues 1-18 SEQ ID NO: 1, an extracellular immunoglobulin-like variable-type (IgV) domain located at amino acid residues 39-122 of SEQ ID NO: 1, two Ig-like C2-type domains located at amino acid residues 150-233 and 240-336 of SEQ ID NO: 1, a transmembrane domain located at amino acid residues 354-376 of SEQ ID NO: 1, an ITIM motif 1 located at amino acid residues 435-440 of SEQ ID NO: 1, and an ITIM motif 2 located at amino acid residues 459-463 of SEQ ID NO: 1. An alignment of human Siglec-7 with Siglec-7 homologs is shown in **FIG. 1A**, and a three-dimensional representation of human Siglec-7 is shown in **FIG. 1B**.

[0478] Siglec-7 amino acid sequence (SEQ ID NO: 1):

```
10         20         30         40         50
MLLLLLLPLL WGRERVEGQK SNRKDYSLTM QSSVTVQEGM CVHVRCSFSY
        60         70         80         90        100
PVDSQTDSDP VHGYWFRAGN DISWKAPVAT NNPAWAVQEE TRDRFHLLGD
       110        120        130        140        150
PQTKNCTLSI RDARMSDAGR YFFRMEKGNI KWNYKYDQLS VNVTALTHRP
       160        170        180        190        200
NILIPGTLES GCFQNLTCSV PWACEQGTPP MISWMGTSVS PLHPSTTRSS
       210        220        230        240        250
VLTLIPQPQH HGTSLTCQVT LPGAGVTTNR TIQLNVSYPP QNLTVTVFQG
       260        270        280        290        300
EGTASTALGN SSSLSVLEGQ SLRLVCAVDS NPPARLSWTW RSLTLYPSQP
       310        320        330        340        350
SNPLVLELQV HLGDEGEFTC RAQNSLGSQH VSLNLSLQQE YTGKMRPVSG
       360        370        380        390        400
VLLGAVGGAG ATALVFLSFC VIFIVVRSCR KKSARPAADV GDIGMKDANT
       410        420        430        440        450
IRGSASQGNL TESWADDNPR HHGLAAHSSG EEREIQYAPL SFHKGEPQDL
       460
SGQEATNNEY SEIKIPK
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[0479] The purpose of the following Example was to produce Siglec-7-binding antibodies (*e.g.*, antagonistic antibodies, Siglec-7 specific antibodies) that enhance the beneficial effects of dendritic cells, monocytes, macrophages, neutrophils, NK cells, T cells, and/or microglia. Antibodies that bind the extracellular domain of Siglec-7, particularly the IgV domain (amino acid residues 39-122 of SEQ ID NO: 1) are generated using mouse hybridoma technology, phage display technology, and yeast display technology. Antibodies are identified and then screened for their ability to compete with Siglec-7 ligands on binding to Siglec-7, to induce Siglec-7 downregulation, to induce Siglec-7

desensitization, to induce Siglec-7 degradation, to induce Siglec-7 targeting to the lysosome, to induce Siglec-7 cleavage, to modulate Siglec-7 signaling and/or one or more functions in cells and in animals *in vivo*, as described in the following Examples. Exemplary ligands bound by Siglec-7 are depicted in **FIG. 2** and **FIG. 3**.

[0480] For example, anti-Siglec-7 antibodies are selected that target the IgV domain (amino acid residues 39-122) of Siglec-7. The IgV domain binds to sialic acid targets, and this binding can be blocked with the antibody. Thus, amino acid residues 39-122 correspond to a Siglec-7 peptide target for antibodies that will block binding of Siglec-7 to one or more endogenous targets (*e.g.*, ligands).

[0481] As described herein, 13 anti-Siglec-7 antibodies were identified and characterized.

Results

Anti-Siglec-7 antibody production

Immunization procedure

[0482] Rapid prime method: Four 50-day old female BALB/c mice were immunized using the following procedure. A series of subcutaneous aqueous injections containing human Siglec-7 antigen but no adjuvant were given over a period of 19 days. Mice were housed in a ventilated rack system from Lab Products. All four mice were euthanized on Day 19 and lymphocytes were harvested for hybridoma cell line generation.

[0483] Standard method: Four 50-day old female BALB/c or NZB/W mice were immunized using the following procedure. Mice were housed in a ventilated rack system from Lab Products. Mice were injected intraperitoneally every 3 weeks with a human Siglec-7 antigen mixed in CpG-ODN adjuvant at 25 μg protein antigen per mouse (total volume 125 μL per mouse). Test bleeds were done by saphenous vein lancing seven days after the second boost. The test bleed (immune sera) was tested by indirect ELISA assay to determine the best two responding mice for the fusion. The mice may require a 3rd and 4th boost and another test bleed 7 days after boost to assess titre before fusion. When the antibody titre is high enough the best two responding mice are given a final intravenous boost via lateral tail vein. Four days after the IV boost the mice were euthanized for fusion. The spleens were harvested and lymphocytes isolated from the spleen were used in the fusion process to produce hybridomas.

Hybridoma development

[0484] Lymphocytes were isolated and fused with murine SP2/0 myeloma cells in the presence of poly-ethylene glycol (PEG 1500) as per standard Roche Protocol. Fused cells were cultured using a single-step cloning method (HAT selection). This method uses a semi-solid methylcellulose-based HAT selective medium to combine the hybridoma selection and cloning into one step. Single cell-derived hybridomas grow to form monoclonal colonies on the semi-solid media. Ten days after the

fusion event, 948 of the resulting hybridoma clones were transferred to 96-well tissue culture plates and grown in HT containing medium until mid-log growth was reached (5 days).

Hybridoma screening

[0485] Tissue culture supernatants from the 948 hybridomas were tested by indirect ELISA on screening antigen (Primary Screening) and probed for both IgG and IgM antibodies using a Goat anti-IgG/IgM(H&L)-HRP secondary and developed with TMB substrate. Clones >0.2 OD in this assay were taken to the next round of testing. Positive cultures were retested on screening antigen to confirm secretion and on an irrelevant antigen (Human Transferrin) to eliminate non-specific or "sticky" mAbs and rule out false positives. All clones of interest were isotyped by antibody trapping ELISA to determine if they are IgG or IgM isotype.

Hybridoma cell culture

[0486] The hybridoma cell lines of interest were maintained in culture in 24-well culture plates for 32 days post transfer to 96-well plates. This is referred to as the stability period and tests whether clones remain stable and secreting. During this stability period time temporary frozen cell line back up is made of all the clones of interest for -80°C storage (viable 6 months). Hybridomas were periodically tested during this time period for secretion and specificity.

Subcloning

[0487] The top hybridoma cell lines (clones) were subcloned to ensure monoclonality. Subcloning was performed by plating parental clones out again using the single-step cloning system. Between 24 and 90 subclones were transferred to 96-well culture plates. Subclones were screened by indirect ELISA and antibody trapping ELISA. The top subclones for each parent were taken for expansion in culture. Any parental clones that were <50% clonal had a second round of subcloning performed.

[0488] The antibodies were then screened for Siglec-7 binding. Antibodies that were positive for binding to human Siglec-7 were tested for ability to block ligand binding and ability to reduce surface levels of Siglec-7 in multiple cell types. Thirteen Silgec-7 antibodies were identified. The isotype and bin category are listed in **Table 1**.

Table 1: Anti-Siglec-7 antibodies

Ab ID	Ab Isotype	Bin
1A12	mIgG2a	2
1E8	mIgG1	2
2G1	mIgG2b	1
2G4	mIgG1/2a*	2
3E11	mIgG1	1
4A1	mIgG2a	2
4D7	mIgG1	5
4E3	mIgG1	1
7A3	mIgG1	4
7E11	mIgG2a	3

7F12	mIgG2a	2
10B5	mIgG2a	5
10G8	mIgG1	4

Antibody heavy chain and light chain variable domain sequences

[0489] Using standard techniques, the amino acid sequences encoding the light chain variable and the heavy chain variable domains of the generated antibodies were determined. The EU or Kabat light chain CDR sequences of the antibodies are set forth in **Table 2A**. The EU or Kabat heavy chain CDR sequences of the antibodies are set forth in **Table 2B**. The EU or Kabat light chain framework (FR) sequences of the antibodies are set forth in **Table 3A**. The EU or Kabat heavy chain framework (FR) sequences of the antibodies are set forth in **Table 3B**.

Table 2A: EU or Kabat light chain CDR sequences of anti-Siglec-7 antibodies

Ab ID	CDR L1	CDR L2	CDR L3
1A12	RSSQSLVHSTGNTY LH (SEQ ID NO: 7)	KVSNRFS (SEQ ID NO: 20)	SQNTHVPYT (SEQ ID NO: 33)
1E8	RASQSISDYLH (SEQ ID NO: 8)	YASQSIS (SEQ ID NO: 21)	QKGLNFPLT (SEQ ID NO: 34)
2G1	SANSSFIYMY (SEQ ID NO: 9)	DTSNLAS (SEQ ID NO: 22)	QQWSSSPLT (SEQ ID NO: 35)
2G4	KASDHINNWLA (SEQ ID NO: 10)	GATSLET (SEQ ID NO: 23)	HQYWNTPYT (SEQ ID NO: 36)
3E11	RSSQSLVHSTGNTY LH (SEQ ID NO: 11)	KVSNRFC (SEQ ID NO: 24)	SQNTHVPYT (SEQ ID NO: 37)
4A1	RSSQSLVHSTGNIY LH (SEQ ID NO: 12)	KVSNRFZ (SEQ ID NO: 25)	SQNTHVPYT (SEQ ID NO: 38)
4D7	KASQKVGTNVA (SEQ ID NO: 13)	SASTRHR (SEQ ID NO: 26)	HQGNSVQYT (SEQ ID NO: 39)
4E3	SANSSFTYMY (SEQ ID NO: 14)	DTSNLAS (SEQ ID NO: 27)	QQWSSSPLT (SEQ ID NO: 40)
7A3	RASQSISEYLH (SEQ ID NO: 15)	FASQSIC (SEQ ID NO: 28)	QNGHNFPYT (SEQ ID NO: 41)
7E11	LASQTIGTWLA (SEQ ID NO: 16)	AATSLAD (SEQ ID NO: 29)	QQLYSTPYT (SEQ ID NO: 42)
7F12	RSSQSLVHSTGNTY LH (SEQ ID NO: 17)	KVSNRFS (SEQ ID NO: 30)	SQNTHVPYT (SEQ ID NO: 43)
10B5	RASQDISZYLN (SEQ ID NO: 18)	LSSRLHS (SEQ ID NO: 31)	QQGHTGAWT (SEQ ID NO: 44)
10B5L1	RASQDINTYLN (SEQ ID NO: 476)	YTSRLHS (SEQ ID NO: 477)	QQGNTLPWT(SEQ ID NO: 478)
10G8	RASQSIREYLH (SEQ ID NO: 19)	FASQSIC (SEQ ID NO: 32)	QKAHNFPYT (SEQ ID NO: 45)

Table 2B: EU or Kabat heavy chain CDR sequences of anti-Siglec-7 antibodies

Ab ID	CDR H1	CDR H2	CDR H3
1A12	SEVFPITYMN (SEQ ID NO: 46)	IGDILPSIGRTMYG (SEQ ID NO: 59)	ARSEGYLLAY (SEQ ID NO: 72)
1E8	FNIKGSLLH (SEQ ID NO: 47)	IGWIDPEDGETRFD (SEQ ID NO: 60)	ARTEYSNPAWFAY (SEQ ID NO: 73)
2G1	FTFSNYDMS	VATISSGGDYTYYP	ARHGYGNYDWYFDV (SEQ ID NO: 74)

Ab ID	CDR H1	CDR H2	CDR H3
	(SEQ ID NO: 48)	(SEQ ID NO: 61)	
2G4	SEVFPITYMN (SEQ ID NO: 49)	IGDILPSIGRTMYG (SEQ ID NO: 62)	ARSEGYLLAY (SEQ ID NO: 75)
3E11	YIFTDYGIT (SEQ ID NO: 50)	IGEISPRSGETYFN (SEQ ID NO: 63)	AREGNPFTY (SEQ ID NO: 76)
4A1	SEVFPITYMN (SEQ ID NO: 51)	IGDILPSIGRTMYG (SEQ ID NO: 64)	ARSEGYLLAY (SEQ ID NO: 77)
4D7	YTFTNYWIN (SEQ ID NO: 52)	IGNIYSGSSRTNYN (SEQ ID NO: 65)	AREGLRAMDY (SEQ ID NO: 78)
4E3	FIFSNYDMS (SEQ ID NO: 53)	VATISSGGGYTYYP (SEQ ID NO: 66)	TRHGYGNYDWYFDV (SEQ ID NO: 79)
4E3H1	FIFSNYDMS (SEQ ID NO: 53)	VSTISSGGGYTYYA (SEQ ID NO: 480)	ARHGYGNYDWYFDV (SEQ ID NO: 74)
4E3H2	FIFSNYDMS (SEQ ID NO: 53)	VATISSGGGYTYYA (SEQ ID NO: 481)	TRHGYGNYDWYFDV (SEQ ID NO: 79)
7A3	FTFSNYAMS (SEQ ID NO: 54)	VASISSGGSYNYYP (SEQ ID NO: 67)	ASQSYGSSYWYFDV (SEQ ID NO: 80)
7E11	FSLSNYGVH (SEQ ID NO: 55)	LGVIWAGGITNYN (SEQ ID NO: 68)	AKQGGTSFSY (SEQ ID NO: 81)
7F12	SEVFPITYMN (SEQ ID NO: 56)	IGDILPSIGRTMYG (SEQ ID NO: 69)	ARSEGYLLAY (SEQ ID NO: 82)
10B5	YAFTNCWMN (SEQ ID NO: 57)	IGRIFPGNGHTNYS (SEQ ID NO: 70)	ARDYSDYYFDY (SEQ ID NO: 83)
10B5H1	GYAFTNCWMN (SEQ ID NO: 479)	RIFPGNGHTN (SEQ ID NO: 482)	DYSDYYFDY (SEQ ID NO: 483)
10G8	FTFSTYAMF (SEQ ID NO: 58)	VASISSGGRYTYYP (SEQ ID NO: 71)	VRHSYGSSYWYLDV (SEQ ID NO: 84)

Table 3A: EU or Kabat light chain Framework sequences of anti-Siglec-7 antibodies

Ab ID	VL FR1	VL FR2	VL FR3	VL FR4
1A12	DVZMTQTPLSLPVS LGDQASISC (SEQ ID NO: 85)	WYLQKPGQSPKLLI Y (SEQ ID NO: 98)	GVPDRFSGSGAGTDFTL KISRVEAEDLGVYFC (SEQ ID NO: 111)	FGGGTKLEIK (SEQ ID NO: 124)
1E8	DIQMTQFPATLSVT PGDRVSLSC (SEQ ID NO: 86)	WYQHKSHESPRLLI K (SEQ ID NO: 99)	GIPSRFSGSGSGWDFTLS INSVEPEDVGIYYC (SEQ ID NO: 112)	FGGGTKLEMK (SEQ ID NO: 125)
2G1	VLTQSPAIMSASPG EKVTMTC (SEQ ID NO: 87)	WYQQKPGSSPRLLI F (SEQ ID NO: 100)	GVPIRFSGSGSGTSYSLTI SRMEAEDTATYYC (SEQ ID NO: 113)	FGGGTKLELK (SEQ ID NO: 126)
2G4	DIQMTQSLSYLSVS LGGRVTITC (SEQ ID NO: 88)	WYQQKPGNAPRLL IS (SEQ ID NO: 101)	GFPSRFSGSGSGKDYTLS ITSLQTEDVATYYC (SEQ ID NO: 114)	FGGGTRLEIK (SEQ ID NO: 127)
3E11	DVZMTQTPLSLPVS LGDQASISC (SEQ ID NO: 89)	WYLQKPGQSPKLLI Y (SEQ ID NO: 102)	GVPDRFSGSGAGTDFTL KISRVEAEDLGVYFC (SEQ ID NO: 115)	FGGGTKLEIK (SEQ ID NO: 128)
4A1	DVVMTQTPLSLPVS LGDQASISC (SEQ ID NO: 90)	WYLQKPGQSPKLLI Y (SEQ ID NO: 103)	GVPDRFSGSGSGTDFTL KISRVEAEDLGVYFC (SEQ ID NO: 116)	FGGGTKLEIK (SEQ ID NO: 129)
4D7	NZMTQFQKFMSTS VGDRVSLTC (SEQ ID NO: 91)	GFQQKPGHSPKAGI Y (SEQ ID NO: 104)	GVQDRFTARGLGSDFILP ITTZQLEDLAEYZC (SEQ ID NO: 117)	FGGGTKLEIK (SEQ ID NO: 130)
4E3	GZQNVLTQSPAILS ASPGEKVTMTC (SEQ ID NO: 92)	WYQQKPGSSPRLLI F (SEQ ID NO: 105)	GVPIRFSGSGSGTSYSLTI SRMEAEDTATYYC (SEQ ID NO: 118)	FGAGTKLELK (SEQ ID NO: 131)

Ab ID	VL FR1	VL FR2	VL FR3	VL FR4
7A3	DIQMTQZPATLSVT PGDRVSLSC (SEQ ID NO: 93)	WYHQKSHESPRLLI K (SEQ ID NO: 106)	GIPSRFSGSGSGSDFTLTI NSVEPEDVGVYYC (SEQ ID NO: 119)	FGGGTKLEIK (SEQ ID NO: 132)
7E11	DIQMTQSPASQSAS LGESVTITC (SEQ ID NO: 94)	WYQQKPGKSPQLLI Y (SEQ ID NO: 107)	GVPSRFSGSGSGTKFSFK ISSLQAEDFVSYYC (SEQ ID NO: 120)	FGGGTKLEIK (SEQ ID NO: 133)
7F12	DVLMTQTPLSLPVS LGDQASISC (SEQ ID NO: 95)	WYLQKPGQSPKLLI Y (SEQ ID NO: 108)	GVPDRFSGSGAGTDFTL KISRVEAEDLGVYFC (SEQ ID NO: 121)	FGGGTKLEIK (SEQ ID NO: 134)
10B5	ZMTQFTSSMSGSEG DRVTISH (SEQ ID NO: 96)	WYEQKADGTANLII Y (SEQ ID NO: 109)	GZPSRLSGZGWVTDYFL PIHTSEQEDRGSYFC (SEQ ID NO: 122)	FGGGTKLEIK (SEQ ID NO: 135)
10G8	DIQMTQFPATLSGT PGDRVZLSR (SEQ ID NO: 97)	WYQQKSHESPRLZI K (SEQ ID NO: 110)	GIPSRFSGSGSGSDFTLSI NTVEPEDVGVYYC (SEQ ID NO: 123)	FGGGTKLEIK (SEQ ID NO: 136)

Table 3B: EU or Kabat heavy chain Framework sequences of anti-Siglec-7 antibodies

Ab ID	VH FR1	VH FR2	VH FR3	VH FR4
1A12	QVQLQQSGSELRSP GSSVKLSCKDFD (SEQ ID NO: 137)	WVRQKPGHGFE W (SEQ ID NO: 150)	EKFEDKATLDADTVSN TAYLELNSLTSEDSAIY YC (SEQ ID NO: 163)	WGQGTLVTVSA (SEQ ID NO: 176)
1E8	QVQLQQSGAELVR PGASVKLSCSASG (SEQ ID NO: 138)	WIKQRPLQGLEW (SEQ ID NO: 151)	PKFQDKAFLTADTSSTT AYLQLSSLTSEDTAIYY C (SEQ ID NO: 164)	WGQGTLVTVSA (SEQ ID NO: 177)
2G1	EVKLVESGGTLVKP GGSLKISCAASG (SEQ ID NO: 139)	WVRQNPEKRLE W (SEQ ID NO: 152)	DIFKGRFTISRDDAKNA LYLQMSSLRSEDTALY YC (SEQ ID NO: 165)	WGAGATVTVSS (SEQ ID NO: 178)
2G4	QVQLQQSGSELRSP GSSVKLSCKDFD (SEQ ID NO: 140)	WVRQKPGHGFE W (SEQ ID NO: 153)	EKFEDKATLDADTVSN TAYLELNSLTSEDSAIY YC (SEQ ID NO: 166)	WGQGTLVTVSA (SEQ ID NO: 179)
3E11	QVQLQQSGAELAR PGASVKLSCKASG (SEQ ID NO: 141)	WVKQRTGQGLE W (SEQ ID NO: 154)	ENYRVKATLTADKSSS TAYMQLFSLTSEDSAV YFC (SEQ ID NO: 167)	WGHGTLVTVSA (SEQ ID NO: 180)
4A1	QVQLQQSGSELRSP GSSVKLSCKDFD (SEQ ID NO: 142)	WVRQKPGHGFE W (SEQ ID NO: 155)	EKFEDKATLDADTVSN TAYLELNSLTSEDSAIY YC (SEQ ID NO: 168)	WGQGTLVTVSA (SEQ ID NO: 181)
4D7	QVQLQQSGAELVK PGASVKLSCKTSG (SEQ ID NO: 143)	WVKQRPGQGLE W (SEQ ID NO: 156)	EKFKSKATLTVDTSSST AYMQLSSLTSDDSAVY YC (SEQ ID NO: 169)	WGQGTSVTVSS (SEQ ID NO: 182)
4E3	EVKLADSGGALVN PGGSLKISCAVSG (SEQ ID NO: 144)	WVRQNPEKRLE W (SEQ ID NO: 157)	DSVKGRFTISRDNAKN ALYLQMSSLRSEDTAL YYC (SEQ ID NO: 170)	WGAGATVTVSS (SEQ ID NO: 183)
7A3	LVZSGGALVKPGGS LKLSCAASG (SEQ ID NO: 145)	WVRQTPEKRLE W (SEQ ID NO: 158)	DSVKGRFTISRDNARNT LYLQMSSLRSKDTAMY YC (SEQ ID NO: 171)	WGAGTTVTVSS (SEQ ID NO: 184)
7E11	QVQLKQSGPVLVA PSQSLSITCTVSG (SEQ ID NO: 146)	WVRQFPGKGLE W (SEQ ID NO: 159)	SVLMSRLSISKDNSKSQ VFLKMNSLQTDDTAMY YC (SEQ ID NO: 172)	WGQGTLVTVSA (SEQ ID NO: 185)
7F12	QVQLQQSGSELRSP GSSVKLSCKDFD (SEQ ID NO: 147)	WVRQKPGHGFE W (SEQ ID NO: 160)	EKFEDKATLDADTVSN TAYLELNSLTSEDSAIY YC (SEQ ID NO: 173)	WGQGTLVTVSA (SEQ ID NO: 186)
10B5	QVQLQQSGPELVKP GASVKISCKASG (SEQ ID NO: 148)	WVRQRPGKGLD W (SEQ ID NO: 161)	GKFKDKATLTEDKSSST AYMQLSSLTSEDSAVY FC (SEQ ID NO: 174)	WGQGTTLTVSS (SEQ ID NO: 187)

Ab ID	VH FR1	VH FR2	VH FR3	VH FR4
10G8	EVKLVEFGGALVK PGGSLKLSCAALG (SEQ ID NO: 149)	RVRQTPEKREEG (SEQ ID NO: 162)	DSAKDRHPIFRDNARNT LYLQMSSLRSKDTAMY YC (SEQ ID NO: 175)	WGAGTTVTVSS (SEQ ID NO: 188)

Characterization of Siglec-7 antibody binding

[0490] Initial characterization of Siglec-7 antibodies involved determining their ability to bind Siglec-7 expressed on human primary monocytes, human primary macrophages, human primary dendritic cells, human primary neutrophils, and human primary natural killer (NK) cells. Cells were harvested, plated at 10^6/ml in a 96 well plate, and incubated in 100ul PBS containing 2% FBS, 2mM EDTA and 10 µg/ml Mab and Fc blocking reagent for 1 hour in ice. Cells were washed twice and incubated in 100ul PBS containing 2% FBS, 2mM EDTA and 5ug/ml PE-conjugated secondary antibody for 30 minutes on ice. Cells were washed twice in cold PBS and analyze by flow cytometry on a BD FACS Canto. Data analysis and calculation of MFI values was performed with FlowJo (TreeStar) software version 10.0.7.

[0491] FACS staining analysis indicates that Siglec-7 is expressed on primary myeloid and lymphoid cells, including human primary monocytes, macrophages, dendritic cells, neutrophils, and NK cells (**FIG. 4**).

[0492] **Table 4A** demonstrates antibody binding to human primary cells expressing Siglec-7. Percent positive binding and mean fluorescent intensity (MFI) values for cell types bound by Siglec-7 antibodies are listed in **Table 4A**. Binding is compared to an isotype control. The antibodies bind to human primary monocytes, human primary dendritic cells, and human primary macrophages. In **Table 4A**, "Buffer" refers to cells that were treated only with the PBS buffer described supra; "Secondary Ab" refers to cells that were treated only with the PE-conjugated secondary antibody; "mIgG1," "mIgG2a," and "mIgG2b" refer to isotype control antibodies; and "RDS7" refers to commercially available anti-Siglec-7 antibody Mab1138 (R&D Systems; Cat. No. MAB 1138). **FIG. 5A** demonstrates antibody binding to human primary dendritic cells.

Table 4A: Siglec-7 antibody binding to human primary cells

Antibody	Monocytes		Dendritic Cells		Macrophages	
	% Positive	MFI	% Positive	MFI	% Positive	MFI
1A12	99.3	505	99.7	6092	99.4	15788
1E8	99.3	428	99.7	2936	99.5	5446
2G1	99.4	577	99.7	10245	99.5	25666
2G4	99.3	512	99.7	5752	99.5	15472
3E11	98.7	380	99.6	2522	99.6	4043
4A1	99.4	486	99.7	5450	99.3	14578
4D7	90.5	262	26.1	250	99.4	4260
4E3	98.6	362	99.7	2648	99.6	4150
7A3	97.9	407	99.7	956	99.7	2841
7E11	93.3	278	98.4	845	99.8	2381
7F12	99.3	472	99.7	4995	99.3	12325

Antibody	Monocytes		Dendritic Cells		Macrophages	
	% Positive	MFI	% Positive	MFI	% Positive	MFI
10B5	99.2	417	99.6	3226	99.7	6028
10G8	99.1	523	99.5	897	99.7	3277
Controls						
Buffer	0.2	63	0.2	39	0.0	122
Secondary Ab	9.1	107	2.4	91	23.9	398
mIgG1	10.6	115	2.8	83	21.7	368
mIgG2a	14.0	141	4.5	134	35.8	648
mIgG2b	13.9	128	5.0	130	79.5	2059
RDS7	19.9	175	73.9	1452	98.6	4219

[0493] Two Siglec-7 antibodies, 4E3 and 10B5, were titrated 2-fold for a 12-point curve with a concentration range of 6.67-0.00325 nM to assess binding and calculate half-maximal concentration (EC_{50}) for binding to primary human dendritic cells (**FIG. 5B**). Antibodies were serially diluted and incubated with cells in PBS with 1% BSA, 1mM EDTA for 1 hour on ice (4°C). Cells were pelleted and resuspended with goat anti-mouse secondary antibody conjugated with APC (BD Biosciences) at a 1:200 dilution in buffer. Secondary detection antibody was incubated for 30 minutes on ice (4°C), then cells were washed 3 times in buffer before analyzing on a BD FACS Canto for APC MFI. Data were analyzed with FlowJo Software (TreeStar).

[0494] *In vitro* studies demonstrated that anti-Siglec-7 antibodies 4E3 and 10B5 bound to human dendritic cells from two different donors (**Table 4B**). Anti-Siglec-7 antibody 4E3 bound to human dendritic cells from donor number 359 with an EC_{50} of 0.3nM (with a 95% confidence interval range of 0.1701 to 0.4313 nM), while anti-Siglec-7 antibody 10B5 bound dendritic cells from this donor with an EC_{50} of 1.158 nM (with a 95% confidence interval range of 0.7821 to 1.533 nM). Anti-Siglec-7 antibodies 4E3 and 10B5 bound to the dendritic cells from a second donor with an EC_{50} of 0.3364 (95% confidence interval of 0.1052 to 0.5677) and 1.427 (with95% confidence interval 0.9209 to 1.933), respectively.

Table 4B: EC_{50} determination of two Siglec-7 antibodies for binding to primary human dendritic cells

Donor #	Antibody: 4E3		Antibody: 10B5	
	EC_{50} value (nM)	95% CI (nM)	EC_{50} value (nM)	95% CI (nM)
358	0.3364	0.1052 to 0.5677	1.427	0.9209 to 1.933
359	0.3007	0.1701 to 0.4313	1.158	0.7821 to 1.533

[0495] After determining the EC_{50} for the two anti-Siglec-7 antibodies on human dendritic cells, the binding affinity of 13 anti-Siglec-7 antibodies for Siglec-7 was determined by measuring their K_Ds by surface plasmon resonance (SPR) assays. SPR data was collected at a rate of 10 Hz at 25° C on a BiaCore T200 instrument. Data analysis was performed using BiaCore T200 Evaluation Software, version 2.0. HBS-EP+ (100 mM HEPES, 1.5 M NaCl, 30 mM EDTA, 0.5% v/v Surfactant P20, pH 7.4) was used as running buffer and for preparing reagents.

[0496] Mouse-derived antibodies (25 nM) against Siglec-7 were captured (60 s contact time, 30 µL/min flow rate, 0 s stabilization time) on a CM5 sensor chip (GE Healthcare) immobilized with anti-mouse IgG. Histidine-tagged human Siglec-7 (NovoProtein) was then flowed over the captured anti-Siglec-7 surface (120 s contact time, 30 µL/min flow rate, 300 s dissociation time). Concentration of antigen ranged from 5 nM to 100 nM, depending on information obtained from an initial screen. Duplicate single-concentration trials were performed and bracketed by a blank (0 nM antigen) sample. The chip surface was regenerated in between cycles using 10 mM glycine-HCl, pH 1.7 (60 s contact time, 30 µL/min flow rate, 60 s stabilization time). The resulting SPR signal was obtained as the difference in response from measurements performed on a blank flow cell.

[0497] Single-concentration kinetic analysis (Canziani, *et al.* (2004) Analytical Biochemistry 325:301-307) was performed using a 1:1 interaction model to extract association and dissociation rate constants (k_a and k_d, respectively) for each antibody. Affinity constants (K_D) were calculated from the ratio k_d/k_a. For one antibody (clone 1E8), we validated the single-concentration analysis with a multiple-concentration approach (five concentrations of antigen used, plus one blank).

[0498] The results are listed in **Table 5**. **FIG. 6A** shows SPR sensograms depicting antibody affinity.

Table 5: Siglec-7 antibody affinities

Antibody	mAb nM	Siglec-7 nM	K_D
1A12	25	100	0.6 nM
1E8	25	5	17 pM
2G1	25	20	0.1 nM
2G4	25	50	0.4 nM
3E11	25	25	1.0 nM
4A1	25	35	0.3 nM
4D7	25	100	2.9 nM
4E3	25	25	0.3 nM
7A3	25	20	1.0 nM

Antibody	mAb nM	Siglec-7 nM	K_D
7E11	25	100	9.5 nM
7F12	25	35	0.4 nM
10B5	25	100	3.0 nM
10G8	25	10	0.6 nM

In silico antibody humanization

[0499] Antibody humanization is used to transform antibodies generated in a different species to best resemble a human antibody through sequence and structural relationships in order to prevent immunogenicity in human administration. Antibodies from different species share characteristic sequence and structural features that allow the grafting of the specificity-determining regions (SDRs) of the non-human antibody onto a human antibody framework. This results in retention of the specificity of the non-human antibody. The humanization process involves identification of the non-human antibody sequence and features, including the framework regions and SDRs. The following criteria are used to humanize an antibody: 1) percent similarity in framework regions between non-human and known human antibodies, 2) length similarity in SDRs between non-human and known human antibodies, 3) genes used to generate the framework regions of the human antibody, and 4) previous use of human antibody frameworks in humanizations and as therapeutics. Similarity in framework regions and SDR lengths are important because differences can generate structural differences in the antibody that can alter the specificity of the antibody. Specific genes used to generate the framework of human antibodies are known to be beneficial or detrimental to the stability or specificity of the antibody and are selectively used or avoided, accordingly. Lastly, previously successful humanization frameworks, including those used in human therapeutics, which are well tolerated with good half-lives, are likely candidates for future successful humanizations.

[0500] As shown in **Tables 6A and 6B**, 10 humanized light chain and 10 humanized heavy variable region sequences were identified for each of the antibodies 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8. In **Tables 6A and 6B**, bolded letters indicate CDR sequences.

Table 6A: Humanized light chain variable regions

Antibody variant	Humanized sequences
Antibody 1A12	**Antibody 1A12**
1A12V2-30	DVVMTQSPLSLPVTLGQPASISC**RSSQSLVHSTGNTYLH**WFQQRPGQSPRRLIY**KV SNRFS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 189)
1A12V2-28	DIVMTQSPLSLPVTPGEPASISC**RSSQSLVHSTGNTYLH**WYLQKPGQSPQLLIY**KV SNRFS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 190)
1A12V4-1	DIVMTQSPDSLAVSLGERATINC**RSSQSLVHSTGNTYLH**WYQQKPGQPPKLLIY**K VSNRFS**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**SQNTHVPYT**FGQGTKVEI K (SEQ ID NO: 191)
1A12V3-11	EIVLTQSPATLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQQKPGQAPRLLIY**KV**

Antibody variant	Humanized sequences
	SNRFSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 192)
1A12V1-33	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**K VSNRFS**GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 193)
1A12V3-15	EIVMTQSPATLSVSPGERATLSC**RSSQSLVHSTGNTYLH**WYQQKPGQAPRLLIY**K VSNRFS**GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 194)
1A12V1-5	DIQMTQSPSTLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**K VSNRFS**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 195)
1A12V1-9	DIQLTQSPSFLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**KV SNRFS**GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 196)
1A12V1-39	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**K VSNRFS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 197)
1A12V3-20	EIVLTQSPGTLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQQKPGQAPRLLIY**KV SNRFS**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 198)
Antibody 1E8	**Antibody 1E8**
1E8V1-39	DIQMTQSPSSLSASVGDRVTITC**RASQSISDYLH**WYQQKPGKAPKLLIY**YASQSIS**G VPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 199)
1E8V1-5	DIQMTQSPSTLSASVGDRVTITC**RASQSISDYLH**WYQQKPGKAPKLLIY**YASQSIS**G VPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 200)
1E8V1-9	DIQLTQSPSFLSASVGDRVTITC**RASQSISDYLH**WYQQKPGKAPKLLIY**YASQSIS**G VPSRFSGSGSGTEFTLTISSLQPEDFATYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 201)
1E8V3-11	EIVLTQSPATLSLSPGERATLSC**RASQSISDYLH**WYQQKPGQAPRLLIY**YASQSIS**GI PARFSGSGSGTDFTLTISSLEPEDFAVYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 202)
1E8V1-33	DIQMTQSPSSLSASVGDRVTITC**RASQSISDYLH**WYQQKPGKAPKLLIY**YASQSIS**G VPSRFSGSGSGTDFTFTISSLQPEDIATYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 203)
1E8V3-15	EIVMTQSPATLSVSPGERATLSC**RASQSISDYLH**WYQQKPGQAPRLLIY**YASQSIS**G IPARFSGSGSGTEFTLTISSLQSEDFAVYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 204)
1E8V3-20	EIVLTQSPGTLSLSPGERATLSC**RASQSISDYLH**WYQQKPGQAPRLLIY**YASQSIS**GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 205)
1E8V2-28	DIVMTQSPLSLPVTPGEPASISC**RASQSISDYLH**WYLQKPGQSPQLLIY**YASQSIS**GV PDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 206)
1E8V2-30	DVVMTQSPLSLPVTLGQPASISC**RASQSISDYLH**WFQQRPGQSPRRLIY**YASQSIS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 207)
1E8V4-1	DIVMTQSPDSLAVSLGERATINC**RASQSISDYLH**WYQQKPGQPPKLLIY**YASQSIS**G VPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO: 208)
Antibody 2G1	**Antibody 2G1**
2G1V3-11	EIVLTQSPATLSLSPGERATLSC**SANSSFIYMY**WYQQKPGQAPRLLIY**DTSNLAS**GI PARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 209)
2G1V1-39	DIQMTQSPSSLSASVGDRVTITC**SANSSFIYMY**WYQQKPGKAPKLLIY**DTSNLAS**G

Antibody variant	Humanized sequences
	VPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 210)
2G1V1-5	DIQMTQSPSTLSASVGDRVTITC**SANSSFIYMY**WYQQKPGKAPKLLIY**DTSNLAS**G VPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 211)
2G1V1-33	DIQMTQSPSSLSASVGDRVTITC**SANSSFIYMY**WYQQKPGKAPKLLIY**DTSNLAS**G VPSRFSGSGSGTDFTFTISSLQPEDIATYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 212)
2G1V1-9	DIQLTQSPSFLSASVGDRVTITC**SANSSFIYMY**WYQQKPGKAPKLLIY**DTSNLAS**G VPSRFSGSGSGTEFTLTISSLQPEDFATYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 213)
2G1V3-15	EIVMTQSPATLSVSPGERATLSC**SANSSFIYMY**WYQQKPGQAPRLLIY**DTSNLAS**GI PARFSGSGSGTEFTLTISSLQSEDFAVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 214)
2G1V3-20	EIVLTQSPGTLSLSPGERATLSC**SANSSFIYMY**WYQQKPGQAPRLLIY**DTSNLAS**GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 215)
2G1V2-28	DIVMTQSPLSLPVTPGEPASISC**SANSSFIYMY**WYLQKPGQSPQLLIY**DTSNLAS**GV PDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 216)
2G1V2-30	DVVMTQSPLSLPVTLGQPASISC**SANSSFIYMY**WFQQRPGQSPRRLIY**DTSNLAS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 217)
2G1V4-1	DIVMTQSPDSLAVSLGERATINC**SANSSFIYMY**WYQQKPGQPPKLLIY**DTSNLAS**G VPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 218)
Antibody 2G4	**Antibody 2G4**
2G4V1-5	DIQMTQSPSTLSASVGDRVTITC**KASDHINNWLA**WYQQKPGKAPKLLIY**GATSLE T**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO: 219)
2G4V1-33	DIQMTQSPSSLSASVGDRVTITC**KASDHINNWLA**WYQQKPGKAPKLLIY**GATSLE T**GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO: 220)
2G4V1-39	DIQMTQSPSSLSASVGDRVTITC**KASDHINNWLA**WYQQKPGKAPKLLIY**GATSLE T**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO: 221)
2G4V1-9	DIQLTQSPSFLSASVGDRVTITC**KASDHINNWLA**WYQQKPGKAPKLLIY**GATSLET** GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO: 222)
2G4V3-15	EIVMTQSPATLSVSPGERATLSC**KASDHINNWLA**WYQQKPGQAPRLLIY**GATSLE T**GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO: 223)
2G4V3-11	EIVLTQSPATLSLSPGERATLSC**KASDHINNWLA**WYQQKPGQAPRLLIY**GATSLET** GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO: 224)
2G4V3-20	EIVLTQSPGTLSLSPGERATLSC**KASDHINNWLA**WYQQKPGQAPRLLIY**GATSLET** GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO: 225)
2G4V4-1	DIVMTQSPDSLAVSLGERATINC**KASDHINNWLA**WYQQKPGQPPKLLIY**GATSLE T**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO: 226)
2G4V2-30	DVVMTQSPLSLPVTLGQPASISC**KASDHINNWLA**WFQQRPGQSPRRLIY**GATSLET** GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO: 227)
2G4V2-28	DIVMTQSPLSLPVTPGEPASISC**KASDHINNWLA**WYLQKPGQSPQLLIY**GATSLET** GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**HQYWNTPYT**FGQGTKVEIK (SEQ

Antibody variant	Humanized sequences
	ID NO: 228)
Antibody 3E11	**Antibody 3E11**
3E11V2-30	DVVMTQSPLSLPVTLGQPASISC**RSSQSLVHSTGNTYLH**WFQQRPGQSPRRLIY**KV SNRFC**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQNTHVPYT**FGQGTKVEI K (SEQ ID NO: 229)
3E11V2-28	DIVMTQSPLSLPVTPGEPASISC**RSSQSLVHSTGNTYLH**WYLQKPGQSPQLLIY**KV SNRFC**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQNTHVPYT**FGQGTKVEI K (SEQ ID NO: 230)
3E11V4-1	DIVMTQSPDSLAVSLGERATINC**RSSQSLVHSTGNTYLH**WYQQKPGQPPKLLIY**K VSNRFC**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**SQNTHVPYT**FGQGTKVEI K (SEQ ID NO: 231)
3E11V3-11	EIVLTQSPATLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQQKPGQAPRLLIY**KV SNRFC**GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 232)
3E11V1-33	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**K VSNRFC**GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 233)
3E11V3-15	EIVMTQSPATLSVSPGERATLSC**RSSQSLVHSTGNTYLH**WYQQKPGQAPRLLIY**K VSNRFC**GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 234)
3E11V3-20	EIVLTQSPGTLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQQKPGQAPRLLIY**KV SNRFC**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 235)
3E11V1-9	DIQLTQSPSFLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**KV SNRFC**GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 236)
3E11V1-39	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**K VSNRFC**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 237)
3E11V1-5	DIQMTQSPSTLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**K VSNRFC**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 238)
Antibody 4A1	**Antibody 4A1**
4A1V2-30	DVVMTQSPLSLPVTLGQPASISC**RSSQSLVHSTGNIYLH**WFQQRPGQSPRRLIY**KV SNRFZ**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 239)
4A1V2-28	DIVMTQSPLSLPVTPGEPASISC**RSSQSLVHSTGNIYLH**WYLQKPGQSPQLLIY**KVS NRFZ**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 240)
4A1V4-1	DIVMTQSPDSLAVSLGERATINC**RSSQSLVHSTGNIYLH**WYQQKPGQPPKLLIY**KV SNRFZ**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 241)
4A1V3-11	EIVLTQSPATLSLSPGERATLSC**RSSQSLVHSTGNIYLH**WYQQKPGQAPRLLIY**KVS NRFZ**GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 242)
4A1V1-33	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNIYLH**WYQQKPGKAPKLLIY**KV SNRFZ**GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 243)
4A1V3-15	EIVMTQSPATLSVSPGERATLSC**RSSQSLVHSTGNIYLH**WYQQKPGQAPRLLIY**KV SNRFZ**GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 244)
4A1V3-20	EIVLTQSPGTLSLSPGERATLSC**RSSQSLVHSTGNIYLH**WYQQKPGQAPRLLIY**KVS NRFZ**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 245)
4A1V1-5	DIQMTQSPSTLSASVGDRVTITC**RSSQSLVHSTGNIYLH**WYQQKPGKAPKLLIY**KV SNRFZ**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**SQNTHVPYT**FGQGTKVEIK

Antibody variant	Humanized sequences
	(SEQ ID NO: 246)
4A1V1-9	DIQLTQSPSFLSASVGDRVTITC**RSSQSLVHSTGNIYLH**WYQQKPGKAPKLLIY**KV SNRFZ**GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 247)
4A1V1-39	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNIYLH**WYQQKPGKAPKLLIY**KV SNRFZ**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 248)
Antibody 4D7	**Antibody 4D7**
4D7V3-15	EIVMTQSPATLSVSPGERATLSC**KASQKVGTNVA**WYQQKPGQAPRLLIY**SASTRH R**GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 249)
4D7V3-11	EIVLTQSPATLSLSPGERATLSC**KASQKVGTNVA**WYQQKPGQAPRLLIY**SASTRHR** GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 250)
4D7V1-9	DIQLTQSPSFLSASVGDRVTITC**KASQKVGTNVA**WYQQKPGKAPKLLIY**SASTRH R**GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 251)
4D7V1-5	DIQMTQSPSTLSASVGDRVTITC**KASQKVGTNVA**WYQQKPGKAPKLLIY**SASTRH R**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 252)
4D7V1-39	DIQMTQSPSSLSASVGDRVTITC**KASQKVGTNVA**WYQQKPGKAPKLLIY**SASTRH R**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 253)
4D7V1-33	DIQMTQSPSSLSASVGDRVTITC**KASQKVGTNVA**WYQQKPGKAPKLLIY**SASTRH R**GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 254)
4D7V3-20	EIVLTQSPGTLSLSPGERATLSC**KASQKVGTNVA**WYQQKPGQAPRLLIY**SASTRHR** GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 255)
4D7V4-1	DIVMTQSPDSLAVSLGERATINC**KASQKVGTNVA**WYQQKPGQPPKLLIY**SASTRH R**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 256)
4D7V2-28	DIVMTQSPLSLPVTPGEPASISC**KASQKVGTNVA**WYLQKPGQSPQLLIY**SASTRHR** GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 257)
4D7V2-30	DVVMTQSPLSLPVTLGQPASISC**KASQKVGTNVA**WFQQRPGQSPRRLIY**SASTRH R**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO: 258)
Antibody 4E3	**Antibody 4E3**
4E3V3-11	EIVLTQSPATLSLSPGERATLSC**SANSSFTYMY**WYQQKPGQAPRLLIY**DTSNLAS**GI PARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 259)
4E3V1-33	DIQMTQSPSSLSASVGDRVTITC**SANSSFTYMY**WYQQKPGKAPKLLIY**DTSNLAS**G VPSRFSGSGSGTDFTFTISSLQPEDIATYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 260)
4E3V1-39	DIQMTQSPSSLSASVGDRVTITC**SANSSFTYMY**WYQQKPGKAPKLLIY**DTSNLAS**G VPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 261)
4E3V1-5	DIQMTQSPSTLSASVGDRVTITC**SANSSFTYMY**WYQQKPGKAPKLLIY**DTSNLAS**G VPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 262)
4E3V1-9	DIQLTQSPSFLSASVGDRVTITC**SANSSFTYMY**WYQQKPGKAPKLLIY**DTSNLAS**G VPSRFSGSGSGTEFTLTISSLQPEDFATYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 263)
4E3V3-15	EIVMTQSPATLSVSPGERATLSC**SANSSFTYMY**WYQQKPGQAPRLLIY**DTSNLAS**G IPARFSGSGSGTEFTLTISSLQSEDFAVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID

Antibody variant	Humanized sequences
	NO: 264)
4E3V3-20	EIVLTQSPGTLSLSPGERATLSC**SANSSFTYMY**WYQQKPGQAPRLLIY**DTSNLAS**GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 265)
4E3V2-28	DIVMTQSPLSLPVTPGEPASISC**SANSSFTYMY**WYLQKPGQSPQLLIY**DTSNLAS**GV PDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 266)
4E3V2-30	DVVMTQSPLSLPVTLGQPASISC**SANSSFTYMY**WFQQRPGQSPRRLIY**DTSNLAS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 267)
4E3V4-1	DIVMTQSPDSLAVSLGERATINC**SANSSFTYMY**WYQQKPGQPPKLLIY**DTSNLAS**G VPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO: 268)
4E3L1	EIVLTQSPATLSLSPGERATLSC**SANSSFTYMY**WYQQKPGQAPRLLIY**DTSNLAS**GI PARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQWSSSPLT**FGQGTKLEIK (SEQ ID NO: 484)
4E3L2	EIVLTQSPATLSLSPGERVTMSC**SANSSFTYMY**WYQQKPGQAPRLLIY**DTSNLAS**G VPARFSGSGSGTDYTLTISSMEPEDFAVYYC**QQWSSSPLT**FGQGTKLEIK (SEQ ID NO: 485)
4E3L3	EIVLTQSPATLSLSPGERVTMSC**SANSSFTYMY**WYQQKPGQAPRLLIF**DTSNLAS**G VPARFSGSGSGTDYTLTISSMEPEDFAVYYC**QQWSSSPLT**FGQGTKLELK (SEQ ID NO: 486)
Antibody 7A3	**Antibody 7A3**
7A3V1-39	DIQMTQSPSSLSASVGDRVTITC**RASQSISEYLH**WYQQKPGKAPKLLIY**FASQSIC**G VPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 269)
7A3V1-9	DIQLTQSPSFLSASVGDRVTITC**RASQSISEYLH**WYQQKPGKAPKLLIY**FASQSIC**G VPSRFSGSGSGTEFTLTISSLQPEDFATYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 270)
7A3V1-5	DIQMTQSPSTLSASVGDRVTITC**RASQSISEYLH**WYQQKPGKAPKLLIY**FASQSIC**G VPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 271)
7A3V3-11	EIVLTQSPATLSLSPGERATLSC**RASQSISEYLH**WYQQKPGQAPRLLIY**FASQSIC**GI PARFSGSGSGTDFTLTISSLEPEDFAVYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 272)
7A3V1-33	DIQMTQSPSSLSASVGDRVTITC**RASQSISEYLH**WYQQKPGKAPKLLIY**FASQSIC**G VPSRFSGSGSGTDFTFTISSLQPEDIATYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 273)
7A3V3-15	EIVMTQSPATLSVSPGERATLSC**RASQSISEYLH**WYQQKPGQAPRLLIY**FASQSIC**G IPARFSGSGSGTEFTLTISSLQSEDFAVYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 274)
7A3V3-20	EIVLTQSPGTLSLSPGERATLSC**RASQSISEYLH**WYQQKPGQAPRLLIY**FASQSIC**GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 275)
7A3V2-30	DVVMTQSPLSLPVTLGQPASISC**RASQSISEYLH**WFQQRPGQSPRRLIY**FASQSIC**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 276)
7A3V2-28	DIVMTQSPLSLPVTPGEPASISC**RASQSISEYLH**WYLQKPGQSPQLLIY**FASQSIC**GV PDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 277)
7A3V4-1	DIVMTQSPDSLAVSLGERATINC**RASQSISEYLH**WYQQKPGQPPKLLIY**FASQSIC**G VPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO: 278)
Antibody 7E11	**Antibody 7E11**
7E11V1-5	DIQMTQSPSTLSASVGDRVTITC**LASQTIGTWLA**WYQQKPGKAPKLLIY**AATSLA D**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QQLYSTPYT**FGQGTKVEIK (SEQ

Antibody variant	Humanized sequences
	ID NO: 279)
7E11V1-39	DIQMTQSPSSLSASVGDRVTITC**LASQTIGTWLA**WYQQKPGKAPKLLIY**AATSLA DG**VPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO: 280)
7E11V1-9	DIQLTQSPSFLSASVGDRVTITC**LASQTIGTWLA**WYQQKPGKAPKLLIY**AATSLAD** GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO: 281)
7E11V3-15	EIVMTQSPATLSVSPGERATLSC**LASQTIGTWLA**WYQQKPGQAPRLLIY**AATSLA DG**IPARFSGSGSGTEFTLTISSLQSEDFAVYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO: 282)
7E11V3-11	EIVLTQSPATLSLSPGERATLSC**LASQTIGTWLA**WYQQKPGQAPRLLIY**AATSLAD** GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO: 283)
7E11V1-33	DIQMTQSPSSLSASVGDRVTITC**LASQTIGTWLA**WYQQKPGKAPKLLIY**AATSLA DG**VPSRFSGSGSGTDFTFTISSLQPEDIATYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO: 284)
7E11V3-20	EIVLTQSPGTLSLSPGERATLSC**LASQTIGTWLA**WYQQKPGQAPRLLIY**AATSLAD** GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO: 285)
7E11V2-28	DIVMTQSPLSLPVTPGEPASISC**LASQTIGTWLA**WYLQKPGQSPQLLIY**AATSLAD** GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO: 286)
7E11V4-1	DIVMTQSPDSLAVSLGERATINC**LASQTIGTWLA**WYQQKPGQPPKLLIY**AATSLA DG**VPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO: 287)
7E11V2-30	DVVMTQSPLSLPVTLGQPASISC**LASQTIGTWLA**WFQQRPGQSPRRLIY**AATSLAD** GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO: 288)
Antibody 7F12	**Antibody 7F12**
7F12V2-30	DVVMTQSPLSLPVTLGQPASISC**RSSQSLVHSTGNTYLH**WFQQRPGQSPRRLIY**KV SNRFS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 289)
7F12V2-28	DIVMTQSPLSLPVTPGEPASISC**RSSQSLVHSTGNTYLH**WYLQKPGQSPQLLIY**KV SNRFS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 290)
7F12V4-1	DIVMTQSPDSLAVSLGERATINC**RSSQSLVHSTGNTYLH**WYQQKPGQPPKLLIY**K VSNRFS**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**SQNTHVPYT**FGQGTKVEI K (SEQ ID NO: 291)
7F12V3-11	EIVLTQSPATLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQQKPGQAPRLLIY**KV SNRFS**GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 292)
7F12V1-33	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**K VSNRFS**GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 293)
7F12V3-15	EIVMTQSPATLSVSPGERATLSC**RSSQSLVHSTGNTYLH**WYQQKPGQAPRLLIY**K VSNRFS**GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 294)
7F12V1-5	DIQMTQSPSTLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**K VSNRFS**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 295)
7F12V1-9	DIQLTQSPSFLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**KV SNRFS**GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 296)
7F12V1-39	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQQKPGKAPKLLIY**K VSNRFS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 297)

Antibody variant	Humanized sequences
7F12V3-20	EIVLTQSPGTLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQQKPGQAPRLLIY**KV SNRFS**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO: 298)
Antibody 10B5	**Antibody 10B5**
10B5V1-39	DIQMTQSPSSLSASVGDRVTITC**RASQDISZYLN**WYQQKPGKAPKLLIY**LSSRLHS** GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 299)
10B5V1-33	DIQMTQSPSSLSASVGDRVTITC**RASQDISZYLN**WYQQKPGKAPKLLIY**LSSRLHS** GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 300)
10B5V1-9	DIQLTQSPSFLSASVGDRVTITC**RASQDISZYLN**WYQQKPGKAPKLLIY**LSSRLHS**G VPSRFSGSGSGTEFTLTISSLQPEDFATYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 301)
10B5V1-5	DIQMTQSPSTLSASVGDRVTITC**RASQDISZYLN**WYQQKPGKAPKLLIY**LSSRLHS** GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 302)
10B5V3-11	EIVLTQSPATLSLSPGERATLSC**RASQDISZYLN**WYQQKPGQAPRLLIY**LSSRLHS**G IPARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 303)
10B5V3-15	EIVMTQSPATLSVSPGERATLSC**RASQDISZYLN**WYQQKPGQAPRLLIY**LSSRLHS** GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 304)
10B5V3-20	EIVLTQSPGTLSLSPGERATLSC**RASQDISZYLN**WYQQKPGQAPRLLIY**LSSRLHS**G IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 305)
10B5V2-28	DIVMTQSPLSLPVTPGEPASISC**RASQDISZYLN**WYLQKPGQSPQLLIY**LSSRLHS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 306)
10B5V2-30	DVVMTQSPLSLPVTLGQPASISC**RASQDISZYLN**WFQQRPGQSPRRLIY**LSSRLHS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 307)
10B5V4-1	DIVMTQSPDSLAVSLGERATINC**RASQDISZYLN**WYQQKPGQPPKLLIY**LSSRLHS** GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO: 308)
10B5L1	DIQMTQSPSSLSASVGDRVTITC**RASQDINTYLN**WYQQKPGKAPKLLIY**YTSRLHS** GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGNTLPWT**FGQGTKLEIK (SEQ ID NO: 487)
10B5L2	DIQMTQSPSSLSASVGDRVTITC**RASQDINTYLN**WYQQKPGKAPKLLIY**YTSRLHS** GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC**QQGNTLPWT**FGQGTKLEIK (SEQ ID NO: 488)
10B5L3	DVQMTQSPSSLSASVGDRVTITC**RASQDINTYLN**WYQQKPGKAPKLLIY**YTSRLH S**GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC**QQGNTLPWT**FGQGTKLEIK (SEQ ID NO: 489)
Antibody 10G8	**Antibody 10G8**
10G8V1-39	DIQMTQSPSSLSASVGDRVTITC**RASQSIREYLH**WYQQKPGKAPKLLIY**FASQSIC** GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 309)
10G8V1-9	DIQLTQSPSFLSASVGDRVTITC**RASQSIREYLH**WYQQKPGKAPKLLIY**FASQSIC**G VPSRFSGSGSGTEFTLTISSLQPEDFATYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 310)
10G8V3-11	EIVLTQSPATLSLSPGERATLSC**RASQSIREYLH**WYQQKPGQAPRLLIY**FASQSIC**GI PARFSGSGSGTDFTLTISSLEPEDFAVYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 311)
10G8V1-5	DIQMTQSPSTLSASVGDRVTITC**RASQSIREYLH**WYQQKPGKAPKLLIY**FASQSIC** GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 312)

Antibody variant	Humanized sequences
10G8V3-15	EIVMTQSPATLSVSPGERATLSC**RASQSIREYLH**WYQQKPGQAPRLLIY**FASQSIC**GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 313)
10G8V1-33	DIQMTQSPSSLSASVGDRVTITC**RASQSIREYLH**WYQQKPGKAPKLLIY**FASQSIC**GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 314)
10G8V3-20	EIVLTQSPGTLSLSPGERATLSC**RASQSIREYLH**WYQQKPGQAPRLLIY**FASQSIC**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 315)
10G8V4-1	DIVMTQSPDSLAVSLGERATINC**RASQSIREYLH**WYQQKPGQPPKLLIY**FASQSIC**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 316)
10G8V2-30	DVVMTQSPLSLPVTLGQPASISC**RASQSIREYLH**WFQQRPGQSPRRLIY**FASQSIC**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 317)
10G8V2-28	DIVMTQSPLSLPVTPGEPASISC**RASQSIREYLH**WYLQKPGQSPQLLIY**FASQSIC**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO: 318)

Table 6B: Humanized heavy chain variable regions

Antibody variant	Humanized sequences
Antibody 1A12	**Antibody 1A12**
1A12V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**SEVFPITYMN**WVRQAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 319)
1A12V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 320)
1A12V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**SEVFPITYMN**WVRQAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 321)
1A12V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**SEVFPITYMN**WVRQMPGKGLEW**IGDILPSIGRTMYG**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 322)
1A12V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 323)
1A12V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 324)
1A12V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 325)
1A12V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 326)
1A12V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 327)
1A12V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO: 328)
Antibody 1E8	**Antibody 1E8**
1E8V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FNIKGSLLH**WVRQAPGQGLEW**IGWIDPE**

Antibody variant	Humanized sequences
	DGETRFDQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**ARTEYSNPAWFA YW**GQGTLVTVSS (SEQ ID NO: 329)
1E8V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FNIKGSLLH**WVRQMPGKGLEW**IGWIDPED GETRFD**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**ARTEYSNPAWFAY**W GQGTLVTVSS (SEQ ID NO: 330)
1E8V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FNIKGSLLH**WVRQAPGKGLEW**IGWIDPED GETRFD**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARTEYSNPAWFAY** WGQGTLVTVSS (SEQ ID NO: 331)
1E8V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FNIKGSLLH**WVRQAPGQGLEW**IGWIDPE DGETRFD**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**ARTEYSNPAWFAY** WGQGTLVTVSS (SEQ ID NO: 332)
1E8V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FNIKGSLLH**WVRQAPGKGLEW**IGWIDPED GETRFD**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARTEYSNPAWFAY** WGQGTLVTVSS (SEQ ID NO: 333)
1E8V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FNIKGSLLH**WVRQAPGKGLEW**IGWIDPED GETRFD**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARTEYSNPAWFAY** WGQGTLVTVSS (SEQ ID NO: 334)
1E8V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FNIKGSLLH**WVRQAPGKGLEW**IGWIDPED GETRFD**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARTEYSNPAWFAY** WGQGTLVTVSS (SEQ ID NO: 335)
1E8V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FNIKGSLLH**WIRQPPGKGLEW**IGWIDPEDG ETRFD**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARTEYSNPAWFAY**WG QGTLVTVSS (SEQ ID NO: 336)
1E8V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FNIKGSLLH**WVRQAPGKGLEW**IGWIDPED GETRFD**APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**ARTEYSNPAWFAY** WGQGTLVTVSS (SEQ ID NO: 337)
1E8V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**FNIKGSLLH**WIRQPPGKGLEW**IGWIDPEDG ETRFD**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARTEYSNPAWFAY**WG QGTLVTVSS (SEQ ID NO: 338)
Antibody 2G1	**Antibody 2G1**
2G1V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FTFSNYDMS**WVRQAPGKGLEW**VATISSGG DYTYYP**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 339)
2G1V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSNYDMS**WVRQAPGKGLEW**VATISSGG DYTYYP**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 340)
2G1V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FTFSNYDMS**WVRQAPGKGLEW**VATISSGG DYTYYP**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 341)
2G1V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSNYDMS**WVRQAPGKGLEW**VATISSGG DYTYYP**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 342)
2G1V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FTFSNYDMS**WVRQAPGQGLEW**VATISSG GDYTYYP**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**ARHGYGNYDWYF DV**WGQGTLVTVSS (SEQ ID NO: 343)
2G1V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FTFSNYDMS**WVRQAPGQGLEW**VATISSG GDYTYYP**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**ARHGYGNYDWYF DV**WGQGTLVTVSS (SEQ ID NO: 344)
2G1V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FTFSNYDMS**WVRQMPGKGLEW**VATISSGG DYTYYP**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**ARHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 345)
2G1V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FTFSNYDMS**WIRQPPGKGLEW**VATISSGGD YTYYP**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARHGYGNYDWYFDV** WGQGTLVTVSS (SEQ ID NO: 346)
2G1V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FTFSNYDMS**WVRQAPGKGLEW**VATISSGG DYTYYP**APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**ARHGYGNYDWYFD**

Antibody variant	Humanized sequences
	VWGQGTLVTVSS (SEQ ID NO: 347)
2G1V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**FTFSNYDMS**WIRQPPGKGLEW**VATISSGGD YTYYP**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARHGYGNYDWYFDV** WGQGTLVTVSS (SEQ ID NO: 348)
Antibody 2G4	**Antibody 2G4**
2G4V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**SEVFPITYMN**WVRQAPGQGLEW**IGDILPS IGRTMYG**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**ARSEGYLLAY**WG QGTLVTVSS (SEQ ID NO: 349)
2G4V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 350)
2G4V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**SEVFPITYMN**WVRQAPGQGLEW**IGDILPSI GRTMYG**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 351)
2G4V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**SEVFPITYMN**WVRQMPGKGLEW**IGDILPSI GRTMYG**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 352)
2G4V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 353)
2G4V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 354)
2G4V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 355)
2G4V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYM**NWIRQPPGKGLEW**IGDILPSIG RTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGT LVTVSS (SEQ ID NO: 356)
2G4V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIG RTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGT LVTVSS (SEQ ID NO: 357)
2G4V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIG RTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGT LVTVSS (SEQ ID NO: 358)
Antibody 3E11	**Antibody 3E11**
3E11V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**YIFTDYGIT**WVRQMPGKGLEW**IGEISPRSG ETYFN**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**AREGNPFTY**WGQGTL VTVSS (SEQ ID NO: 359)
3E11V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**YIFTDYGIT**WVRQAPGQGLEW**IGEISPRS GETYFN**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**AREGNPFTY**WGQG TLVTVSS (SEQ ID NO: 360)
3E11V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**YIFTDYGIT**WVRQAPGKGLEW**IGEISPRSG ETYFN**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**AREGNPFTY**WGQGTL VTVSS (SEQ ID NO: 361)
3E11V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**YIFTDYGIT**WVRQAPGQGLEW**IGEISPRSG ETYFN**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**AREGNPFTY**WGQGTL VTVSS (SEQ ID NO: 362)
3E11V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**YIFTDYGIT**WVRQAPGKGLEW**IGEISPRSG ETYFN**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**AREGNPFTY**WGQGTL VTVSS (SEQ ID NO: 363)
3E11V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**YIFTDYGIT**WVRQAPGKGLEW**IGEISPRSG ETYFN**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**AREGNPFTY**WGQGTL VTVSS (SEQ ID NO: 364)
3E11V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**YIFTDYGIT**WVRQAPGKGLEW**IGEISPRSG ETYFN**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**AREGNPFTY**WGQGTL

Antibody variant	Humanized sequences
	VTVSS (SEQ ID NO: 365)
3E11V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**YIFTDYGIT**WIRQPPGKGLEW**IGEISPRSGET YFN**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**AREGNPFTY**WGQGTLVTV SS (SEQ ID NO: 366)
3E11V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**YIFTDYGIT**WVRQAPGKGLEW**IGEISPRSG ETYFN**APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**AREGNPFTY**WGQGTL VTVSS (SEQ ID NO: 367)
3E11V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**YIFTDYGIT**WIRQPPGKGLEW**IGEISPRSGE TYFN**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**AREGNPFTY**WGQGTLVT VSS (SEQ ID NO: 368)
Antibody 4A1	**Antibody 4A1**
4A1V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**SEVFPITYMN**WVRQAPGQGLEW**IGDILPS IGRTMYG**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**ARSEGYLLAY**WG QGTLVTVSS (SEQ ID NO: 369)
4A1V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 370)
4A1V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**SEVFPITYMN**WVRQAPGQGLEW**IGDILPSI GRTMYG**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 371)
4A1V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**SEVFPITYMN**WVRQMPGKGLEW**IGDILPSI GRTMYG**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 372)
4A1V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 373)
4A1V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 374)
4A1V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 375)
4A1V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIG RTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGT LVTVSS (SEQ ID NO: 376)
4A1V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIG RTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGT LVTVSS (SEQ ID NO: 377)
4A1V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIG RTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGT LVTVSS (SEQ ID NO: 378)
Antibody 4D7	**Antibody 4D7**
4D7V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**YTFTNYWIN**WVRQMPGKGLEW**IGNIYSGS SRTNYN**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**AREGLRAMDY**WGQ GTLVTVSS (SEQ ID NO: 379)
4D7V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**YTFTNYWIN**WVRQAPGKGLEW**IGNIYSGS SRTNYN**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**AREGLRAMDY**WGQ GTLVTVSS (SEQ ID NO: 380)
4D7V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**YTFTNYWIN**WVRQAPGQGLEW**IGNIYSG SSRTNYN**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**AREGLRAMDY**WG QGTLVTVSS (SEQ ID NO: 381)
4D7V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**YTFTNYWIN**WVRQAPGKGLEW**IGNIYSGS SRTNYN**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**AREGLRAMDY**WGQ GTLVTVSS (SEQ ID NO: 382)
4D7V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**YTFTNYWIN**WVRQAPGQGLEW**IGNIYSGS SRTNYN**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**AREGLRAMDY**WGQ

Antibody variant	Humanized sequences
	GTLVTVSS (SEQ ID NO: 383)
4D7V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**YTFTNYWIN**WVRQAPGKGLEW**IGNIYSGS SRTNYN**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**AREGLRAMDY**WGQ GTLVTVSS (SEQ ID NO: 384)
4D7V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**YTFTNYWIN**WVRQAPGKGLEW**IGNIYSGSS RTNYN**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**AREGLRAMDY**WGQG TLVTVSS (SEQ ID NO: 385)
4D7V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**YTFTNYWIN**WIRQPPGKGLEW**IGNIYSGSSR TNYN**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**AREGLRAMDY**WGQGTL VTVSS (SEQ ID NO: 386)
4D7V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**YTFTNYWIN**WVRQAPGKGLEW**IGNIYSGS SRTNYN**APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**AREGLRAMDY**WGQ GTLVTVSS (SEQ ID NO: 387)
4D7V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**YTFTNYWIN**WIRQPPGKGLEW**IGNIYSGSS RTNYN**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**AREGLRAMDY**WGQGT LVTVSS (SEQ ID NO: 388)
Antibody 4E3	**Antibody 4E3**
4E3V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FIFSNYDMS**WVRQAPGKGLEW**VATISSGG GYTYYP**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**TRHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 389)
4E3V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FIFSNYDMS**WVRQAPGKGLEW**VATISSGG GYTYYP**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**TRHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 390)
4E3V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FIFSNYDMS**WVRQAPGKGLEW**VATISSGG GYTYYP**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**TRHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 391)
4E3V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FIFSNYDMS**WVRQAPGKGLEW**VATISSGG GYTYYP**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**TRHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 392)
4E3V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FIFSNYDMS**WVRQAPGQGLEW**VATISSGG GYTYYP**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**TRHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 393)
4E3V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FIFSNYDMS**WVRQAPGQGLEW**VATISSGG GYTYYP**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**TRHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 394)
4E3V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FIFSNYDMS**WVRQMPGKGLEW**VATISSGG GYTYYP**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**TRHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 395)
4E3V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FIFSNYDMS**WIRQPPGKGLEW**VATISSGGG YTYYP**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**TRHGYGNYDWYFDV**W GQGTLVTVSS (SEQ ID NO: 396)
4E3V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FIFSNYDMS**WVRQAPGKGLEW**VATISSGG GYTYYP**APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**TRHGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 397)
4E3V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**FIFSNYDMS**WIRQPPGKGLEW**VATISSGGGY TYYP**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**TRHGYGNYDWYFDV**WG QGTLVTVSS (SEQ ID NO: 398)
4E3H1	EVQLVESGGGLVKPGGSLRLSCAASG**FIFSNYDMS**WVRQAPGKGLEWVS**TISSGG GYTY**YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR**HGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 490)
4E3H2	EVQLVESGGGLVKPGGSLRLSCAV**SGFIFSNYDMS**WVRQAPGKGLEWVA**TISSGG GYTY**YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCTR**HGYGNYDWYFD V**WGQGTLVTVSS (SEQ ID NO: 491)

Antibody variant	Humanized sequences
4E3H3	EVQLVESGGGLVKPGGSLRISCA**VSGFIFSNYDMS**WVRQAPGKGLEWVA**TISSGG GYTY**YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**TRHGYGNYDWYFD V**WGQGALVTVSS (SEQ ID NO: 492)
Antibody 7A3	**Antibody 7A3**
7A3V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSNYAMS**WVRQAPGKGLEW**VASISSGG SYNYYP**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ASQSYGSSYWYFDV** WGQGTLVTVSS (SEQ ID NO: 399)
7A3V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FTFSNYAMS**WVRQAPGKGLEW**VASISSGG SYNYYP**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ASQSYGSSYWYFDV** WGQGTLVTVSS (SEQ ID NO: 400)
7A3V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FTFSNYAMS**WVRQAPGKGLEW**VASISSGG SYNYYP**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ASQSYGSSYWYFDV** WGQGTLVTVSS (SEQ ID NO: 401)
7A3V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSNYAMS**WVRQAPGKGLEW**VASISSGG SYNYYP**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ASQSYGSSYWYFDV** WGQGTLVTVSS (SEQ ID NO: 402)
7A3V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FTFSNYAMS**WVRQAPGQGLEW**VASISSGG SYNYYP**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**ASQSYGSSYWYFDV** WGQGTLVTVSS (SEQ ID NO: 403)
7A3V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FTFSNYAMS**WVRQAPGQGLEW**VASISSG GSYNYYP**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**ASQSYGSSYWYFD V**WGQGTLVTVSS (SEQ ID NO: 404)
7A3V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FTFSNYAMS**WVRQMPGKGLEW**VASISSGG SYNYYP**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**ASQSYGSSYWYFDV** WGQGTLVTVSS (SEQ ID NO: 405)
7A3V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FTFSNYAMS**WIRQPPGKGLEW**VASISSGGS YNYYP**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ASQSYGSSYWYFDV**W GQGTLVTVSS (SEQ ID NO: 406)
7A3V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FTFSNYAMS**WVRQAPGKGLEW**VASISSGG SYNYYP**APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**ASQSYGSSYWYFDV** WGQGTLVTVSS (SEQ ID NO: 407)
7A3V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**FTFSNYAMS**WIRQPPGKGLEW**VASISSGGS YNYYP**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ASQSYGSSYWYFDV**W GQGTLVTVSS (SEQ ID NO: 408)
Antibody 7E11	**Antibody 7E11**
7E11V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FSLSNYGVH**WIRQPPGKGLEW**LGVIWAGGI TNYN**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**AKQGGTSFSY**WGQGTL VTVSS (SEQ ID NO: 409)
7E11V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FSLSNYGVH**WVRQAPGKGLEW**LGVIWAG GITNYN**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**AKQGGTSFSY**WGQG TLVTVSS (SEQ ID NO: 410)
7E11V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FSLSNYGVH**WVRQAPGKGLEW**LGVIWAG GITNYN**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**AKQGGTSFSY**WGQ GTLVTVSS (SEQ ID NO: 411)
7E11V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FSLSNYGVH**WVRQAPGKGLEW**LGVIWAG GITNYN**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**AKQGGTSFSY**WGQ GTLVTVSS (SEQ ID NO: 412)
7E11V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FSLSNYGVH**WVRQAPGKGLEW**LGVIWAG GITNYN**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**AKQGGTSFSY**WGQG TLVTVSS (SEQ ID NO: 413)
7E11V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FSLSNYGVH**WVRQMPGKGLEW**LGVIWAG GITNYN**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**AKQGGTSFSY**WGQG TLVTVSS (SEQ ID NO: 414)
7E11V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FSLSNYGVH**WVRQAPGQGLEW**LGVIWAG GITNYN**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**AKQGGTSFSY**WGQG TLVTVSS (SEQ ID NO: 415)

Antibody variant	Humanized sequences
7E11V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FSLSNYGVH**WVRQAPGQGLEW**LGVIWA GGITNYN**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**AKQGGTSFSY**WG QGTLVTVSS (SEQ ID NO: 416)
7E11V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**FSLSNYGVH**WIRQPPGKGLEW**LGVIWAGGI TNYN**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**AKQGGTSFSY**WGQGTL VTVSS (SEQ ID NO: 417)
7E11V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**FSLSNYGVH**WIRQPPGKGLEW**LGVIWAGGI TNYN**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**AKQGGTSFSY**WGQGTL VTVSS (SEQ ID NO: 418)
Antibody 7F12	**Antibody 7F12**
7F12V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**SEVFPITYMN**WVRQAPGQGLEW**IGDILPS IGRTMYG**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**ARSEGYLLAY**WG QGTLVTVSS (SEQ ID NO: 419)
7F12V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 420)
7F12V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**SEVFPITYMN**WVRQAPGQGLEW**IGDILPSI GRTMYG**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 421)
7F12V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**SEVFPITYMN**WVRQMPGKGLEW**IGDILPSI GRTMYG**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 422)
7F12V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 423)
7F12V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 424)
7F12V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**SEVFPITYMN**WVRQAPGKGLEW**IGDILPSI GRTMYG**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQ GTLVTVSS (SEQ ID NO: 425)
7F12V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIG RTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGT LVTVSS (SEQ ID NO: 426)
7F12V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIG RTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGT LVTVSS (SEQ ID NO: 427)
7F12V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**SEVFPITYMN**WIRQPPGKGLEW**IGDILPSIG RTMYG**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARSEGYLLAY**WGQGT LVTVSS (SEQ ID NO: 428)
Antibody 10B5	**Antibody 10B5**
10B5V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**YAFTNCWMN**WVRQMPGKGLEW**IGRIFPG NGHTNYS**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**ARDYSDYYFDY**WG QGTLVTVSS (SEQ ID NO: 429)
10B5V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**YAFTNCWMN**WVRQAPGQGLEW**IGRIFP GNGHTNYS**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**ARDYSDYYFDY** WGQGTLVTVSS (SEQ ID NO: 430)
10B5V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**YAFTNCWMN**WVRQAPGQGLEW**IGRIFPG NGHTNYS**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**ARDYSDYYFDY**WG QGTLVTVSS (SEQ ID NO: 431)
10B5V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPG NGHTNYS**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARDYSDYYFDY**W GQGTLVTVSS (SEQ ID NO: 432)
10B5V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPG NGHTNYS**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARDYSDYYFDY**W GQGTLVTVSS (SEQ ID NO: 433)

Antibody variant	Humanized sequences
10B5V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPG NGHTNYS**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARDYSDYYFDY**W GQGTLVTVSS (SEQ ID NO: 434)
10B5V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPG NGHTNYS**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARDYSDYYFDY**W GQGTLVTVSS (SEQ ID NO: 435)
10B5V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**YAFTNCWMN**WIRQPPGKGLEW**IGRIFPGN GHTNYS**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARDYSDYYFDY**WGQ GTLVTVSS (SEQ ID NO: 436)
10B5V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPG NGHTNYS**APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**ARDYSDYYFDY**W GQGTLVTVSS (SEQ ID NO: 437)
10B5V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**YAFTNCWMN**WIRQPPGKGLEW**IGRIFPGN GHTNYS**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARDYSDYYFDY**WGQ GTLVTVSS (SEQ ID NO: 438)
10B5H1	QVQLVQSGAEVKKPGASVKVSCKAS**GYAFTNCWMN**WVRQAPGQGLEWMG**RIFP GNGHTN**YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**DYSDYYFDY** WGQGTLVTVSS (SEQ ID NO: 493)
10B5H2	QVQLVQSGAEVKKPGASVKVSCKAS**GYAFTNCWMN**WVRQAPGQGLEWIG**RIFP GNGHTN**YAQKFQGRVTMTEDTSTSTVYMELSSLRSEDTAVYYCAR**DYSDYYFDY** WGQGTLVTVSS (SEQ ID NO: 494)
10B5H3	QVQLVQSGAEVKKPGASVKISCKAS**GYAFTNCWMN**WVRQAPGQGLEWIG**RIFPG NGHTN**YAQKFQGRATLTEDTSTSTAYMELSSLRSEDTAVYYCAR**DYSDYYFDY**W GQGTLLTVSS (SEQ ID NO: 495)
10B5H4	QVQLVQSGAEVKKPGASVKISCKAS**GYAFTNCWMN**WVRQAPGQGLEWIG**RIFPG NGHTN**YAQKFQGRATLTEDKSTSTAYMELSSLRSEDTAVYYCAR**DYSDYYFDY**W GQGTLLTVSS (SEQ ID NO: 496)
Antibody 10G8	**Antibody 10G8**
10G8V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FTFSTYAMF**WVRQAPGKGLEW**VASISSGG RYTYYP**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**VRHSYGSSYWYLDV** WGQGTLVTVSS (SEQ ID NO: 439)
10G8V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSTYAMF**WVRQAPGKGLEW**VASISSGG RYTYYP**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**VRHSYGSSYWYLD V**WGQGTLVTVSS (SEQ ID NO: 440)
10G8V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSTYAMF**WVRQAPGKGLEW**VASISSGG RYTYYP**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**VRHSYGSSYWYLD V**WGQGTLVTVSS (SEQ ID NO: 441)
10G8V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FTFSTYAMF**WVRQAPGKGLEW**VASISSGG RYTYYP**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**VRHSYGSSYWYLDV** WGQGTLVTVSS (SEQ ID NO: 442)
10G8V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FTFSTYAMF**WVRQAPGQGLEW**VASISSG GRYTYYP**QKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC**VRHSYGSSYWYL DV**WGQGTLVTVSS (SEQ ID NO: 443)
10G8V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FTFSTYAMF**WVRQAPGQGLEW**VASISSGG RYTYYP**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**VRHSYGSSYWYLDV** WGQGTLVTVSS (SEQ ID NO: 444)
10G8V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FTFSTYAMF**WVRQMPGKGLEW**VASISSGG RYTYYP**PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC**VRHSYGSSYWYLDV** WGQGTLVTVSS (SEQ ID NO: 445)
10G8V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FTFSTYAMF**WIRQPPGKGLEW**VASISSGGR YTYYP**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**VRHSYGSSYWYLDV**W GQGTLVTVSS (SEQ ID NO: 446)
10G8V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FTFSTYAMF**WVRQAPGKGLEW**VASISSGG RYTYYP**APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**VRHSYGSSYWYLDV** WGQGTLVTVSS (SEQ ID NO: 447)
10G8V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**FTFSTYAMF**WIRQPPGKGLEW**VASISSGGR**

Antibody variant	Humanized sequences
	YTYYPPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**VRHSYGSSYWYLDV**W GQGTLVTVSS (SEQ ID NO: 448)

Humanization of antibody 4E3

[0501] The heavy chain variable region (VH) and light chain variable region (VL) sequences of murine anti-Siglec-7 antibody 4E3 (S7-4E3) were used as input to the IgBLAST program on the NCBI website (Ye, J. et al. Nucleic Acids Research 41:W34-W40 (2013)). IgBLAST takes a murine VH or VL sequence and compares it to a library of known human germline sequences. The databases used were IMGT human VH genes (F+ORF, 273 germline sequences) and IMGT human VLkappa genes (F+ORF, 74 germline sequences). For the 4E3 antibody VL, human germline IGKV3-11 (allele 1) was chosen as the acceptor sequence and human light chain IGKJ2(allele 1) joining region (J gene) was chosen from human joining region sequences compiled at *IMGT® the international ImMunoGeneTics information system®* (**FIG. 6B**). For the 4E3 antibody VH, human germline IGHV3-21 (allele 1) was chosen as the acceptor sequence and the human heavy chain IGHJ4 (allele 1) joining region (J gene) was chosen from human joining region sequences compiled at *IMGT® the international ImMunoGeneTics information system®* (**FIG. 6C**). Complementarity determing regions (CDRs) for the antibody VL and VH were defined according to the AbM definition (*AbM* antibody modeling software).

[0502] Alteration of human germline framework (i.e., non-CDR residues in the VH and VL) positions to corresponding parental murine sequences may be required to optimize binding of the humanized antibody. Potential changes for each humanized sequence are noted in **FIG. 6B and 6C**.

[0503] **FIG. 6B and 6C** show sequences of humanized versions of anti-Siglec-7 antibody 4E3. In the VL domain of antibody 4E3, Asp26 within the CDR-L1 and Asn52 within the CDR-L2 have low potential for deamidation based on sequence and conformation and may show a low level of this post-translational modification (**FIG. 6B**). Trp90 within the CDR-L3 of antibody 4E3 appears to be solvent-exposed and may show a low level of oxidation, more so under stress conditions (**FIG. 6B**). Variant VL sequences based on the above are listed in **Table 6A**.

[0504] In the VH domain of antibody 4E3, Asn31 within the CDR-H1 and Asn103 within the CDR-H3 have a low potential for deamidation based on sequence and conformation but could show a low level of this post-translational modification (**FIG. 6C**). Trp106 within the CDR-H3 appears to be solvent-exposed and may show a low level of oxidation, more so under stress conditions (**FIG. 6C**). Variant VH sequences based on the above are listed in **Table 6B**.

Humanization of antibody 10B5

[0505] The heavy chain variable region (VH) and light chain variable region (VL) sequences of murine anti-Siglec-7 antibody 10B5 (S7-10B5) were used as input to the IgBLAST program on the

NCBI website (Ye, J. et al. Nucleic Acids Research 41:W34-W40 (2013)). IgBLAST takes a murine VH or VL sequence and compares it to a library of known human germline sequences. The databases used were IMGT human VH genes (F+ORF, 273 germline sequences) and IMGT human VLkappa genes (F+ORF, 74 germline sequences). For the 10B5 antibody VL, human germline IGKV1-39 (allele 1) was chosen as the acceptor sequence and human light chain IGKJ2 (allele 1) joining region (J gene) was chosen from human joining region sequences compiled at *IMGT® the international ImMunoGeneTics information system®* (**FIG. 6D**). For the 10B5 antibody VH, human germline IGHV1-46 (allele 1) was chosen as the acceptor sequence and the human heavy chain IGHJ4 (allele 1) joining region (J gene) was chosen from human joining region sequences compiled at *IMGT® the international ImMunoGeneTics information system®* (**FIG. 6E**). Complementarity determing regions (CDRs) for the antibody VL and VH were defined according to the AbM definition (*AbM* antibody modeling software).

[0506] Alteration of human germline framework (i.e., non-CDR residues in the VH and VL) positions to corresponding parental murine sequences may be required to optimize binding of the humanized antibody. Potential changes for each humanized sequence are noted in **FIG. 6D and 6E**.

[0507] **FIG. 6D and 6E** show sequences of humanized versions of anti-Siglec-7 antibody 10B5. In the VL domain of antibody 10B5, Asp30 within the CDR-L1 and Asn92 within the CDR-L3 have low to medium potential for deamidation based on sequence and conformation and may show a low level of this post-translational modification (**FIG. 6D**). Trp33 within the CDR-L1 of antibody 10B5 appears to be solvent-exposed and may show a low level of oxidation, more so under stress conditions (**FIG. 6D**). There is also a free Cys within the CDR-L1 that is likely to be solvent-exposed, and which may be altered to a Ser to evaluate its effect on binding. Variant VL sequences based on the above are listed in **Table 6A**.

[0508] In the VH domain of antibody 10B5, Asp54-Gly55 within the CDR-H2 has a medium potential for deamidation followed by isoaspartate formation (**FIG. 6E**). Post- translational modification at this site may affect binding of the antibody to target. The parental mouse antibody may be analyzed to determine the level of post-translational modification. Alternatively, antibody 10B5 can be humanized and then in a final step the NG may be modified to, for example QG, to determine if binding is maintained. Asn31 within the CDR-H1 and Asn58 within the CDR-H2 have a low potential for deamidation based on sequence and conformation but could show a low level of this post-translational modification (**FIG. 6E**). Modifications to the CDRs may be made after humanization, such as by analyzing the Asn54-Gly55 within the CDR-H2 and altering the Cys32Ser within the CDR-H1 (**FIG. 6E**). Variant VH sequences based on the above are listed in **Table 6B**.

Example 2: Epitope mapping of Siglec-7 antibodies

[0509] Siglec-7 antibodies were tested for their ability to bind 15 or 25-mer peptides spanning the entire human Siglec-7. The Siglec-7 antibodies were also compared to a reference Siglec-7 antibody by determining their Siglec-7 binding region.

Methodology

[0510] Linear 15-mer peptides were synthesized based on the sequence of human Siglec-7 (SEQ ID NO: 1), with a 14 residue overlap. In addition, linear 25-mer peptides were synthesized based on sequence of human Siglec-7 (SEQ ID NO: 1) with a single residue shift. The binding of Siglec-7 antibodies to each of the synthesized peptides was tested in an ELISA based method. In this assay, the peptide arrays were incubated with primary antibody solution (overnight at 4°C). After washing, the peptide arrays were incubated with a 1/1000 dilution of an antibody peroxidase conjugate (SBA, cat. nr. 2010-05) for one hour at 25°C. After washing, the peroxidase substrate 2,2'- azino-di-3-ethylbenzthiazoline sulfonate (ABTS) and 2 µl/ml of 3% H_2O_2 were added. After one hour, the color development was measured. The color development was quantified with a charge coupled device (CCD) camera and an image processing system.

[0511] Epitope binning of the antibodies was performed on a Forte Bio Octet Red384 system (Pall Forte Bio Corporation, Menlo Park, CA) using a standard sandwich format binning assay (see Estep *et al*, (2013) *MAbs* 5(2):270-8). Control anti-target IgG was loaded onto AHQ sensors and unoccupied Fc-binding sites on the sensor were blocked with a non-relevant human IgG1 antibody. The sensors were then exposed to 100 nM target antigen followed by a second anti-target antibody. Data was processed using ForteBio's Data Analysis Software 7.0. Additional binding by the second antibody after antigen association indicates an unoccupied epitope (non-competitor), while no binding indicates epitope blocking (competitor).

[0512] Alternatively, to reconstruct epitopes of the target molecule, libraries of looped and combinatorial peptides were synthesized. An amino functionalized polypropylene support was obtained by grafting with a proprietary hydrophilic polymer formulation, followed by reaction with t-butyloxycarbonyl- hexamethylenediamine (BocHMDA) using dicyclohexylcarbodiimide (DCC) with *N*-hydroxybenzotriazole (HOBt) and subsequent cleavage of the Boc-groups using trifluoroacetic acid (TFA). Standard Fmoc-peptide synthesis was used to synthesize peptides on the amino-functionalized solid support by custom modified JANUS liquid handling stations (Perkin Elmer).

[0513] Synthesis of structural mimics was done using Pepscan's proprietary Chemically Linked Peptides on Scaffolds (CLIPS) technology. CLIPS technology allows to structure peptides into single loops and double-loops. CLIPS templates are coupled to cysteine residues. The side-chains of multiple cysteines in the peptides are coupled to one or two CLIPS templates. For

example, a 0.5 mM solution of the mP2 CLIPS (2,6-bis(bromomethyl)pyridine) is dissolved in ammonium bicarbonate (20 mM, pH 7.8)/acetonitrile (1:3(v/v)). This solution is added onto the peptide arrays. The CLIPS template will bind to side-chains of two cysteines as present in the solid-phase bound peptides of the peptide- arrays (455 wells plate with 3 µl wells). The peptide arrays are gently shaken in the solution for 30 to 60 minutes while completely covered in solution. Finally, the peptide arrays are washed extensively with excess of H_2O and sonicated in disrupt-buffer containing 1 % SDS/0.1 % β-mercaptoethanol in PBS (pH 7.2) at 70°C for 30 minutes, followed by sonication in H_2O for another 45 minutes. The T3 CLIPS (2,4,6-tris(bromomethyl)pyridine) carrying peptides were made in a similar way but now with three cysteines.

[0514] Looped peptides: constrained peptides of length 17. Positions 2-16 are 15-mers derived from the target sequence. Native Cys residues are protected by acetamidomethyl group (ACM). Positions 1 and 17 are Cys that are linked by mP2 CLIPS moieties. Combinatorial peptides (discontinuous mimics): constrained peptides of length 33. Positions 2-16 and 18-32 are 15-mer peptides derived from the target sequence with native Cys residues protected by ACM. Positions 1, 17 and 33 are Cys that are linked by T3 CLIPS moieties.

[0515] The binding of antibody to each of the synthesized peptides is tested in a PEPSCAN-based ELISA. The peptide arrays are incubated with test antibody solution composed of the experimentally optimized concentration of the test antibody and blocking solution (for example 4% horse serum, 5% ovalbumin (w/v) in PBS/1% Tween80). The peptide arrays are incubated with the test antibody solution overnight at 4°C. After extensive washing with washing buffer (1×PBS, 0.05% Tween80), the peptide arrays are incubated with a 1/1000 dilution of an appropriate antibody peroxidase conjugate for one hour at 25°C. After washing with the washing buffer, the peroxidase substrate 2,2'-azino-di-3- ethylbenzthiazoline sulfonate (ABTS) and 2 µl/ml of 3% H_2O_2 are added. After one hour, the color development is measured. The color development is quantified with a charge coupled device (CCD) - camera and an image processing system.

[0516] Alternatively a mass spectrometry method is used to identify conformational epitopes. In order to determine the key residues of conformational epitopes on the Siglec 7 protein that anti-Siglec 7 antibodies bind to, with high resolution, antibody/antigen complexes are incubated with deuterated cross-linkers and subjected to multi-enzymatic proteolytic cleavage. After enrichment of the cross-linked peptides, the samples are analyzed by high resolution mass spectrometry (nLC-Orbitrap MS) and the data generated is analyzed using XQuest software. Specifically, Siglec 7 ECD/antibody complexes are generated by mixing equimolar solutions of Siglec-7 antigen and antibody (4 µM in 5 µl each). One µl of the mixture obtained is mixed with 1 µl of a matrix composed of a re-crystallized sinapinic acid matrix (10 mg/ml) in acetonitrile/water (1:1, v/v), TFA

0.1% (K200 MALDI Kit). After mixing, 1 µl of each sample is spotted on a MALDI plate (SCOUT 384). After crystallization at room temperature, the plate is introduced in aMALDI mass spectrometer and analyzed immediately. The analysis is repeated in triplicate. Peaks representing monomeric antibody, the antigen, and antibody and antigen/antibody complexes are detected at the predicted molecular weights.

[0517] It is then determined whether the epitope in conformational binding competes with unstructured C1q peptides generated by proteolysis. Specifically, to determine if Siglec-7 ECD/antibody complexes can compete with linear peptides, the Siglec-7 ECD antigen is digested with immobilized pepsin. 25 µl of the antigen with a concentration of 10 µM are mixed with immobilized pepsin 5 µM and incubate at room temperature for 30 minutes. After the incubation time, the samples are centrifuged and the supernatant is pipetted. The completion of the proteolysis is controlled by High-Mass MALDI mass spectrometry in linear mode. The pepsin proteolysis is optimized in order to obtain a large amount of peptide in the 1000-3500 Da range. Next, 5 µl of the antigen peptides generated by proteolysis are mixed with 5 µl of antibodies (8 µM) and incubated at 37°C for 6 hours. After incubation of the antibodies with the Siglec-7 antigen peptides, 5 µl of the mixture is mixed with 5 µl of the intact Siglec-7 antigen (4 µM) so the final mix contains 2 µM/2 µM/2.5 µM of Siglec-7/ antibody /Siglec-7antigen peptides. The MALDI ToF MS analysis is performed using CovalX's HM3 interaction module with a standard nitrogen laser and focusing on different mass ranges from 0 to 2000 kDa. For the analysis, the following parameters are applied for the mass spectrometer: Linear and Positive mode; Ion Source 1: 20 kV; Ion Source 2: 17 kV; Pulse Ion Extraction: 400 ns; for HM3: Gain Voltage: 3.14 kV; Gain Voltage: 3.14 kV; Acceleration Voltage: 20 kV. To calibrate the instrument, an external calibration with clusters of Insulin, BSA and IgG is being applied. For each sample, 3 spots are analyzed (300 laser shots per spots). Presented spectrum corresponds to the sum of 300 laser shots. The MS data are analyzed using the Complex Tracker analysis software version 2.0 (CovalX Inc). To identify the conformational epitopes for Siglec-7 binding to antibodies, using chemical cross-linking, High-Mass MALDI mass spectrometry and nLCOrbitrap mass spectrometry the interaction interface between the antigen and antibodies the following procedure is followed. 5µl of the sample antigen (concentration 4 µM) is mixed with 5 µl of the sample antibody (Concentration 4 µM) in order to obtain an antibody/antigen mix with final concentration 2 µM/2 µM. The mixture is incubated at 37°C for 180 minutes. In a first step, 1 mg of DiSuccinimidylSuberate H12 (DSS-H12) cross-linker is mixed with 1 mg of DiSuccinimidylSuberate D12 (DSS-D12) cross-linker. The 2 mg prepared were mixed with 1 ml of DMF in order to obtain a 2mg/ml solution of DSS H12/D12. 10 µl of the antibody/antigen mix prepared previously were mixed with 1 µl of the solution of cross-linker d0/d12 prepared (2 mg/ml). The solution is incubated 180 minutes at room temperature in order to achieve the cross-linking reaction.

[0518] In order to facilitate the proteolysis, it is necessary to reduce the disulfide bonds present in the protein. The cross-linked samples are mixed with 20 µl of ammonium bicarbonate (25 mM, pH 8.3). After mixing 2.5 µl of DTT (500 mM) is added to the solution. The mixture is then incubated 1 hour at 55°C. After incubation, 2.5 µl of iodioacetamide (1 M) is added before 1 hour of incubation at room temperature in a dark room. After incubation, the solution is diluted 1/5 by adding 120 µl of the buffer used for the proteolysis. 145 µl of the reduced/alkyled cross-linked sample is mixed with 2 µl of trypsin (Sigma, T6567). The proteolytic mixture is incubated overnight at 37°C. For a-chymotrypsin proteolysis, the buffer of proteolysis is Tris-HCL 100 mM, CaCl2 10 mM, pH7.8. The 145 µl of the reduced/alkyled cross-linked complex is mixed with 2 µl of α-chymotrypsin 200 µM and incubated overnight at 30°C. For this analysis, an nLC in combination with Orbitrap mass spectrometry is used. The cross-linker peptides are analyzed using Xquest version 2.0 and stavrox software. The peptides and cross-linked amino acids are then identified.

Results

[0519] The Siglec-7 binding region was determined for 4 anti-Siglec-7 antibodies. The binding region is listed in **Table 7A**. **FIG. 1B-1E** show a schematic representation of human Siglec-7, indicating the regions bound by anti-Siglec-7 antibodies.

Table 7A: Siglec-7 antibody binding region

Antibody	Siglec-7 binding region	Amino acid region of SEQ ID:1
1A12 4D7	^{111}RDARMSDAGRYF^{122} and ^{282}PPARLSWTWR^{291}	111-122 and 282-291
1A12 1E8 2G1 4D7	^{113}ARMSDAGRYFF^{123}	113-123
4A1	^{113}ARMSDAGRYFFRM^{125}	113-125
7E11	^{68}AGNDISWKAPV^{78}	68-78
10G8	^{60}PVHGYWFRAG^{69} and ^{84}AWAVQEETRDRF^{95}	60-69 and 84-95
2G4 3E11 10B5 2G1 7F12	^{60}PVHGYWFRAG^{69} and ^{117}DAGRYFFRMEK^{127}	60-69 and 117-127

[0520] As indicated in **Table 7A**, antibodies 1A12 and 4D7 showed robust binding exclusively for peptides within two extracellular domains (including the IgV domain and the second Ig-like C2-type domain) of Siglec-7. As indicated in **Table 7A**, the peptides recognized by antibodies 1A12and 4D7 correspond to amino acid residues 111-122 and 282-291of SEQ ID NO: 1 and have the amino acid sequences of: RDARMSDAGRYF and PPARLSWTWR.

[0521] As further indicated in **Table 7A**, antibodies1A12, 1E8, 2G1, 4D7, 4A1, 7E11, 10G8, 2G4, 3E11, 10B5, 2G1, and 7F12 showed robust binding exclusively for a peptide within the extracellular domain (including the IgV domain) of Siglec-7. As indicated in **Table 7A**, the peptide recognized by antibodies 1A12, 1E8, 2G1, and 4D7 corresponds to amino acid residues 113-123 of SEQ ID NO: 1 and has the amino acid sequence of: ARMSDAGRYFF. The peptide recognized by antibody 4A1 corresponds to amino acid residues 113-125 of SEQ ID NO: 1 and has the amino acid sequence of: ARMSDAGRYFFRM. The peptide recognized by antibody 7E11 corresponds to amino acid residues 68-78 of SEQ ID NO: 1 and has the amino acid sequence of: AGNDISWKAPV. The peptides recognized by antibody 10G8 correspond to amino acid residues 60-69 and 84-95 of SEQ ID NO: 1 and have the amino acid sequences of: PVHGYWFRAG and AWAVQEETRDRF. The peptides recognized by antibodies 2G4, 3E11, 10B5, 2G1, and 7F12 correspond to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1 and have the amino acid sequences of: PVHGYWFRAG and DAGRYFFRMEK.

[0522] The Siglec-7 peptides bound by antibodies 4A1, 10G8, 2G4, 3E11, 10B5, 2G1, 7F12, and 7E11 are depicted in **FIG. 1B-1E**. The discontinuous peptides recognized by antibody 4A1 are shown in **FIG. 1B and 1E**. The discontinuous peptides recognized by antibodies 2G4, 3E11, 10B5, 2G1, and 7F12 are depicted in **FIG. 1C**. The peptides recognized by antibody 10G8 is depicted in **FIG. 1D**. **FIG. 1E** depicts putative binding sites of a conformational epitope of Siglec-7 bound by antibody 7E11. The putative epitope includes a binding region that corresponds to amino acid residues 68-78 of SEQ ID NO: 1 and has the amino acid sequence of: AGNDISWKAPV.

Functional mapping

[0523] Shotgun mutagenesis epitope mapping of anti-siglec-7 antibodies was performed using an alanine-scanning library for the siglec-7 protein. A siglec-7 expression construct (Uniprot id Q9Y286) encoding a C-terminal V5 epitope tag was subjected to high-throughput alanine scanning mutagenesis (outlined in Davidson and Doranz, 2014 Immunology 143, 13-20) to generate a comprehensive mutation library. Each of residues 19 to 353 was mutated, representing the siglec-7 extracellular domain, most to alanine, while alanine codons were mutated to serine. In total, 335 siglec-7 mutant expression constructs were generated, sequences confirmed, and arrayed into a 384-well plate, one mutant per well.

[0524] The siglec-7 mutation library clones, arrayed in a 384-well microplate, were transfected individually into HEK-293T cells and allowed to express for 22 hours. Cells were then incubated with MAbs diluted in 10% normal goat serum (NGS) (Sigma-Aldrich, St. Louis, MO). Prior to library screening, primary MAb concentrations were determined using an independent immunofluorescence titration curve against cells expressing wild-type siglec-7 to ensure that signals were within the linear range of detection. MAbs were detected using 3.75 µg/ml AlexaFluor488-conjugated secondary

antibody (Jackson ImmunoResearch Laboratories, Westgrove, PA) in 10% NGS. Cells were washed twice with PBS -/- and resuspended in Cellstripper (Cellgro, Manassas, VA) with 0.1% BSA (Sigma-Aldrich, St. Louis, MO). Mean cellular fluorescence was detected using the Intellicyt high throughput flow cytometer (HTFC, Intellicyt, Albuquerque, NM). MAb reactivities against each mutant clone were calculated relative to wild-type siglec-7 protein reactivity by subtracting the signal from mock-transfected controls, and normalizing to the signal from wild-type siglec-7-transfected controls.

[0525] Mutated residues within critical clones were identified as critical to the MAb epitope if they did not support reactivity of the test MAb but did support reactivity of commercially available reference MAbs 6-434 or S7.7 (Biolegend, Cat#:339202, 347702), or additional anti-siglec-7 MAbs. This counter-screen strategy facilitated the exclusion of siglec-7 mutants that were locally misfolded or that had an expression defect.

[0526] **FIG. 1F** depicts the mean binding reactivities and ranges for all critical residues identified in the screens. The range was the difference between the duplicate experimental binding values. Primary critical residues were identified as residues where mutations were negative for test antibody binding (<30% of binding to WT) but positive for the control antibody (>80% WT). **FIG. 1G** depicts a crystal structure model of the IgV domain of Siglec-7 (PDB ID 1O7V; Alphey et al., 2003) indicating the critical residues as red spheres and secondary residues as pink spheres for each antibody tested. The amino acid residues critical for antibody binding, as well as the secondary residues, are listed in **Table 7B**.

Table 7B: Residues involved in anti-Siglec-7 antibody binding

Antibody	Critical Siglec-7 residues	Secondary Siglec-7 residues
4E3 Fab	I_{72}; W_{74}; N_{81}; and R_{124}	
10B5 MAb	K_{104}	
10B5 Fab	R_{45}; S_{47}; T_{103}; K_{104}; and T_{107}	M_{30}; Q_{31}; V_{44}; F_{48}; and Y_{50}

[0527] As indicated in **Table 7B**, the critical Siglec-7 residues involved in binding by antibody 4E3 corresponded to amino acid residues I_{72}, W_{74}, N_{81}, and R_{124} of SEQ ID NO: 1. The critical Siglec-7 residues involved in binding by antibody 10B5 corresponded to amino acid residues R_{45}, S_{47}, T_{103}, K_{104}, and T_{107} of SEQ ID NO: 1; and the secondary residues involved in binding by antibody 10B5 corresponded to amino acid residues M_{30}, Q_{31}, V_{44}, F_{48}, and Y_{50} of SEQ ID NO: 1.

Example 3: Siglec-7 antibody-induced decrease in cell surface levels of Siglec-7 *in vitro* and *in vivo*

In vitro expression of Siglec-7

[0528] The purpose of the following Example was to test whether anti-Siglec-7 and/or Siglec-7 bispecific antibodies reduce the cell surface level of Siglec-7 on monocytes, macrophages, neutrophils, NK cells, dendritic cells, T cells, and/or microglia.

[0529] The ability of anti-Siglec-7 antibodies to reduce cell surface levels of Siglec-7 on the histiocytic lymphoma cell line U937, as well as human primary monocytes, human primary dendritic cells (DC) derived from peripheral blood monocytes, human primary macrophages and NK cells derived from peripheral blood monocytes, and human primary microglia was evaluated. Cell samples were plated in 24-well plates at 200,000 cells per ml or in 6-well dishes at 500,000 cells in 2 ml of RPMI supplemented with 10% Hyclone FBS, 2 mM glutamine, pen/strep, and non-essential amino acids. Siglec-7 antibodies or control isotypes were added at 1.0 µg/ml, and incubated for 24 hours at 37ºC with 5% CO_2.

[0530] To assess receptor dynamics, antibodies were allowed to bind cells for one hour, washed out and surface levels of Siglec-7 were determined 24 and 48 hours later.

[0531] Cell surface receptor expression was detected by FACS analysis. Cells were incubated with anti-Siglec-7-PE clone 6-434 (Biolegend), as well as a control surface marker (U937: Siglec-5, human monocytes: CD14, human dendritic cells: CD11c, human macrophages: CD11b, human NK cells: CD56) for 30 minutes on ice in the dark. Cells were washed 2X in FACS buffer (PBS +2% FBS, 2mM EDTA) and flow cytometry was performed on a BD FACS Canto. Data was analyzed using TreeStar FlowJo software. Data was calculated as a percent of receptor expression in the absence of antibody using MFI values for the respective fluorophores.

[0532] **Table 8A and 8B** depict the results of Siglec-7 cell surface levels from human cells. In **Table 8A and 8B**, "No Ab" refers to cells that were that were not treated with an antibody; "mIgG1," "mIgG2a," and "mIgG2b" refer to isotype control antibodies; and "RDS7" refers commercially available anti-Siglec-7 antibody Mab1138 (R&D Systems; Cat. No. MAB 1138).

Table 8A: Siglec-7 antibodies reduce cell surface level of Siglec-7 in a human cell line and in human primary cells

	Percent Siglec-7 Surface Expression					
	U937 cells		Monocytes		DCs	
Ab	%Siglec-7	% control	%Siglec-7	%control	%Siglec-7	% control
1A12	87.3	136.8	39.9	93.4	100.5	95.7
1E8	114.0	134.2	36.7	94.1	23.0	97.0
2G1	121.4	129.5	139.5	98.6	110.4	102.2
2G4	84.6	136.2	29.3	95.1	98.1	96.2
3E11	82.4	128.1	23.9	89.0	19.9	97.6
4A1	89.5	131.9	39.8	90.4	99.6	95.1
4D7	84.7	119.0	33.9	83.5	73.3	106.5
4E3	30.8	94.0	15.1	87.8	11.2	96.9
7A3	76.3	136.3	23.7	69.7	11.0	119.3
7E11	75.2	127.1	8.1	77.4	19.3	103.9
7F12	86.3	124.4	39.0	88.4	96.9	91.5
10B5	36.5	122.6	6.7	75.3	16.8	112.1
10G8	83.8	133.4	30.9	70.1	10.5	121.4
No Ab	100	100	100	100	100	100
mIgG1	101.8	100.4	96.2	93.9	100.8	97.7
mIgG2a	99.8	100.4	99.4	93.3	100.5	97.4

	Percent Siglec-7 Surface Expression					
	U937 cells		Monocytes		DCs	
Ab	%Siglec-7	% control	%Siglec-7	%control	%Siglec-7	% control
mIgG2b	99.3	99.0	96.2	94.9	100.1	95.1
RDS7	98.2	96.0	99.6	81.3	96.7	105.9

Table 8B: Siglec-7 antibodies reduce cell surface level of Siglec-7 in human primary cells

	Percent Siglec-7 Surface Expression					
	Macrophages		NK cells		Microglia	
Ab	%Siglec-7	% control	%Siglec-7	%control	%Siglec-7	% control
1A12	13.4	103.6	136.5	99.6	28.6	88.6
1E8	9.1	88.8	143.6	98.5	41.3	71.1
2G1	95.7	92.3	113.9	98.8	106.2	82.6
2G4	14.1	96.2	126.1	101.5	23.0	81.9
3E11	7.4	85.7	107.9	101.6	34.2	82.1
4A1	13.1	96.0	132.4	98.8	26.3	85.8
4D7	24.1	74.8	87.6	101.2	44.3	84.1
4E3	4.2	78.3	31.2	100.8	20.9	92.7
7A3	8.3	85.0	77.1	102.1	ND	ND
7E11	5.7	83.9	50.7	101.6	11.5	74.1
7F12	13.1	93.0	124.1	98.5	28.1	78.8
10B5	3.2	84.0	25.5	101.9	5.5	72.1
10G8	9.2	84.0	74.7	103.7	ND	ND
No Ab	100	100	100	100	100	100
mIgG1	100.0	90.9	99.6	98.4	88.7	76.8
mIgG2a	100.0	96.0	100.9	99.2	84.2	85.2
mIgG2b	100.3	89.9	101.3	99.6	88.8	83.6
RDS7	98.7	90.4	102.6	100.4	80.2	74.6

[0533] As shown in **Table 8A and 8B**, a majority of the antibodies were able to decrease cell surface levels of Siglec-7 on multiple types of human cells. However, using a threshold value of 80% or higher cell surface expression levels of Siglec-7, it was found that antibody 2G1 does not decrease cell surface levels of Siglec-7 on any of the tested human cells.

[0534] **FIG. 7A-7F** further demonstrates that a majority of the antibodies were able to decrease cell surface levels of Siglec-7 on U937 cells (**FIG. 7A**), human primary monocytes (**FIG. 7B**), human primary dendritic cells (**FIG. 7C**), human primary macrophages (**FIG. 7D**), human primary NK cells (**FIG. 7E**), and human primary microglia (**FIG. 7F**).

[0535] Additionally, *in vitro* surface Siglec-7 downregulation studies were performed in which Siglec-7 antibodies 4E3 and 10B5 were titrated 2-fold for a 12-point curve. Primary human dendritic cells differentiated with GM-CSF and IL-4 from isolated human monocytes were harvested Day 5, and plated at 100,000 cells per well in a round bottom 96 well non-TC treated plate. Siglec-7 antibodies were titrated 2-fold for a 12-point curve with a concentration range of 6.67-0.00325 nM to assess binding and calculate half-maximal effective concentration (EC_{50}) values. Antibodies were serially diluted and incubated with cells at 37°C overnight in RPMI media with 10% FBS (Hyclone)

and normal supplements. The following day, cells were pelleted and resuspended with a non-competing FACS detection Siglec-7 APC-conjugated antibody clone 6-434 (Biolegend) and control receptor CD11c PE-Cy7 antibody (BD Biosciences) in PBS with 1% BSA and 1mM EDTA. Cells were incubated with detection antibodies for 30 minutes on ice, then washed 3 times in buffer before analyzing on a BD FACS Canto. Data were analyzed with FlowJo Software (TreeStar).

[0536] As shown in **FIG. 7M**, anti-Siglec-7 antibodies 4E3 and 10B5 were capable of downregulating cell surface expression of Siglec-7 on primary human dendritic cells. Cell surface expression of the CD11c control receptor was not affected by treatment with either Siglec-7 antibody (**FIG. 7N**). **Table 8C** summarizes the results of cell surface downregulation of Siglec-7 by the indicated antibodies on primary human dendritic cells isolated from four different donors.

Table 8C: Siglec-7 cell surface downregulation on primary human dendritic cells by two Siglec-7 antibodies

Donor #	Antibody: 4E3		Antibody: 10B5	
	EC_{50} value (pM)	95% CI (pM)	EC_{50} value (pM)	95% CI (pM)
365	33.56	18.58 to 48.53	71.33	54.41 to 88.24
364	49.94	23.09 to 76.80	102.5	67.33 to 137.6
362	114.1	78.37 to 149.8	143.7	113.2 to 174.3
363	94.96	27.75 to 162.2	350.4	220.2 to 480.5

[0537] The *in vitro* studies in which antibodies 4E3 and 10B5 were titrated 2-fold for a 12-point curve demonstrated robust Siglec-7 receptor downregulation with mouse Siglec-7 antibodies, while the CD11c control receptor was not affected upon antibody treatment. These data showed that mouse Siglec-7 antibody 4E3 downregulated 50% of the Siglec-7 receptor on human primary myeloid cells taken from donor 363 with an EC_{50} of 94.96pM (with a 95% confidence interval of 27.75 to 162.2pM), and mouse Siglec-7 antibody 10B5 downregulated 50% of Siglec-7 receptor on human primary myeloid cells taken from the same donor with an EC_{50} of 350.4 pM (with a 95% confidence interval of 220.2 to 480.5pM).

Effect of Siglec-7 antibody on expression of TREM2

[0538] To test the ability of Siglec-7 antibodies that decrease cell surface levels of Siglec-7 to modulate TREM2 expression, human monocyte-derived dendritic cells differentiated with GM-CSF and IL-4 were harvested at day 6, and were plated at 500,000 cells per well in a 24 well dish overnight with 1.0 µg/ml anti-Silglec-7 antibody 10B5, isotype control antibody, or left untreated. Cell surface receptor expression for CD11c, TREM2, and Siglec-7 were detected the following day by FACS analysis. Cells were incubated with biotinylated anti-Siglec-7 clone 10A9 for 20 minutes on ice. After one wash, cells were incubated in FACS buffer with APC conjugated Strepavidin (BD Biosciences, 1:150 dilution), anti-Siglec-7-PE clone 6-434 (Biolegend), and anti-CD11c-PECy7 (BD Biosciences), for 30 minutes on ice in the dark. Cells were washed 3X in FACS buffer (PBS + 2%

FBS, 2mM EDTA) and flow cytometry was performed on a BD FACS Canto. Data was analyzed using TreeStar FlowJo software. Data was calculated as a percent of receptor expression in the absence of antibody using MFI values for the respective fluorophores.

[0539] As shown in **FIG. 7G and 7H**, anti-Siglec-7 antibody 10B5, which was able to able to decrease cell surface levels of Siglec-7, did not affect TREM2 expression.

[0540] Loss-of-function mutations in TREM2 have been associated with severe neurodegeneration, including Nasu-Hakola disease, frontotemporal dementia, and Alzheimer's disease. It is believed that modulation of ITIM-containing Siglec receptors may affect TREM2 expression. Therefore, anti-SIglec-7 antibodies that do not decrease TREM2 expression on human immune cells may be key to positive therapeutic outcomes. The results in **FIG. 7G and 7H** demonstrate that anti-Siglec-7 antibody clone 10B5, which robustly decreases cell surface levels Siglec-7, does not reduce TREM2 expression on human dendritic cells.

In vivo expression of Siglec-7

[0541] To test the ability of Siglec-7 antibodies to reduce cell surface level of Siglec-7 *in vivo*, humanized NOG mice (hu-NOG) were utilized. The genetic background of Hu-NOG mice is NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Sug}/JicTac and engrafted with human CD34^{+} hematopoietic stem cells. Female Hu-NOG mice were purchased from Taconic and utilized 15 weeks after engraftment with human cells. Mice received an intraperitoneal injection of 40 mg/kg anti-Siglec-7 antibodies 4E3 or 10B5, or an isotype control mouse IgG1 antibody (clone MOPC-21) at day 0. At day 1, blood samples were drawn from mice into heparin and processed for FACS analysis. Briefly, blood samples were first incubated for 5 minutes in ice-cold ACK lysis buffer to lyse red blood cells and then washed extensively with cold PBS. This procedure was repeated twice. Cells were then incubated in FACS buffer (PBS +2% FBS, 2mM EDTA) in the presence of anti-human-CD45-Pe-Cy7, anti-mouse-CD45-APC-Cy7, anti- human-CD3-PerCP-Cy5.5, anti-human-CD14-FITC, anti-human-CD11c-PB, anti-Siglec-7-APC, anti-CD33-PE, and a viability die (Life Technologies, Cat# L34957) for 30 min. on ice in the presence of Fc block solution, then washed twice with cold FACS buffer. 4% PFA-fixed samples were then acquired. Data were acquired on a BD FACS CANTO™ II cytometer (Becton Dickinson) and analyzed with FlowJo software by TreeStar. The level of expression of Siglec 7 and CD33 was determined in an hCD45+, hCD14+ cell population at day -7, 1, 7, and 14 post antibody treatment.

[0542] As shown in **FIG. 7I-7L**, treatment with the anti-Siglec-7 antibodies 4E3 and 10B5 was able to decrease cell surface levels of Siglec-7 in cells of peripheral blood of the treated hu-NOG mice, when compared to isotype control MOPC21 antibody treatment. Siglec-7 expression was decreased by ~60% as early as 1 day post antibody treatment with antibody 4E3, and ~80% as early as 1 day post antibody treatment with antibody 10B5 (**FIG. 7J**). As a comparison, cell surface

expression of the unrelated surface receptor CD33 did not decrease significantly after anti-Siglec-7 antibody treatment, as compared to cell surface levels of CD33 after treatment with mIgG1 control antibody (**FIG. 7K**).

[0543] These results demonstrate that when utilizing humanized mice, Siglec-7 antibodies engage the Siglec-7 *in vivo* and functionally downregulate Siglec-7 on human immune cells. The results further demonstrate that Siglec-7 antibodies 4E3 and 10B5, when injected into humanized mice, engage Siglec-7 on peripheral monocytes circulating in the blood of the mice. Antibody engagement of Siglec-7 leads to receptor downregulation specifically for Siglec-7 and not a control receptor, CD33. After a single injection of 10B5 antibody, 80% of Siglec-7 expressed on human monocytes is downregulated 1 day after treatment. Receptor loss is sustained 7 and 14 days after treatment with a single treatment for both 4E3 and 10B5 antibodies.

Example 4: Siglec-7 antibodies compete with Siglec-7 ligand for binding to human Siglec-7

[0544] The purpose of the following Example was to test whether anti-Siglec-7 antibodies recognize the ligand-binding site on Siglec-7 and compete with ligand binding on Siglec-7 receptors.

[0545] To determine which antibodies compete with ligand binding to Siglec-7, a red blood cell (RBC) solid adhesion assay was carried out in accordance with standard protocols (Kelm et al., *Current Biology*, 1994). Red blood cells are highly decorated with glycoproteins containing sialic acids; therefore, the ability of an antibody to block RBC binding to immobilized Siglec-7 can be used to determine ligand interference. Briefly, 5 µg/ml Siglec-7-Fc was coated overnight at RT in 96 well Immunolon plates, then washed with PBS, blocked for one hour with binding buffer (PBS containing %0.25 BSA 1mM $CaCl_2$). Siglec-7 antibodies (0.5 µg/ml or 1.0 µg/ml) were bound for one hour at RT with gentle rocking. After removal of unbound antibody, red blood cells were added to each well at a concentration of 3.0 x10^6 cells per ml and incubated at RT for one hour. Unbound RBCs were then carefully washed off 3X with PBS, and water was added to each well for hypotonic lysis of bound RBCs. The plate was transferred to -80ºC for 10 minutes, followed by 37ºC for 15 minutes. Bound RBCs were detected by peroxidase activity, followed by 2N sulfuric acid to stop the reaction. Signal was detected at 450nM. Data was calculated as a percent of RBC binding to plate bound Siglec-7-Fc in the absence of antibody.

[0546] The results of the ligand competition assay are depicted in **Table 9**. In **Table 9**, "mIgG1," and "mIgG2b" refer to isotype control antibodies; "RDS7" refers commercially available anti-Siglec-7 antibody Mab1138 (R&D Systems; Cat. No. MAB 1138); and "RBC alone" refers to RBC that were not incubated with an antibody.

Table 9: Siglec-7 antibodies compete with ligand binding

Antibody	Percent RBC Binding to Siglec-7
1A12	16.5
1E8	16.4

Antibody	Percent RBC Binding to Siglec-7
2G1	14.5
2G4	11.6
3E11	26.8
4A1	11.2
4D7	96.5
4E3.	20.2
7A3	89.5
7E11	89.3
7F12	7.9
10B5	88.4
10G8	111.4
mIgG1	106.9
mIgG2b	101.6
RDS7	97.1
RBC alone	100.0

[0547] As shown in **Table 9**, antibodies 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4E3, and 7F12 were able to block RBC binding to Siglec-7, thus indicating competitive binding of the antibodies to the ligand-binding site on Siglec-7, and their ability to inhibit the interaction between Siglec-7 and one or more Siglec-7 ligands (i.e., to block ligand binding to Siglec-7). However, using a threshold value of 80% or higher of RBC binding to Siglec-7, it was found that antibodies 4D7, 7A3, 7E11, 10B5, and 10G8 do not inhibit the interaction between Siglec-7 and one or more Siglec-7 ligands.

[0548] **FIG. 8** further demonstrates that antibodies 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4E3, and 7F12 are able to block RBC binding to Siglec-7, thus indicating competitive binding of the antibodies to the ligand-binding site on Siglec-7, and their ability to inhibit the interaction between Siglec-7 and one or more Siglec-7 ligands (i.e., to block ligand binding to Siglec-7).

Example 5: Summary of Siglec-7 antibody functional studies.

[0549] **Table 10** summarizes results of the cell surface expression and ligand binding studies described in Examples 3 and 4 above. As indicated in **Table 10**, there were three general classes of Siglec-7 antibodies. One class of antibodies decreases cell surface level of Siglec-7 without inhibiting the interaction between Siglec-7 and one or more Siglec-7 ligands. A second class of antibodies both decreases cell surface level of Siglec-7and inhibits the interaction between Siglec-7 and one or more Siglec-7 ligands. The third class of antibodies inhibits the interaction between Siglec-7 and one or more Siglec-7 ligands without decreasing cell surface level of Siglec-7.

[0550] Antibodies in the class of antibodies that decreases cell surface level of Siglec-7 without inhibiting the interaction between Siglec-7 and one or more Siglec-7 ligands include: 4D7, 7A3, 7E11, 10B5, and 10G8.

[0551] Antibodies in the class of antibodies that decreases cell surface level of Siglec-7 and inhibits the interaction between Siglec-7 and one or more Siglec-7 ligands include: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4E3, and 7F12.

[0552] Antibodies in the class of antibodies that inhibits the interaction between Siglec-7 and one or more Siglec-7 ligands without decreasing cell surface level of Siglec-7 include: 2G1.

Table 10: Siglec-7 antibody functional studies

Antibody	Decreases cell surface Siglec-7	Inhibits Siglec-7 ligand binding
1A12	X	X
1E8	X	X
2G1		X
2G4	X	X
3E11	X	X
4A1	X	X
4D7	X	
4E3	X	X
7A3	X	
7E11	X	
7F12	X	X
10B5	X	
10G8	X	

Example 6: Ligand binding to Siglec-7 on dendritic cells inhibits T cell proliferation and phagocytosis

[0553] Human dendritic cells (DCs) were differentiated from peripheral blood monocytes with GM-CSF and IL-4 and cultured for 5 days. Immature (suspension) DCs were harvested and plated at a density of 200,000 cells per ml in a 12 well dish. DCs were activated with a cytokine cocktail of TNFa (50 µg/ml), IL-1b (50 µg/ml), IL-6 (150 ng/ml), and Prostaglandin E2 (1 µg/ml) for 24 hours. Dendritic cell maturation was determined by flow cytometry with commercially available antibodies for LIN, CD11c, HLA-DR, CD86, and CD83 (BD Biosciences). Immediately prior to co-culture with allogenic isolated T cells, activated DCs were sialidase treated, or left untreated, for 2 hours at 37ºC with 100 mU/ml neuraminidase from *Vibrio cholera* in serum free media. Enzymatic activity was quenched by addition of serum-containing media, cells pelleted and resuspended in complete media. Sialidased activated, untreated activated, or unactivated DCs were co-cultured at a ratio of 1:10 with allogenic CFSE labeled T cells. CD3/CD28 Dynal beads were added to T cells alone as a positive control. Five days later T cell proliferation was measured by CFSE dilution on a BD FACS Canto.

[0554] **FIG. 9 and 10** show that sialic acids on dendritic cells restrict T cell proliferation during mixed lymphocyte reaction (MLR). **FIG. 10** shows that DCs that normally express inhibitory ligands induce low levels of T cell proliferation (left panel), while the removal of the inhibitory ligands on DCs increases T cell proliferation (right panel).

[0555] As shown in **FIG. 9 and 10**, enzymatic removal of sialic acids from activated DCs increased T cell proliferation when compared to untreated activated DCs. These results indicate that sialic acids present on DCs act on T cells in a suppressive manner to restrict T cell proliferation when co-cultured with allogenic DCs. These results indicate that antibodies that block Siglec-7 on T cells or dendritic cells enhance T cell and/or dendritic cell functionality. CD3/CD28 Dynal beads were used as a positive control. Furthermore, these results indicate that blocking sialic acid interactions with DCs or any other cellular or biological source may increase T cell function.

Example 7: Inflammatory conditions induce Siglec-7 sialic acid ligand expression in myeloid cells

[0556] Human dendritic cells (DCs) were differentiated from peripheral blood monocytes with GM-CSF and IL-4 and cultured for 5 days. Immature human DCs were harvested on day 5 and co-cultured with sterile-filtered supernatant from B16, Lewis lung, MC38 tumor supernatant or 10 ng/ml LPS. 24 hours later Siglec-7 expression was determined by flow cytometry with a directly conjugated Siglec-7-PE antibody. Sialic acid ligand expression was assessed by incubation for 30 minutes on ice with 50 µg/ml soluble Siglec-7 fused to human IgG1-Fc, IgG1-Fc alone was used a negative control in the presence of human Fc block. Binding of the soluble receptor to sialic acids on cells was detected after a wash step and incubation for 30 minutes on ice with anti-human secondary conjugated to PE. Flow cytometry analysis was performed on a BD FACS Canto.

[0557] To elicit primary macrophages, human monocytes from peripheral human blood samples are isolated and either used directly or differentiated into macrophages with 50 µg/ml M-CSF for 5 days. In order to determine the role of Siglec-7 in inflammatory cytokine production, human macrophages are cultured with various inflammatory mediators, and cytokine levels are measured in the culture supernatants. To generate human macrophages, monocytes from peripheral human blood samples are isolated and either used directly or differentiated into macrophages with 50 µg/ml M-CSF or dendritic cells with 100 µg/ml GM-CSF and 100 µg/ml IL-4 for 5 days. Cells are cultured for 5 days, and adherent cells were detached with 1mM EDTA in PBS. Cells are plated on 96-well plates at 10^5cells/well and allowed to adhere for 4 h at 37°C. Cells are then stimulated with TLR agonists LPS (*Salmonella abortus equi*) or zymosan (*Saccharomyces cerevisiae*) at concentrations ranging from 0.01-100ng/ml (LPS) or 0.01-100 µg/ml (zymosan). Alternatively, macrophages are cultured in the presence of 10 ng/ml of the cytokine IL-4 or 50 ng/ml of IFN-g. Cell culture supernatant are collected 24 or 48 hours after stimulation and the levels of TNFa, IL-6, IL-10, and MCP-1 cytokines are measured by using Cytometric Bead Array Inflammation Kit (BD) according to manufacturer's protocol. Macrophages stimulated with the inflammatory mediators LPS or zymosan are expected to secrete more inflammatory cytokines TNFa, IL-6, IL-10, and MCP-1 when treated with Siglec-7 antagonistic antibodies or with enzymes that remove the inhibitory glycol ligands.

[0558] **FIG. 11A and 11B** show that Siglec-7 expression is maintained on human dendritic cells after exposure to tumor supernatant. **FIG. 11C and 11D** show that tumor supernatant increases expression of sialic acid (a Siglec-7 ligand). **FIG. 11E and 11F** show that Siglec-7 expression is maintained on human dendritic cells during LPS-induced inflammation. **FIG. 11G and 11H** show that LPS-induced inflammation increases expression of sialic acid (a Siglec-7 ligand).

[0559] These results indicate that inflammatory conditions and tumor environment lead to upregulation of both Siglec-7 and sialic acid ligands. The results also demonstrate that increased Siglec-7 function can immunosuppress human primary dendritic cells. These results indicate that inhibiting Siglec-7 with downregulating or blocking antibodies may relieve immunosuppressed myeloid-derived or tumor-associated myeloid cells and restore immune function. These results further indicate that antibodies that block Siglec-7 on myeloid cells enhance myeloid cell functionality.

Example 8: Increased *E.coli* phagocytosis by dendritic cells with sialidase treatment

[0560] The purpose of the following Example was to test whether antagonistic anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibodies induce phagocytosis of apoptotic neurons, nerve tissue debris, non-nerve tissue debris, bacteria, other foreign bodies, and disease-causing proteins, such as A beta peptide, alpha synuclain protein, Tau protein, TDP-43 protein, prion protein, huntingtin protein, RAN, translation products antigene, including the DiPeptide Repeats,(DPRs peptides) composed of glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), proline-alanine (PA), or proline-arginine (PR) in cells from the myeloid lineage, such as monocytes, dendritic cells macrophages and microglia. The bispecific antibodies may be antibodies that recognize the Siglec-7 antigen and a second antigen that includes, without limitation, CD3, A beta peptide, antigen or an alpha synuclain protein antigene or, Tau protein antigene or, TDP-43 protein antigene or, prion protein antigene or, huntingtin protein antigene, or RAN, translation Products antigene, including the DiPeptide Repeats,(DPRs peptides) composed of glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), proline-alanine (PA), or proline-arginine (PR).

[0561] Monocytes from peripheral human blood samples were isolated using the RosetteSep™ monocyte isolation antibody cocktail (StemCell Technologies), and differentiated into dendritic cells with GM-CSF and IL-4 (PeproTech) and cultured for 5 days. Cells were plated on culture dishes in RPMI medium (Invitrogen) containing 10% fetal calf serum (Hyclone) and cultured at 37°C in 5% CO_2. Non-adherent cells were collected and used for phagocytosis experiments.

[0562] To conduct bacterial phagocytosis assay, dendritic cells were harvested and plated in 96 well flat bottom plates without cytokine for 2 hours. pHrodo-labeled *E. coli* BioParticles were resuspended according to manufacturer's protocol and were treated with 0.2 U/ml or 0.4 U/ml sialidase from *Vibro cholera*, or PBS alone for 2.5 hours at 37°C. BioParticles were washed,

resuspended in RPMI and added 20 µg/well. Dendritic cells and *E. coli* cells were mixed, pelleted, and incubated at 37°C for 30 minutes. Cytochalasin D was added at 10 µM to control wells. Immediately prior to FACS analysis, cells were transferred to ice and washed 2X in FACS buffer at 4°C. pHrodo-labeled *E.coli* phagocytosis was detected in the PE channel by flow cytometry on a BD FACS Canto.

[0563] **FIG. 12** shows that sialidase treatment increased dendritic cell-mediated phagocytosis of *E. coli*. These results indicate that antagonistic anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibodies that, for example, decrease cell surface expression of Siglec-7 and/or inhibit the binding of one or more Siglec-7 ligands to Siglec-7 can also be used to induce or otherwise increase phagocytosis.

Example 9: Increased expression of Siglec-7 ligand in brain sections of Alzheimer's disease patients

[0564] Sialic acid ligand expression was detected in the brains of normal and Alzheimer's disease (AD) patients by immunohistochemistry with biotinylated Siglec-7-Fc (R&D). The Siglec-7-Fc protein was biotinylated with the EZ-Link Sulfo-NHS-Biotin (Thermo Scientific) according to manufacturer's instructions. The IHC procedure, with the exception of the overnight incubation, was performed on a shaker. Samples were incubated for 15 minutes in 10% MeOH, 3% H_2O_2 in PBS, followed by 3 washes in PBS with 4% serum. Next, samples were incubated for 30 minutes in 0.2% triton-X, 4% serum, 0.019% L-lysine in PBS, followed by an hour in primary antibody then overnight at 4C in PBS with 4% serum. The next day samples were placed on a shaker for one hour followed by 3 washes, then samples were incubated for one hour in ABC buffer and washed 3 times. Samples were developed with a Vector DAB peroxidase kit, washed 3 times and dehydrated and imaged with a Nikon 90i microscope with color camera, magnification of 200X. The quantification was performed using Nikon Elements BR image analysis software.

[0565] **FIG. 13A and 13B** show that sialic acid Siglec-7 ligands are upregulated in brain sections from two AD patients (Donor 1 and Donor 2). Data from 5 AD and 5 non-AD human brains show a statistically significant increase in expression of Siglec-7 sialic acid ligands by one way ANOVA, p=0.0159 (**FIG. 13B**).

[0566] These results indicate that antibodies that remove Siglec-7 from the cell surface or block increased ligand interactions may relieve inhibitory Siglec-7-dependent signaling on microglia or other myeloid cells in the brain and restore normal functions to these cells, with beneficial effects for Alzheimer's disease.

Example 10: Increased expression of Siglec-7 ligand in cancer cells

In vitro studies

[0567] Mouse melanoma (B16), Lewis lung tumor cells, or colon carcinoma (MC38) were cultured and incubated with 50ug/ml Siglec-7-Fc or an IgG1-Fc control on ice for 30 minutes to

determine the level of Siglec-7 binding sialic acid ligand expression on these cell types. Binding interactions were performed in PBS with 0.25% BSA, 1mM $CaCl_2$. To detect Siglec-7 receptor binding, a goat anti-human Fc-PE secondary antibody was incubated for 30 minutes on ice after washing off unbound Siglec-7-Fc. Cells were washed three times in Binding Buffer and analyzed by flow cytometry on a BD FACS Canto.

[0568] **FIG. 14** shows that the expression of an inhibitory Siglec-7 ligand is increased at least 20-fold over background in melanoma cells, lung tumor cells, and colon cancer cells. Without wishing to be bound by theory, identification of inhibitory sialic acid ligand expression on these tumor cells indicates a contributing mechanism by which cancer cells evade immune recognition and clearance. Sialic acid ligands on tumor cells can mediate immunosuppressive interactions via Siglec-7 expressed on myeloid and lymphoid immune cells. These results indicate that antibodies that remove Siglec-7 from the cell surface or block increased ligand interactions may relieve inhibitory effects of tumors on the immune system and enhance cancer therapy.

In vivo studies

[0569] Four week-old female Taconic NOG mice were myeloablated approximately 24hours before engraftment with human fetal liver $CD34^+$ cells (100,000cells/mouse) by intravenous injection. Reconstitution of immune cells was monitored by flow cytometry of peripheral blood. Twelve weeks after engraftment, the Champions tumorgraft melanoma model was implanted subcutaneously. Approximately 8-10 weeks later, when the tumor reached a size of 150-200mm^3, blood, spleen and tumors were harvested and processed for analysis by flow cytometry on a BD FACS Canto. Flow cytometric analysis was performed to determine the expression of Siglec-7 in different compartments of the human ($hCD45^+$) immune system. Specifically, expression was analyzed in $CD3^+$ T cells, $CD14^+$ monocyte/macrophages and other CD3-CD14- human immune cells cells. Data were analyzed with FlowJo software version 10.0.6 by TreeStar.

[0570] As depicted in **FIG. 15**, the results indicated that Siglec-7 is expressed in peripheral blood, spleen, and tumor infiltrating immune cells in transplanted melanoma tumors of humanized mice. Importantly, Siglec-7 is significantly upregulated in human immune cells infiltrating melanoma tumors. This demonstrates the relevance of this mouse model to assessing the therapeutic ability of S Siglec-7 antibodies.

Example 11: Reduction of the anti-inflammatory cytokine IL-10 in myeloid cells by antagonistic and/or bispecific Siglec-7 antibodies

[0571] The purpose of this Example is to test whether bone marrow-derived myeloid cells show a decrease in the anti-inflammatory cytokine IL-10 and other anti-inflammatory mediators following treatment with antagonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies and stimulation with 100 ng/ml LPS (Sigma), by co-culturing with apoptotic cells, or by a similar stimulus.

[0572] Isolation of human myeloid precursor cells is performed as previously described. Medium is changed after 5 d and cells are cultured for an additional 10-11 d. Supernatant is collected after 24 h, and the level of IL-10 and other anti-inflammatory cytokines released from the cells is determined by IL-10 ELISA according to manufacturer's instructions (R&D Systems) (JEM (2005), 201; 647–657; and PLoS Medicine (2004), 4 | Issue 4 | e124).

Example 12: Induction of phagocytosis in cells from the myeloid lineage by antagonistic and/or bispecific Siglec-7 antibodies

[0573] The purpose of this Example is to test whether antagonistic anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibodies induce phagocytosis of apoptotic neurons, nerve tissue debris, non-nerve tissue debris, bacteria, other foreign bodies, and disease-causing proteins, such as A beta peptide, alpha synuclain protein, Tau protein, TDP-43 protein, prion protein, huntingtin protein, RAN, translation products antigene, including the DiPeptide Repeats,(DPRs peptides) composed of glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), proline-alanine (PA), or proline-arginine (PR) in cells from the myeloid lineage, such as monocytes, Dendritic cells macrophages and microglia. The bispecific antibodies may be antibodies that recognize the Siglec-7 antigen and a second antigen that includes, without limitation, A beta peptide, antigen or an alpha synuclain protein antigene or, Tau protein antigene or, TDP-43 protein antigene or, prion protein antigene or, huntingtin protein antigene, or RAN, translation Products antigene, including the DiPeptide Repeats,(DPRs peptides) composed of glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), proline-alanine (PA), or proline-arginine (PR).

[0574] Monocytes from peripheral human blood samples are isolated using the RosetteSep monocyte isolation antibody cocktail (StemCell Technologies) and differentiated into macrophages, neutrophils, and NK cells with 50 µg/ml M-CSF (PeproTech) for 5 days. Cells are plated on culture dishes in RPMI medium (Invitrogen) containing 10% fetal calf serum (Hyclone) and cultured at 37°C in 5% CO_2. Adherent cells are collected by gentle scraping and used for phagocytosis experiments.

[0575] Human microglial cells are prepared from peripheral blood monocytes by culture in serum-free RPMI with 1% Pen/Strep, 10 ng/ml GM-CSF, 10 ng/ml M-CSF, 10 ng/ml beta-NGF, 100 ng/ml CCL-2, 100ng/ml IL-34 according to protocols described in Etemad et al., *JI* (2012), and Ohgidani et al., *Scientific Reports* (2014). Cells were harvested at day 7-10 when ramified morphology appeared.

[0576] To conduct phagocytosis assays microglia, macrophages, neutrophils, NK cells or dendritic cells are cultured with apoptotic neurons, nerve tissue debris, non-nerve tissue debris, bacteria, other foreign bodies, and disease-causing proteins. Neurons are cultured for 5-10 d, and okadaic acid is then added at the final concentration of 30 nM for 3 h to induce apoptosis. Neuronal cell membranes are labeled with CellTracker CM-DiI membrane dye (Molecular Probes). After incubation, apoptotic neurons or other targets of phagocytosis are washed two times and added to the

transduced microglial culture at an effector/target ratio of 1:20. At 1 and 24 h after addition of apoptotic neurons, the number of microglia having phagocytosed neuronal cell membranes is counted under a confocal fluorescence microscope (Leica). Apoptotic cells are counted in three different areas at a magnification of 60. The amount of phagocytosis is confirmed by flow cytometry. Moreover, 24, 48, or 72 h after the addition of apoptotic neurons, cells are collected and used for RT-PCR of cytokines.

[0577] To conduct microsphere bead or bacterial phagocytosis assay, microglia, macrophages, neutrophils, NK cells, or dendritic cells are treated with anti-Siglec-7 agonistic antibodies. Cells are harvested and plated in 96 well flat bottom plates without cytokine for 2 hours. pHrodo-labeled *E. coli* BioParticles are resuspended according to manufacturer's protocol and are treated with 0.2 U/ml or 0.4 U/ml sialidase from *Vibro cholera*, or PBS alone for 2.5 hours at 37C. BioParticles are washed, resuspended in RPMI and added 20ug/well. Cells and *E. coli* were mixed, pelleted, and incubated at 37C for 30 minutes. Cytochalasin D is added at 10uM to control wells. Immediately prior to FACS analysis, cells are transferred to ice and washed 2X in FACS buffer at 4C. The pHrodo-labeled *E.coli* phagocytosis is detected in the PE channel by flow cytometry on a BD FACS Canto.

[0578] After 24 h, 1.00 μm of red fluorescent microsphere beads (Fluoresbrite Polychromatic Red Mi-crospheres; Polysciences Inc.) are added for 1 h. Phagocytosis of microsphere beads by microglia is analyzed by fluorescence microscopy. Furthermore, microglia are collected from the culture plates and analyzed by flow cytometry. The percentage of microglia having phagocytosed beads is determined. Because phagocytosis varies from one experiment to the other, the relative change in phagocytosis is also determined. Data are shown as the relative change in phagocytosis between microglia cultured with agonistic antibodies and control antibody.

[0579] To conduct RT-PCR for analysis of inflammatory gene transcripts, microglia are transduced with a Siglec-7 vector or a GFP1 control vector. Cells are then cultured on dishes and treated with anti-Siglec-7 agonistic antibodies. After 24, 48, and 72 h, RNA is isolated from microglia using an RNeasy Mini Kit (QIAGEN). RNA is also collected from microglia that have been transduced with sh-Siglec-7 RNA, sh-control RNA, wSiglec-7, GFP2, mtDAP12-GFP, and GFP1 vector and co-cultured with apoptotic neurons for 48 h.

[0580] Reverse transcription of RNA is then performed. Quantitative RT-PCR by SYBR Green is performed on an ABI Prism 5700 Sequence Detection System (PerkinElmer). Amplification of GAPDH is used for sample normalization. The amplification protocol followed the GeneAmp 5700 Sequence Detection System Software (version 1.3). For detection of GAPDH, TNF-alpha, IL-1, NOS2, and TGF-beta transcripts, the following forward and reverse primers were used at final concentrations of 200 nM:

GAPDH forward primer: 5'-CTCCACTCACGGCAAATTCAA-3' (SEQ ID NO: 526), and GAPDH reverse primer: 5'-GATGACAAGCTTCCCATTCTCG-3' (SEQ ID NO: 527);

TNF-α forward primer: 5'-CCGTCAGCCGATTTGCTATCT-3' (SEQ ID NO: 528), and TNF-α reverse primer: 5'-ACGGCAGAGAGGAGGTTGACTT-3' (SEQ ID NO: 529);

IL-1α forward primer: 5'-ACAA- CAAAAAAGCCTCGTGCTG-3' (SEQ ID NO: 530), and IL-1α reverse primer: 5'-CCATTGAGGTGGAGAGCTTTCA-3' (SEQ ID NO: 531);

NOS2 forward primer: 5'-GGCAAACCCAAGGTCTACGTTC-3' (SEQ ID NO: 532), NOS2 reverse primer: 5'-TACCTCATTGGCCAGCTGCTT-3' (SEQ ID NO: 533); and

TGF-β1 forward primer: 5'-AGGACCTGGGTTGGAAGTGG-3' (SEQ ID NO: 534), and TGF-β1reverse primer: 5'-AGTTGGCATGGTAGCCCTTG-3' (SEQ ID NO: 535).

[0581] To conduct amyloid phagocytosis assay, HiLyteFluor™ 647 (Anaspec)-Abeta-(1–40) is resuspended in Tris/EDTA (pH 8.2) at 20 mM and then incubated in the dark for 3 d at 37°C to promote aggregation. Microglia, macrophages, neutrophils, NK cells, or dendritic cells are pretreated in low serum (0.5% FBS supplemented with insulin), LPS (50 ng/ml), IFNc (100 units/ml), and anti-Siglec-7 antagonistic antibodies for 24 h prior to the addition of aggregated fluorescently labeled a beta peptide. Amyloid phagocytosis and surface expression of Siglec-7 are determined by flow cytometric analysis 5 h post-addition of 100 nM aggregated HiLyteFluor^{TM} 647–Ab-(1–40) (ASN NEURO (2010) 2(3): 157-170). Phagocytosis of other disease-causing proteins is conducted in a similar manner.

Example 13: Induction of SYK and/or ERK activation by antagonistic Siglec-7 antibodies and/or bispecific antibodies

[0582] The purpose of this Example is to test whether agonistic anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibodies induce Syk and ERK activation.

[0583] Microglia, macrophages, neutrophils, NK cells, or dendritic cells are exposed to agonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies for 1 h. After stimulation, cells are lysed in reducing sample buffer for Western blot analysis. Phosphorylation of ERK and total amount of Syk and/or ERK are determined by immuno-detection with anti-phospho-Syk or ERK and anti- Syk or ERK antibodies, respectively (both from Cell Signaling Technology) by Western blot analysis (JEM (2005), 201, 647–657).

Example 14: Siglec-7 antibodies and/or bispecific antibodies induce Syk phosphorylation

[0584] Spleen tyrosine kinase (Syk) is an intracellular signaling molecule that functions downstream of Siglec-7 by phosphorylating several substrates, thereby facilitating the formation of a signaling complex leading to cellular activation and inflammatory processes. The ability of agonist Siglec-7 antibodies to induce Syk activation is determined by culturing human macrophages, human

neutrophils, human NK cells, and human primary dendritic cells and measuring the phosphorylation state of Syk protein in cell extracts.

[0585] Human primary dendritic cells are starved for 4 hours in 1% serum RPMI and then removed from tissue culture dishes with PBS-EDTA, washed with PBS, and counted. The cells are coated with full-length agonist Siglec-7 antibodies, or control antibodies for 15 minutes on ice. After washing with cold PBS, cells are incubated at 37°C for the indicated period of time in the presence of goat anti-human IgG. After stimulation, cells are lysed with lysis buffer (1% v/v NP-40%, 50 Mm Tris-HCl (pH 8.0), 150 mM NaCl, 1 mM EDTA, 1.5 mM $MgCl_2$, 10% glycerol, plus protease and phosphatase inhibitors) followed by centrifugation at 16,000 *g* for 10 min at 4°C to remove insoluble materials. Lysates are then immunoprecipitated with anti-Syk Ab (4D10 for human DCs, Santa Cruz Biotechnology). Precipitated proteins are fractionated by SDS-PAGE, transferred to PVDF membranes and probed with anti-phosphotyrosine Ab (4G10, Millipore). To confirm that all substrates are adequately immunoprecipitated, immunoblots are reprobed with anti-Syk (Novus Biological, for human DCs). Visualization is performed with the enhanced chemiluminescence (ECL) system (GE healthcare), as described (*e.g.*, Peng et al., (2010) Sci Signal., 3(122): ra38).

Example 15: Induction of CCR7 and migration toward CCL19 and CCL21 in microglia, macrophages, neutrophils, NK cells, and dendritic cells by antagonistic Siglec-7 antibodies and/or bispecific antibodies

[0586] The purpose of this Example is to test whether anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibodies induce CCR7 and migration toward CCL19 and CCL21 in microglial cells, macrophages, neutrophils, NK cells, and dendritic cells.

[0587] Microglial, macrophages or dendritic cells are either cultured with agonistic anti-Siglec-7 and/or Siglec-7/DAP12 bispecific antibodies, or with a control antibody. Cells are collected after 72 h, immuno-labeled with CCR7 specific anti-bodies, and analyzed by flow cytometry.

[0588] To determine any functional consequences of increased CCR7 expression, a chemotaxis assay is performed. Microglia, macrophages, neutrophils, NK cells, or dendritic cells are stimulated via Siglec-7 with the antagonistic anti-Siglec-7 and/or Siglec-7/DAP12 bispecific antibodies and placed in a two-chamber system. The number of microglial cells migrating toward the chemokine ligands CCL19 and CCL21 is quantified (JEM (2005), 201, 647–657).

[0589] For the chemotaxis assay, microglial, macrophages, neutrophils, NK cells, or dendritic cells are exposed to the antagonistic anti-Siglec-7 antibodies or Siglec-7 bispecific antibodies and treated with 1 µg/ml LPS. Microglia, macrophages, neutrophils, NK cells, or dendritic cells are transferred into the upper chamber of a transwell system (3 µm pore filter; Millipore) containing 450µl medium with 100 ng/ml CCL19 or CCL21 (both from PeproTech) in the lower chamber. After a 1 h incubation period, the number of microglial macrophages, neutrophils, NK cells, or dendritic

cells that have migrated to the lower chamber is counted in three independent areas by microscopy (JEM (2005), 201, 647–657).

Example 16: Induction of F-actin in microglia, macrophages, neutrophils, NK cells, and dendritic cells by antagonistic Siglec-7 antibodies and/or bispecific antibodies

[0590] The purpose of this Example is to test whether antagonistic anti-Siglec-7 antibodies, or Siglec-7 bispecific antibodies induce F-actin in microglial cells, macrophages, neutrophils, NK cells, and dendritic cells.

[0591] Microglia, macrophages, neutrophils, NK cells, or dendritic cells and other cells of interest that are transduced with Siglec-7 or that express Siglec-7 are added to culture plates and then exposed to antagonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies, or a control antibody. Cells are fixed, blocked, and then stained with Alexa Fluor 546-conjugated phalloidin (Molecular Probes) after 1 h and F-actin is labeled with a fluorescence dye. Images are collected by confocal laser scanning microscopy with a 40x objective lens (Leica). (JEM (2005), 201, 647–657).

Example 17: Induction of osteoclast production and increased rate of osteoclastogenesis by antagonistic Siglec-7 antibodies and/or bispecific antibodies

[0592] The purpose of this Example is to test whether antagonistic anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibodies induce osteoclast production and increase the rate of osteoclastogenesis.

[0593] Human monocyte derived monocyte/macrophage are maintained in RPMI-1640 medium (Mediatech), or another appropriate medium, supplemented with 10% FBS (Atlantic Biologics, Atlanta, GA, USA) and penicillin-streptomycin-glutamine (Mediatech). Cells are seeded in 96-well plates with 3000 cells/well in alpha-MEM medium supplemented with 10% FBS, penicillin-streptomycin-glutamine, 50 ng/ml RANKL, and 20 ng/ml M-CSF. The medium is changed every 3 days, exposed to anti-Siglec-7 antagonistic antibodies and the number of multinucleated (at least three nuclei) $TRACP^+$ osteoclasts are counted and scored by light microscopy. To determine complexity and size, osteoclasts are counted by number of nuclei (>10 or 3–10 nuclei). The surface area of osteoclasts is also measured by using Image J software (NIH). In addition, expression levels of osteoclasts genes are determined. Total RNA is extracted from osteoclastogenic cultures at different time points using TRIzol reagent (Invitrogen). After first-strand cDNA synthesis using a SuperScript III kit (Invitrogen), real-time quantitative PCR reactions are performed for Nfatc1, Acp5, Ctsk, Calcr, and Ccnd1. Relative quantification of target mRNA expression is calculated and normalized to the expression of cyclophilin and expressed as (mRNA of the target gene/mRNA of cyclophilin) 3 $X10^6$. (J. OF BONE AND MINERAL RESEARCH (2006), 21, 237–245; *J Immunol* 2012; 188:2612-2621).

[0594] Alternatively, macrophages, neutrophils, or NK cells are seeded onto the plates in triplicate wells and treated with RANKL, M-CSF, and with an anti-Siglec-7 and/or Siglec-7 bispecific antibody, or an isotype-matched control monoclonal antibody. The medium is changed every 3 days until large multinucleated cells are visible. After 3 to 5 days in culture, cells are fixed with 3.7% formaldehyde in PBS for 10 min. Plates are then washed twice in PBS, incubated for 30 s in a solution of 50% acetone and 50% ethanol, and washed with PBS. Cells are stained for tartrate-resistant acid phosphatase (TRAP) with a kit from Sigma (product 435). Multinucleated (more than two nuclei), TRAP-positive cells are then counted by light microscopy, as described (*e.g.*, Peng et al., (2010) Sci Signal., 3(122): ra38).

Example 18: *In vivo* protection from EAE and cuprizone in a whole animal

[0595] Adult 7-9 week-old female C57BL/6 mice (obtained from Charles River Laboratories) are injected in the tail base bilaterally with 200 µl of an innoculum containing 100 µg of myelin oligodendrocyte glycoprotein peptide 35–55 (amino acids MEVGWYRSPFSRVVHLYRNGK (SEQ ID NO: 536); Seqlab) and 1 mg of Mycobacterium tuberculosis H37 Ra (Difco) in incomplete Freund adjuvant (Difco). Pertussis toxin (200 ng; List Bio- logical Laboratories) is injected at day 0 and at day 2 after immunization. Clinical signs are scored as follows: 0, no clinical signs; 1, complete limp tail; 2, complete limp tail and abnormal gait; 3, one hind-limb paraparesis; 4, complete hindlimb paraparesis; and 5, fore- and hind-limb paralysis or moribund. Only mice having disease onset (clinical score of 1 or more) at day 14 are used for experiments. Agonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies are injected intraperitoneally or intravenously in EAE-diseased mice at the day of the first clinical symptoms or at any other desired time (PLoS Med (2007) 4(4): e124).

[0596] Young or aged wild-type (WT) mice are fed a standard diet (Harlan) containing 0.2 % cuprizone (CPZ) powdered oxalic bis(cyclohexylidenehydrazide) (Sigma-Aldrich) for 4, 6 or 12 weeks. For Histological and immunohistochemical analyses brains are removed after mouse perfusion with 4 % paraformaldehyde (PFA), fixed in 4 % PFA for 24 h, followed by immersion in 30 % sucrose for 24–48 h. To evaluate myelin integrity and damage, as well as cell proliferation and inflammation sections or mouse brain are stained with anti-MBP (1:100; Abcam, ab7349), -dMBP (1:2000; Millipore, ab5864), -β APP (1:100; Invitrogen, 51-2700), -SMI-31 (1:1000;Covance, smi-31R), -Iba1 (1:600; Wako, 019-19741),-BrdU (1:250; Abcam, ab1893), -GFAP (1:200; Invitrogen,13-0300), -iNOS (1:100; BD Pharmingen, 610329), -LPL(1:400, from Dr. G. Olivecrona) and -MHC II (1:100; BD Pharmingen, 553549). For behavioral effects of the antibodies, mice are analyzed for locomotor activity using transparent polystyrene enclosures and computerized photobeam instrumentation. General activity variables (total ambulations, vertical rearings), along with indices of emotionality including time spent, distance traveled and entries, are analyzed. A battery of sensorimotor tests is performed to assess balance (ledge and platform), strength (inverted screen),

coordination (pole and inclined screens) and initiation of movement (walking initiation). Motor coordination and balance are studied using a rotarod protocol (Cantoni et al., Acta Neuropathol (2015)129(3):429-47).

Example 19: Characterization of the therapeutic use of antagonistic Siglec-7 antibodies and/or Siglec-7 bispecific antibodies in established animal models of traumatic brain injury

[0597] The therapeutic utility of antagonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies is tested in established animal models of traumatic brain injury (Tanaka, Y et al. (2013) Neuroscience 231 49-60). Either regular mice or mice that express the human Siglec-7 gene under a bacterial artificial chromosome or under a myeloid promoter can be used. For example, a model of traumatic brain injury that induces the activation of microglia and astrocytes is used. Eight or nine week-old male C57BL/6J WT mice are used (purchased from Charles River Laboratories or Jackson Laboratories). Mice are anesthetized by intraperitoneal administration of xylazine hydrochloride (8 mg/kg) and chloral hydrate (300 mg/kg) dissolved in sterile saline, and subsequently placed in a stereotaxic apparatus (Narishige, Tokyo, Japan). An incision is made in the scalp and the cranium is exposed. The periosteum is cleaned from the skull, a hole is drilled over the right cerebral hemisphere with a dental drill, and the duramater is removed with a needle tip. A stainless steel cannula, with a 0.5 mm outer diameter, is used to make a longitudinal stab wound in the right hemisphere. The cannula is positioned at 1.3 mm lateral to the midline, and 1 mm posterior to bregma, and introduced into the brain until the tip reaches a depth of 2 mm. The cannula is then shifted 2 mm caudally (bregma 3 mm), and then shifts back 2 mm rostrally to its initial position. Finally, the cannula is removed from the brain, and the scalp wound is sutured. Mice are then treated with antagonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies according to standard procedures and then analyzed by histology and immunofluorescence staining and behavioral tests. Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 20: Characterization of therapeutic use of antagonistic Siglec-7 antibodies and/or Siglec-7 bispecific antibodies in a model of neuro-inflammation and neuron loss following toxin-induced injury

[0598] The therapeutic utility of agonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies is tested in a model of neuro-inflammation and neuron loss following toxin-induced injury (Martens, LH et al., (2012) The Journal of Clinical Investigation, 122, 3955). Three-month-old regular mice, are treated with 4 intraperitoneal injections of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) per day for 2 days (4 μg/g body weight) (Sigma-Aldrich) or PBS. Mice are treated with agonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies according to standard protocols and then analyzed

using Stereological counting to quantify dopamine neurons and microglia in the substantia nigra pars compacta (SNpc), as described. Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 21: Characterization of the therapeutic use of antagonistic Siglec-7 antibodies and/or Siglec-7 bispecific antibodies in animal models of aging, seizures, spinal cord injury, retinal dystrophy, frontotemporal dementia, and Alzheimer's disease

[0599] The therapeutic utility of antagonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies is tested in animal models for aging, seizures, spinal cord injury, retinal dystrophy, frontotemporal dementia, Huntington disease, Parkinson's disease amyotrophic lateral sclerosis and Alzheimer's disease, as previously described (*e.g.*, Beattie, MS et al., (2002) Neuron 36, 375-386; Volosin, M et al., (2006) J. Neurosci. 26, 7756-7766; Nykjaer, A et al., (2005) Curr. Opin. Neurobiol. 15, 49-57; Jansen, P et al., (2007) Nat. Neurosci. 10, 1449-1457; Volosin, M et al., (2008) J. Neurosci. 28, 9870-9879; Fahnestock, M et al., (2001) Mol. Cell Neurosci. 18, 210-220; Nakamura, K et al., (2007) Cell Death. Differ. 14, 1552-1554; Yune, T et al., (2007) Brain Res. 1183, 32-42; Wei, Y et al., (2007) Neurosci. Lett. 429, 169-174; Provenzano, MJ et al., (2008) Laryngoscope 118, 87-93; Nykjaer, A et al., (2004) Nature 427, 843-848; Harrington, AW et al., (2004) Proc. Natl. Acad. Sci. U.S.A. 101, 6226-6230; Teng, HK et al., (2005) J. Neurosci. 25, 5455-5463; Jansen, P et al., (2007) Nat. Neurosci. 10, 1449-1457; Volosin, M et al., (2008) J. Neurosci. 28, 9870-9879; Fan, YJ et al., (2008) Eur. J. Neurosci. 27, 2380-2390; Al-Shawi, R et al., (2008) Eur. J. Neurosci. 27, 2103-2114; and Yano, H et al., (2009) J. Neurosci. 29, 14790-14802). Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 22: Characterization of the therapeutic use of antagonistic Siglec-7 antibodies and/or Siglec-7 bispecific antibodies in a model of infection

[0600] The therapeutic utility of antagonistic anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibodies is tested in a model of infection. For example, *Listeria monocytogenes* or other infection in normal mice can be used, as previously described (*e.g.*, Yin, F et al., (2009) J. Exp. Med, 207, 117-128). Either regular mice or mice that express the human Siglec-7 gene under a bacterial artificial chromosome or under a myeloid promoter can be used.

Example 23: Characterization of the therapeutic use of antagonistic Siglec-7 antibodies and/or Siglec-7 bispecific antibodies in a model of inflammatory diseases

[0601] The therapeutic utility of antagonistic anti-Siglec-7 and/or Siglec-7 bispecific antibodies is tested in a model of inflammatory diseases. For example rheumatoid arthritis or in an established

model of another inflammatory disease (Mizoguchi (2012) Prog Mol Biol Transl Sci.,105:263-320; and Asquith et al., (2009) Eur J Immunol. 39:2040-4). Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 24: Screening for anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibodies that induce or inhibit phosphorylation of Siglec-7 and downstream signaling molecules.

[0602] Cells (J774, RAW 264.7, BMM cells, human primary monocytes, macrophages, neutrophils, NK cells, dendritic cells, T cells, microglia, or osteoclasts) are removed from tissue culture dishes with PBS-EDTA, washed with PBS, and counted. Cells are incubated with an anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibody or with an isotype-matched control antibody at 1 μg/10^6 cells for 20 min on ice or under other conditions. Cells are lysed in ice-cold radioimmunoprecipitation assay (RIPA) buffer for 20 min followed by centrifugation at 16,000 *g* for 10 min at 4°C to remove insoluble materials. The resulting supernatant is subjected to immunoprecipitation reactions with the indicated antibodies (DAP12, ERK, or AKT) and protein A- or protein G-agarose (Sigma). The beads are extensively washed with RIPA buffer and the proteins are separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE). The proteins are then transferred to nitrocellulose membranes by Western blotting, incubated with the appropriate antibodies (antibodies that specifically recognize phosphorylated tyrosine or phosphorylated form of DAP12, ERK, Syk, LCK, FYN, C-Cbl, VAV, or AKT) and visualized with the enhanced chemiluminescence (ECL) system (Pierce), as described (*e.g.*, Peng et al., (2010) Sci Signal., 3(122): ra38).

Example 25: Screening for anti-Siglec-7 and/or Siglec-7 bispecific antibodies that induce or inhibit calcium flux

[0603] BMM cells are washed twice with HEPES-containing buffer [20 mM HEPES (pH 7.3), 120 mM NaCl, 1 mM CaCl, 1 mM MgCl, 5 mM KCl, glucose (1 mg/ml), bovine serum albumin (1 mg/ml)] followed by incubation in 0.05% Pluronic F-127 (Invitrogen) and 1 μM Indo-1 AM (Invitrogen) for 20 min at 37°C. Cells are washed twice with HEPES buffer and are then stimulated with an anti-Siglec-7 antibodies and/or Siglec-7 bispecific antibody (16 μg/ml) or with a control antibody (16 μg/ml) and monitored by spectrophotometer (PTL Photon Technology International). The Indo-1 fluorescence emission is converted to calcium (Ca^{2+}) according to manufacturer's instructions (*e.g.*, Peng et al., (2010) Sci Signal., 3(122): ra38).

Example 26: Siglec-7 increases the survival of macrophages, neutrophils, NK cells, and dendritic cells

[0604] To evaluate the role of Siglec-7 in cell survival, human or mouse macrophages, neutrophils, NK cells, microglia, T cells, and dendritic cells are cultured in the presence of inflammatory mediators, and cell survival is measured.

[0605] Murine bone marrow precursor cells from Siglec-7-expressing or WT mice are obtained by flushing tibial and femoral marrow cells with cold PBS. After one wash with PBS, erythrocytes are lysed using ACK Lysing Buffer (Lonza), washed twice with PBS and suspended at $0.5x10^6$ cells/ml in complete RPMI media (10% FCS, Pen/Strep, Gln, neAA) with the indicated amounts of 50ng/ml M-CSF to produce macrophages, neutrophils, or NK cells, or 10ng/ml GM-CSF to produce dendritic cells. For M2-type macrophages, 10ng/ml IL-4 is added to the cultured cells. For M1-type macrophages, 50 ng/ml IFN is added. In some experiments LPS or zymosan is added to the cell culture at day 5 at a concentration range of 1 μg/ml-0.01 ng/ml. Recombinant cytokines are purchased from Peprotech.

[0606] To analyze viability of bone marrow-derived macrophages, neutrophils, or NK cells, cells are prepared as above and cultured in MCSF. Cells are either plated at 10^5/200 μL in a 96-well plate (for viability analysis using a luciferase based-assay) or at $0.5x10^6$/1ml in a 6-well plate (for Tripan Blue exclusion cell count) in non-tissue culture treated plates. Media containing fresh M-CSF is added at day 3. At the indicated time points cells are gently detached from the plates with 3 mM EDTA and counted using a Burker chamber. For FACS analysis of live cells, macrophages are cultured either in 50 ng/ml MCSF for 6 days (+MCSF) or in 50 ng/ml MCSF for 4 days before MCSF is removed for an additional 36 hrs (-MCSF). Cells are stained using CD11b antibody and DAPI. For luciferase viability assays, cell viability is measured at day 5 of culture in graded concentrations of growth factors GMCSF (dendritic cells), MCSF (M1 macrophages), or MCSF+IL-4 (M2 macrophages). Cells are directly incubated with ToxGlo reagent (Promega) and luciferase activity (luminescence) is determined. For FACS analysis of viable macrophages cultured in the presence of inflammatory mediators IFN, LPS, or zymosan, cells are collected at day 5 and stained using CD11b antibody and DAPI.

Example 27: Siglec-7 increases the expression of inflammatory cell surface markers on macrophages, neutrophils, or NK cells

[0607] In order to determine the role of Siglec-7 in inflammatory marker expression, macrophages, neutrophils, and NK cells are cultured with various inflammatory mediators, and the expression of surface markers (e.g., CD86 and CD206) is measured in the presence or absence of Siglec-7 antibodies.

[0608] Macrophages, neutrophils, and NK cells are plated and allowed to adhere for 4 h at 37°C, and TLR agonists LPS (*Salmonella abortus equi*) and zymosan (*Saccharomyces cerevisiae*) are added at concentrations ranging from 0.01-100 ng/ml (LPS) or 0.01-10 µg/ml (zymosan). Alternatively, macrophages, neutrophils, and NK cells are cultured in the presence of the cytokines IL-4 (10 ng/ml) or IFN (0.5-50 ng/ml). FACS analysis of CD86 and CD206 is performed on a BD FACS Canto 48 hours later. Data analysis is performed with FlowJo (TreeStar) software version 10.0.7.

Example 28: Analysis of the anti-cancer effect of Siglec-7 antibodies and/or bispecific antibodies

[0609] Groups of 10 C57Bl6/NTac mice at 8 weeks (+/- 2 weeks) of age, either regular mice or mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a myeloid promoter, are challenged subcutaneously with tumor cells (e.g. $1x10^5$ to $1x10^6$ MC38, Lewis Lung, or B16 cells) suspended in 100ul PBS. Animals are anesthetized with isoflurane prior to implant. Starting at day 2, groups of mice are injected i.p. every 3 days for 4 doses with 200ug of each of antagonistic anti-Siglec-7 antibodies. Tumor growth is monitored with a caliper biweekly to measure tumor growth starting at day 4. The endpoint of the experiment is a tumor volume of 2000 mm^3 or 60 days. Tumor growth and % survival are the outcome measures. Reduced tumor take and growth rate, reduced number of tumor infiltrating immune suppressor macrophages, neutrophils, and/or NK cells, and increased effector T cell influx into the tumor indicate the anti-cancer effects of blocking anti-Siglec-7 antibodies.

[0610] Immunodeficient mice or immunodeficient transgenic mice that express human IL-3, human GM-CSF, human IL-6, human IL-2, and were seeded with human immune cells from human placenta, fetal liver, peripheral blood or another source can also be used for such studies (Ito M et al., (2008) Curr Top Microbiol Immunol.;324:53-76; Ito R., et al., (2012) *Cellular & Molecular Immunology* 9, 208–214; Brehm et al., (2010) Curr Opin Endocrinol Diabetes Obes. 17(2): 120–125; Zhou et al., (2013) Cancer Letters. 344,13–19). Such mice can be used in conjunction with either cell line tumors or patient-derived human tumor xenografts (Siolas et al., (2013) Cancer Res.; 73(17): 5315–5319).

[0611] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 29: Analysis of additive anti-tumor effect of combination therapy that combines Siglec-7 antibodies and/or bispecific antibodies with antibodies against inhibitory checkpoint proteins or inhibitory cytokines/chemokines and their receptors

[0612] Groups of 15 C57Bl6/NTac mice at 8 weeks (+/- 2 weeks) of age are challenged subcutaneously with tumor cells as described in Example 28. Animals are anesthetized with isoflurane prior to implant. Starting at day 2, mice are injected i.p. every 3 days for 4 doses with

200ug anti-Siglec-7 antibodies alone or in combination with antibodies against checkpoint proteins (e.g. anti-PDL1 mAb clone 10F.9G2 and/or anti-CTLA4 mAb clone UC10-4F10-11) at day 3, 6, and 9. Treatment groups include anti-Siglec-7; anti-CTLA4; anti-PDL1; anti-Siglec-7+anti-CTLA4; anti-Siglec-7+anti-PDL1; and isotype control. Tumor growth is monitored with a caliper biweekly to measure tumor growth starting at day 4. The endpoint of the experiment is a tumor volume of 2000 mm^3 or 60 days. Tumor growth and % survival are the outcome measures. A decrease in tumor growth and an increase in % survival with combination therapy indicate that anti-Siglec-7 antibodies have additive or synergistic therapeutic effects with anti-checkpoint antibodies. Antagonistic antibodies against checkpoint molecules include antibodies against PDL1, PDL2, PD1, CTLA4, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG-3, and Phosphatidyl Serine. Antagonist antibodies against inhibitory cytokines include antibodies against CCL2, CSF-1, and IL-2. Immuno-deficient mice or immuno-deficient transgenic mice that express human IL-3, human GM CSF, human IL-6, human Il2, and were seeded with human immune cells from human placenta, fatal liver, peripheral blood or another source can also be used for such studies (Ito M et al., (2008) Curr Top Microbiol Immunol.;324:53-76; Ito R., et al., (2012) *Cellular & Molecular Immunology* 9, 208–214; Brehm et al., (2010) Curr Opin Endocrinol Diabetes Obes. 17(2): 120–125; Zhou et al., (2013) Cancer Letters. 344,13–19). Such mice can be used in conjunction with either cell line tumors or Patient derived human tumors xenografts (Siolas et al., (2013) Cancer Res.; 73(17): 5315–5319).

[0613] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 30: Analysis of additive anti-tumor effect of combination therapy that combines Siglec-7 antibodies and/or bispecific antibodies with antibodies that activate stimulatory checkpoint proteins

[0614] Groups of 15 C57Bl6/NTac mice at 8 weeks (+/- 2 weeks) of age are challenged subcutaneously with tumor cells as described in Example 28. Animals are anesthetized with isoflurane prior to implant. Starting at day 2, mice are injected i.p. every 3 days for 4 doses with 200 µg anti-Siglec-7 antibodies alone or in combination with agonistic antibodies that activate stimulatory checkpoint proteins (e.g. OX40 or ICOS mAb) at day 3, 6, and 9. Tumor growth is monitored with a caliper biweekly to measure tumor growth starting at day 4. The endpoint of the experiment is a tumor volume of 2000 mm^3 or 60 days. Tumor growth and % survival are the outcome measures. A decrease in tumor growth and an increase in % survival with combination therapy indicate that anti-Siglec-7 antibodies have additive or synergistic therapeutic effects with stimulatory checkpoint antibodies. Stimulatory checkpoint antibodies include agonistic/stimulatory antibodies against CD28, ICOS, CD137, CD27, CD40, and GITR.

[0615] Immuno-deficient mice or immuno-deficient transgenic mice that express human IL-3, human GM CSF, human IL-6, human Il2, and were seeded with human immune cells from human placenta, fatal liver, peripheral blood or another source can also be used for such studies (Ito M et al., (2008) Curr Top Microbiol Immunol.;324:53-76; Ito R., et al., (2012) *Cellular & Molecular Immunology* 9, 208–214; Brehm et al., (2010) Curr Opin Endocrinol Diabetes Obes. 17(2): 120–125; Zhou et al., (2013) Cancer Letters. 344,13–19). Such mice can be used in conjunction with either cell line tumors or Patient derived human tumors xenografts (Siolas et al., (2013) Cancer Res.; 73(17): 5315–5319).

[0616] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lentivirus or AAV virus containing human Siglec-7 cDNA.

Example 31: Analysis of additive anti-tumor effect of combination therapy that combines Siglec-7 antibodies and/or bispecific antibodies with stimulatory cytokines

[0617] Groups of 15 C57Bl6/NTac mice at 8 weeks (+/- 2 weeks) of age are challenged subcutaneously with tumor cells as described in Example 28. Animals are anesthetized with isoflurane prior to implant. Starting at day 2, mice are injected i.p. every 3 days for 4 doses with 200ug anti-Siglec-7 antibodies alone or in combination with stimulatory cytokines (e.g. IL-12, IFN-a). Tumor growth is monitored with a caliper biweekly to measure tumor growth starting at day 4. The endpoint of the experiment is a tumor volume of 2000 mm^3 or 60 days. Tumor growth and % survival are the outcome measures. A decrease in tumor growth and an increase in % survival with combination therapy indicate that anti-Siglec-7 antibodies have additive or synergistic therapeutic effects with immune-stimulatory cytokines. Stimulatory cytokines include IFN-a/b, IL-2, IL-12, IL-18, GM-CSF, and G-CSF.

[0618] Immuno-deficient mice or immuno-deficient transgenic mice that express human IL-3, human GM CSF, human IL-6, human Il2, and were seeded with human immune cells from human placenta, fatal liver, peripheral blood or another source can also be used for such studies (Ito M et al., (2008) Curr Top Microbiol Immunol.;324:53-76; Ito R., et al., (2012) *Cellular & Molecular Immunology* 9, 208–214; Brehm et al., (2010) Curr Opin Endocrinol Diabetes Obes. 17(2): 120–125; Zhou et al., (2013) Cancer Letters. 344,13–19). Such mice can be used in conjunction with either cell line tumors or Patient derived human tumors xenografts (Siolas et al., (2013) Cancer Res.; 73(17): 5315–5319).

[0619] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 32: Analysis of ability of Siglec-7 antibody and/or bispecific antibody Fabs to stimulate viability of innate immune cells

[0620] The agonistic functionality of plate bound, cross-linked anti-Siglec-7 antibody Fab fragments is evaluated in innate immune cells (e.g., macrophages, neutrophils, and NK cells).

[0621] Macrophages, neutrophils, and NK cells are cultured in the presence of M-CSF and plate bound Siglec-7 antibody Fabs, and cell viability is measured.

[0622] Macrophages, neutrophils, NK cells, and DC derived from human monocytes, as well as T cells and human microglia derived from human monocytes are plated on non-tissue-culture-treated 96-well plates, pre-coated with either 12.5nM or 100nM of cross-linked Siglec-7 Fabs. Cells are cultured for 48 hours in the presence of 10ng/ml M-CSF. Analysis of viability is performed using CellTiter-Glo® kit (Promega). Plates are read with a BioTek Synergy Microplate Reader using GEN5 2.04 software.

Example 33: Analysis of the ability of Siglec-7 antibodies and/or bispecific antibodies to modulate NFAT-dependent genes

[0623] The ability of antagonistic anti-Siglec-7 antibodies activate NFAT-dependent genes is evaluate using a luciferase reporter gene under the control of an NFAT (nuclear factor of activated T cells) promoter.

[0624] A cell line derived from mouse T lymphocytes BW5147.G.1.4 (ATCC® TIB48™) that express the ITAM motif containing co-receptor DAP12 and its ligand binding partner TREM2 is infected with human Siglec-7, and with Cignal Lenti NFAT-Luciferase virus (Qiagen). Luciferase signaling is activated by plate bound anti-TREM2 antibodies. Full-length and Fab fragment anti-Siglec-7 antibodies are either co-plated with the TREM2 antibodies or applied in solution. For plate binding, antibodies are applied at 10 µg/ml in DPBS on tissue-culture treated clear bottom white 96well plates (100ul/well), overnight at 4°C. Wells are rinsed three times with DPBS and subsequently plated at 100,000 cells/well in media with 1% serum. As a positive control for signaling, PMA (0.05ug/ml) and ionomycin (0.25uM) are added together. Cells are incubated for 6 hours and luciferase activity is measured by adding ONE-Glo™ reagent (Promega) to each well and incubating 3min at RT on a plate shaker. Luciferase signal is measured using a BioTek plate reader.

Example 34: Analysis of anti-stroke effect of Siglec-7 antibodies and/or bispecific antibodies

[0625] Transient occlusion of the middle cerebral artery (MCAO) – a model that closely resembles human stroke is used to induce cerebral infarction in mice. Monofilament (70SPRe, Doccol Corp, USA) is introduced into the internal carotid artery through an incision of the right common carotid artery. The middle cerebral artery is occluded for 30 minutes with a range of reperfusion times (6 h, 12 h, 24 h, 2 d, 7 d and 28 d). The effect of surgery is controlled using sham animals at 12 h and at 7 d. Sham animals undergo the same surgical procedure without occlusion of

the middle cerebral artery. MCAO animals treated with antagonistic anti-Siglec-7 antibodies or control antibodies are tested for infarct volumetry, acute inflammatory response (12 h reperfusion), transcription of pro-inflammatory cytokines TNFa, IL-1a, and IL-1b, microglial activity (CD68, Iba1), transcription of chemokines CCL2 (MCP1), CCL3 (MIP1a and the chemokine receptor CX3CR1 and invasion of CD3-positive T cells (Sieber et al. (2013) PLoS ONE 8(1): e52982. doi:10.1371/journal.pone.0052982.). Such experiment can be conducted in regular mice or alternatively in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 35: Analysis of anti-Alzheimer's disease effect of anti-Siglec-7 antibodies and/or bispecific antibodies

[0626] To evaluate the ability of antagonistic anti-Siglec-7 antibodies to delay, prevent, or reverse the development of Alzheimer's disease (AD), 5X FAD mice are used. 5X FAD mice overexpress mutant human APP (695) with the Swedish (K670N, M671L), Florida (I716V), and London (V717I) familial Alzheimer's disease (FAD) mutations, along with human PS1 harboring two FAD mutations, M146L and L286V. Both transgenes are regulated by the mouse Thy1 promoter to drive over expression on the brain and recapitulate major features of AD. Mice treated with the agonistic anti-Siglec-7 antibodies or with control antibodies are tested for A beta plaque load with immunohistochemistry and by ELISA of tissue extracts. They are further tested for the number of microglia in the brain, and for reduction in cognitive deficit using Morris Water maze, a spatial learning and memory task, Radial Arm Water Maze, a spatial learning and memory task, Y Maze (quantifies spontaneous alternation as a measure of spatial cognition), novelty preference in in an open field, operant learning to assess learning and memory, and fear conditioning (mousebiology.org website; Wang et al.,(2015) Cell. pii: S0092-8674(15)00127-0). Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 36: Analysis of the protective effect of Siglec-7 antibodies and/or bispecific antibodies in respiratory tract infections

[0627] To evaluate the ability of antagonist Siglec-7 antibodies to delay, prevent, or treat bacterial respiratory tract infections, a preclinical mouse model involving challenge of C57Bl6 mice with *Streptococcus pneumoniae* is used. This model involves intranasal (i.n.) administration of 105 CFU *S. pneumoniae* serotype 3 (ATCC 6303) as described (see, e.g., Sharif O et al, 2014 *PLoS Pathog*. 2014 Jun; 10(6): e1004167; and Schabbauer G et al, 2010 *J Immunol* 185: 468–476). In this model ~90% WT C57Bl6 mice succumb to infection within 6 days post infection.

[0628] Ten to fifteen mice/group are challenged with *S. pneumoniae* and concomitantly are treated with antagonist anti-Siglec-7 antibodies every other day starting from day 0. The first dose of anti-Siglec-7 antibodies is administered 3 hours prior to challenge with *S. pneumonia*. Mice are monitored daily for 15 days to check for death events. % of mice surviving *bacteria* challenge is determined.

[0629] In separate experiments, count of bacterial load and cytokine expression in the blood and in the lungs is also determined. 24 or 48 hours after infection blood is collected in EDTA-containing tubes and plated on agar plates to enumerate bacterial CFU in the plasma. Plasma is stored at -20°C for cytokine analysis by ELISA. Lungs are harvested, homogenized and plated on agar plates to enumerate bacterial CFU, or incubated for 30 min in lysis buffer and supernatants analyzed for cytokine measurements.

[0630] In separate experiments, lungs are collected 40 hours post bacterial infection, fixed in 10% formalin, and embedded in paraffin for H&E pathology analysis.

[0631] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 37: Analysis of the protective effect of Siglec-7 antibodies and/or bispecific antibodies in sepsis

[0632] To evaluate the ability of antagonist Siglec-7 antibodies to delay, prevent, or treat sepsis, a preclinical mouse model involving systemic challenge of C57Bl6 mice with LPS is used. This model involves intraperitoneal (i.p.) administration of 37 mg/ml LPS as described *(see, e.g.*, Gawish R et al, 2014 *FASEB J*). In this model >95% WT C57Bl6 mice succumb infection within 40 hours post LPS injection.

[0633] Cohorts of mice are challenged with LPS and concomitantly are treated with antagonist anti-Siglec-7 antibodies every day starting from day 0. The first dose of anti-Siglec-7 antibodies is administered 3 hours prior to challenge with LPS. Mice are monitored every ~4 hours during daytime, to check for death events. Percentage of mice surviving LPS challenge is determined.

[0634] In separate experiments, peritoneal lavage fluid (PLF) is collected. Supernatants are stored at -20°C for cytokine analysis by ELISA; pelleted cells are counted to quantify inflammatory cells recruited in the peritoneal cavity. Similar studies can be conducted to test the efficacy of Siglec-7 antibodies in other models of infection (*see, e.g.*, Sun et al., (2013) *Invest Ophthalmol Vis Sci*. 17;54(5):3451-62).

[0635] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 38: Analysis of the protective effect of Siglec-7 antibodies and/or bispecific antibodies in acute and chronic colitis

[0636] To evaluate the ability of antagonist anti-Siglec-7 antibodies to delay, prevent, or treat colitis, preclinical mouse models of acute or chronic colitis are used. For DSS-induced colitis, mice receive 3% DSS in drinking water *ad libitum* for 8 days. For TNBS-induced colitis, mice are anesthetized and treated with an intra-rectal injection of 3 mg TNBS in 20% ethanol (vol/vol) or vehicle alone as a control. For the chronic colitis model, all mice are treated with 3 cycles of 2% DSS for 5 days, followed by a 10-day recovery period. For all models, weight loss, stool consistency, and presence of fecal occult blood are monitored daily and used to calculate the disease activity index, as described (*see, e.g.*, Correale C, 2013, *Gastroenterology*, February 2013, pp. 346-356.e3).

[0637] Cohorts of mice are treated with antagonist anti-Siglec-7 antibodies every day starting from day 0 and subjected to DSS or TNBS administration. Mice are monitored every day, to check for weight loss, stool consistency, and presence of fecal occult blood were monitored daily and used to calculate the disease activity index, as described (*see, e.g.*, S. Vetrano, *Gastroenterology*, 135 (2008), pp. 173–184).

[0638] In separate experiments, endoscopic and histological images of mucosal damage are collected to evaluate inflammatory cell infiltration and mucosal damage. Similar studies can be conducted to test the benefit of Siglec-7 antibodies in other models of autoimmunity including Crohn's disease, inflammatory bowel disease ,and ulcerative colitis (*see, e.g.*, Low et al., (2013) *Drug Des Devel Ther.*; 7: 1341-1357; and Sollid et al., (2008) *PLoS Med* 5(9): e198).

[0639] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 39: Analysis of the protective effect of Siglec-7 antibodies and/or bispecific antibodies in wound healing

[0640] To evaluate the ability of agonistic anti-Siglec-7 antibodies to increase colonic wound repair following injury, a mouse model of biopsy injury in the colon is used. In this model, the endoscope with outer operating sheath is inserted to the mid-descending colon and the mucosa is surveyed to the ano-rectal junction. Then, a single full thickness area of the entire mucosa and submucosa is removed with flexible biopsy forceps with a diameter of 3 French, avoiding penetration of the muscularis propria. Each mouse is biopsy injured at 3–5 sites along the dorsal side of the colon (*see, e.g.*, Seno H, 2008, *Proc Natl Acad Sci U S A*. 2009 Jan 6; 106(1): 256-261).

[0641] Cohorts of mice are treated with agonist anti-Siglec-7 antibodies 2 or 3 days after biopsy injury. Mice are monitored every day for 15 days, to check for weight loss and wound healing by measuring the surface area of lesions.

[0642] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 40: Analysis of the protective effect of Siglec-7 antibodies and/or bispecific antibodies in retinal degeneration

[0643] AMD is a degenerative disease of the outer retina. It is thought that inflammation, particularly inflammatory cytokines and macrophages, neutrophils, and/or NK cells contribute to AMD disease progression.

[0644] The presence of macrophages, neutrophils, and NK cells in the proximity of AMD lesions is documented, in the drusen, Bruch's membrane, choroid and retina. Macrophages, neutrophils, and NK cells release tissue factor (TF) and vascular endothelial growth factor (VEGF), which triggers the expansion of new blood vessels formation in patients showing choroidal neovasulcarization.

[0645] The type of macrophage present in the macular choroid changes with age, displaying elevated levels of M2 macrophages, neutrophils, and NK cells in older eyes compared to younger eyes. However, advanced AMD maculae had higher M1 to M2 rations compared to normal autopsied eyes of similar age. (*see, e.g.*, Cao X et al, (2011), *Pathol Int* 61(9): pp528-35). This suggests a link between classical M1 macrophage activation in the eye in the late onset of AMD progression.

[0646] Retinal microglia cells are tissue-resident macrophages that are also normally present in the inner retina. In the event of damage, microglia can be activated and act as mediator of inflammation. Activated microglia has been detected in the AMD tissue samples and has been proposed as one potential contributor of inflammatory processed that lead to AMD pathogenesis (Gupta et al., (2003) *Exp Eye Res*., 76(4):463-71.). The ability of Siglec-7 antibodies to prevent, delay, or reverse AMD is tested in one or more of AMD models (*see*, *e.g.*, Pennesi et al., (2012) *Mol Aspects Med*.; 33(4): 487–509).

[0647] Overall inflammatory macrophages, neutrophils, and NK cells (either M1 and/or activated microglia) are documented to correlate with AMD disease progression and therefore represent a therapeutic target for antagonist Siglec-7 antibodies. Similar therapeutic benefit can be achieved in glaucoma and genetic forms or retinal degeneration such as retinitis pigmentosa.

[0648] The ability of Siglec-7 antibodies to prevent, delay, or reverse retinal ganglion cell degeneration in glaucoma is tested in a glaucoma model (*see, e.g.*, El-Danaf et al., (2015) .*J Neurosci*. 11;35(6):2329-43). Likewise, the therapeutic benefit of REM2 in genetically induced retinal degeneration and retinitis pigmentosa is tested as described in Chang et al., (2002) Vision Res.; 42(4):517-25, and in "Retinal Degeneration Rat Model Resource Availability of P23H and S334ter

Mutant Rhodopsin Transgenic Rats and RCS Inbred and RCS Congenic Strains of Rats," MM LaVail, June 30, 2011.

[0649] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 41: Analysis of the protective effect of Siglec-7 antibodies and/or bispecific antibodies in adipogenesis and diet-induced obesity

[0650] To test the effect of Siglec-7 antibodies in adipogenesis and obesity, a mouse model of high-fat diet (HFD) is used (*see, e.g.*, Park et al., (2015) *Diabetes*. 64(1):117-27).

[0651] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 42: Analysis of the protective effect of antagonist Siglec-7 antibodies and/or bispecific antibodies in osteoporosis

[0652] Bone is a dynamic organ constantly remodeled to support calcium homeostasis and structural needs. The osteoclast is the cell responsible for removing both the organic and inorganic components of bone. The osteoclast is derived from hematopoietic progenitors in the macrophage lineage and differentiates in response to the tumor necrosis factor family cytokine receptor activators of NFκB ligand. Osteoclasts, the only bone-resorbing cells, are central to the pathogenesis of osteoporosis and osteoporosis (Novack et al., (2008) *Annual Rev Pathol.*, 3:457-84).

[0653] Osteoporosis is a progressive bone disease that is characterized by a decrease in bone mass and density which can lead to an increased risk of fracture. It is mostly manifested in the first years following menopause, when bone turnover is accelerated, with increased activity of both osteoclasts and osteoblasts. Owing to an imbalance in the processes of resorption and synthesis, however, the net effect is bone loss, which is largely trabecular. Thus, the most prevalent sites of fracture in osteoporosis are the wrist, femoral neck, and vertebral bodies, in which the trabecular structure is key to overall bone strength.

[0654] Reduced osteoclast function results in osteoporosis, with increased bone mass and elimination of bone marrow space, as observed in animal models lacking DAP12 ITAM signaling adapter and resulting in a significant defect in differentiation of osteoclast-like cells (Koga, et al., (2004) *Nature* 428: 758–763).

[0655] Thus, administering an antagonist anti-Siglec-7 antibody of the present disclosure can prevent, reduce the risk of, and/or treat osteoporosis. In some embodiments, administering an agonist anti-Siglec-7 antibody may induce one or more Siglec-7 activities in an individual having osteoporosis (*e.g.*, DAP12 phosphorylation, Syk activation, and accelerated differentiation into

osteoclasts) (Peng et al (2010). *Sci Signal.* 2010 18;3 122; and Humphrey et al., (2006) *J Bone Miner Res.*,21(2):237-45).

[0656] Such experiment can be also conducted in in mice that express the human Siglec-7 gene from a bacterial artificial chromosome or from a cDNA driven by a myeloid promoter or in mice that were transduced with lenti or AAV virus containing hSiglec-7 cDNA.

Example 43: Analysis of the ability of Siglec-7 antibodies and/or bispecific antibodies to modulate binding of Siglec-7 to SHP1, SHP2 and other signaling molecules

[0657] Human primary monocytes, macrophages, neutrophils, NK cells, dendritic cells, T cells, microglia or osteoclasts are removed from tissue culture dishes with PBS-EDTA, washed with PBS, and counted. Cells are incubated with an anti-Siglec-7 and/or Siglec-7 bispecific antibody or with an isotype-matched control antibody at 1μg/10^6 cells for 20 min on ice or under other conditions. Cells are lysed in ice-cold radioimmunoprecipitation assay (RIPA) buffer for 20 min followed by centrifugation at 16,000 *g* for 10 min at 4°C to remove insoluble materials. The resulting supernatant is subjected to immunoprecipitation reactions with the indicated antibodies (SHP1, SHP2, c-Cbl., Vav, Syk, LcK, Fyn, GRb2, PLC-gamma. Toll like receptor, DAMP receptors, pattern recognition receptor) and protein A- or protein G-agarose (Sigma). The beads are extensively washed with RIPA buffer and the proteins are separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE). The proteins are then transferred to nitrocellulose membranes by Western blotting, incubated with the appropriate Siglec-7 antibodies and visualized with the enhanced chemiluminescence (ECL) system (Pierce), as described (*e.g.*, Peng et al., (2010) Sci Signal., 3(122): ra38). Alternatively, the cells are incubated with an anti-Siglec-7 and/or Siglec-7 bispecific antibody or with an isotype-matched control antibody at 1 μg/10^6 cells for 20 min on ice or under other conditions. Cells are lysed in ice-cold radioimmunoprecipitation assay (RIPA) buffer for 20 min followed by centrifugation at 16,000 *g* for 10 min at 4°C to remove insoluble materials. The resulting supernatant is subjected to immunoprecipitation reactions with a second Siglec-7 antibody. The proteins are then transferred to nitrocellulose membranes by Western blotting and incubated with the indicated antibodies (SHP1, SHP2, c-Cbl., Vav, Syk, LcK, Fyn, GRb2, PLC-gamma. Toll like receptor, DAMP receptors, pattern recognition receptor).

Example 44: *In vivo* effects of anti-Siglec-7 and anti-PD1 antibody combination treatment

[0658] A CTG-0202 patient-derived melanoma tumor was first passaged in pre-study animals prior to implantation to humanized mice. When tumors reached 1-1.5 cm^3 in stock animals, they were harvested for re-implantation into pre-study animals. Pre-study animals were implanted unilaterally on the left flank with tumor fragments. The CTG-0202 melanoma tumors were used at passage number 6.

[0659] Immunocompromised female mice (Taconic NOG) were humanized with fetal liver-derived $CD34^+$ hematopoietic cells. Mice were housed on irradiated papertwist-enriched 1/8" corncob bedding (Sheperd) in individual HEPA ventilated cages (Innocage® IVC, Innovive USA) on a 12-hour light-dark cycle at 68-74°F (20-23°C) and 30-70% humidity. Mice were fed water ad libitum (reverse osmosis, 2 ppm Cl_2) and an irradiated test rodent diet (Teklad 2919) consisting of 19% protein, 9% fat, and 4% fiber. 48 humanized mice were implanted, and pre-study tumor volumes were recorded for each experiment beginning seven to ten days after implantation. When tumors reached approximately 80-200 mm^3 in volume, mice were matched by tumor volume into treatment or control groups to be used for dosing, and dosing was initiated on Day 0. Test groups were administered anti-PD-1 antibody Keytruda® (pembrolizumab) in combination with a control monoclonal antibody (Group 1), or in combination with anti-Siglec-7 antibody 10B5 (Group 2). **Table 11** and **FIG. 16A** depict the dosing schedule, dosing amounts, and route of administration.

Table 11: Antibody dosing schedule and route of administration for the *in vivo* cancer efficacy study of the Siglec-7 antibody 10B5

Group	n	Antibody Treatment	Dose Volume (mg/kg)	ROA	Schedule	Total # of Doses
1	8	Keytruda	5/2.5	IP	q5dx6	6
		Alector CTR mAb	40	IP	q5dx6	6
2	8	Keytruda	5/2.5	IP	q5dx6	6
		Alector 10B5	40	IP	q5dx6	6

[0660] In **Table 11**, "n" refers to the number of mice in each treatment group; "Alector CTR mAb" refers to an isotype control antibody; "Alector 10B5" refers to anti-Siglec-7 antibody 10B5; "ROA" refers to route of administration; "IP" refers to intraperitoneal; "q5dx6" refers to a dosing schedule of administration every five days for a total of six doses.

[0661] Beginning at Day 0, mice were observed daily and weighed twice weekly using a digital scale. Tumor dimensions were measured twice weekly by digital caliper and data including individual and mean estimated tumor volumes (Mean TV ± SEM) was recorded for each group. Tumor volume was calculated using the formula (1): *TV= width2 x length x 0.52*. At study completion, percent tumor growth inhibition (% TGI) values were calculated and reported for each treatment group (T) versus control (C) using initial (i) and final (f) tumor measurements by the formula (2): *%TGI= 1-(Tf-Ti) / (Cf-Ci)*.

[0662] Individual mice reporting a tumor volume ≤50% of the Day 0 measurement for two consecutive measurements were considered partial responders (PR). Individual mice lacking palpable tumors (< 4x4 mm^2 for two consecutive measurements) were classified as complete responders (CR); a CR that persisted until study completion was considered a tumor-free survivor (TFS). Tumor doubling time (DT) was determined for the vehicle treated groups using the formula *DT = (Di - Df) **

log2 / (logTVi – logTV)$_f$ where D = Day and TV = Tumor Volume. Statistical differences in tumor volume were determined using two-way ANOVA. The study was concluded when the mean tumor volume of the control group reached 1500 mm^3 at day 28.

[0663] At study termination harvested tumors were shipped overnight in media on ice packs and processed the following day. Whole blood samples were collected by cardiac puncture and shipped in sodium heparin and processed the following day upon delivery. Tumor samples were treated with collagenase for 30 min at 37°C. Samples were dissociated through a cell strainer and resuspended in 2% FBS in PBS. Red blood cells in whole blood samples were lysed using ACK lysing buffer and cells were then washed in 2% FBS in PBS twice. Cells were counted using a hemocytometer and one million cells were stained with fluorochrome-conjugated antibodies for 30 minutes on ice, then washed with 2% FBS in PBS. Cells were fixed with 4% paraformaldehyde in PBS. All the stained cells were analyzed on a FACS Canto (BD Biosciences) and the data analyzed with FlowJo software (TreeStar). To asses receptor downregulation, mouse (m) CD45, human (h) CD45, human (h) CD3, and human (h) CD14 antibodies were used to gate on the CD14$^+$ population. To identify tumor-infiltrating immune cells, hCD45, hCD3, hCD4, hCD8, and hCD14 antibodies were used to gate on populations according to standard procedure.

[0664] As shown in **FIG. 16B** and **16C**, the combination treatment with Siglec-7 antibody 10B5 and the anti-PD-1 antibody Keytruda® (pembrolizumab) significantly inhibited tumor growth *in vivo* in the patient-derived melanoma tumor model in mice engrafted with human immune stem cells. Tumor volume at each time point was corrected for donor, tumor size at time 0 and mouse weight by multiple linear regression using R *lm()* function. At each time point, statistical significance was assessed by using R *lm()* function.

[0665] As shown in **FIG. 16D** and **16E**, the combination treatment with the Siglec-7 antibody10B5 and the anti-PD-1 antibody Keytruda® (pembrolizumab) inhibited tumor growth *in vivo* in the patient-derived melanoma tumor model that was implanted in mice engrafted with human immune stem cells from different human donors (donor #: 984480112, 165547112, and 17509112). Tumor volume at each time point was corrected for donor, tumor size at time 0 and mouse weight by multiple linear regression using R *lm()* function. At each time point, statistical significance was assessed by using R *lm()* function.

[0666] **FIG. 16B-E** depict pre-clinical efficacy of the anti-Siglec-7 antibody 10B5 as a therapeutic for treating human cancer. The Siglec-7 antibody 10B5, when delivered in combination with the anti-PD1 antibody Keytruda® (pembrolizumab), significantly reduced tumor volume in melanoma tumors (**FIG. 16B-E**). Notably, Keytruda® (pembrolizumab) in combination with an isotype control (Alector CTR mAb) did not inhibit tumor growth (**FIG. 16B-E**).

[0667] As shown in **FIG. 16F**, the combination treatment with the Siglec-7 antibody 10B5 and the anti-PD-1 antibody Keytruda® (pembrolizumab) reduced cell surface levels of Siglec-7 in peripheral blood hCD45$^+$ CD14$^+$ myeloid cells from peripheral blood in a mouse tumor model that was engrafted with human immune stem cells and the patient-derived xenograft CTG-0202 melanoma tumors. Statistical significance was assessed by using the R *lm()* function.

[0668] As shown in **FIG. 16G**, the combination treatment with the Siglec-7 antibody 10B5 and the anti-PD-1 antibody Keytruda® (pembrolizumab) reduced the number of tumor infiltrating hCD45$^+$ CD14$^+$ myeloid cells in a mouse tumor model that was engrafted with human immune stem cells and the patient-derived xenograft CTG-0202 melanoma tumors. Statistical significance was assessed by using the R *lm()* function.

[0669] As shown in **FIG. 16H**, the combination treatment with the Siglec-7 antibody10B5 and the anti-PD-1 antibody Keytruda® (pembrolizumab) increased the number of tumor infiltrating hCD45$^+$ CD3$^+$ T cells in a mouse tumor model that was engrafted with human immune stem cells and the patient-derived xenograft CTG-0202 melanoma tumors. Statistical significance was assessed by using the R *lm()* function.

[0670] As shown in **FIG. 16I**, the combination treatment with the Siglec-7 antibody 10B5 and the anti-PD-1 antibody Keytruda® (pembrolizumab) reduced the number of peripheral blood hCD45$^+$ CD14$^+$ myeloid cells in a mouse tumor model that was engrafted with human immune stem cells and the patient-derived xenograft CTG-0202 melanoma tumors. Statistical significance was assessed by using the R *lm()* function.

[0671] Importantly for the studies described herein, both the tumor and the immune system responding to the tumor were human. The immune system of the mouse was humanized using a method whereby the mouse immune system was genetically ablated and myeloablated with irradiation, then replaced with human donor CD34$^+$ hematopoietic stem and progenitor cells that repopulated and developed myeloid and lymphoid immune cells. The tumor was a patient-derived melanoma. The human-specific Siglec-7 antibody 10B5 displayed target specific engagement and downregulation of human Siglec-7. Receptor downregulation was significant on peripheral and tumor CD14$^+$ myeloid cells. Therefore any effects on tumor volume, tumor growth rate, increased tumor infiltration of CD3$^+$ T-cells, and reduced CD14+ cells were the result of 10B5 antibody-mediated downregulation of Siglec-7 on human myeloid immune cells.

[0672] The data presented above showed that the Siglec-7 antibody 10B5 was a potent and significant receptor-downregulating antibody on peripheral and tumor infiltrating myeloid cells. Analysis of the tumor infiltrating immune cell populations demonstrated a significant increase of CD3$^+$ T-cells. Additionally, myeloid cell populations were also affected by Siglec-7 antibody treatment. A significant decrease in CD14$^+$ myeloid cells was observed in tumors, as well as in

peripheral blood cell populations. This data suggested that downregulation of Siglec-7 functionally altered tumor infiltrating immune cell populations. Taken together, these studies demonstrated the pre-clinical efficacy of anti-Siglec-7 antibodies as a therapeutic for treating human cancer.

Example 45: Effects of Siglec-7 antibodies on myeloid-derived suppressor cells (MDSC)

[0673] Peripheral blood mononuclear cells (PBMCs) were separated from whole blood by ficoll centrifugation. After ACK lysis of red blood cells, human PBMCs were cultured in RPMI media supplemented 10% FBS (Hyclone), L-glutamine, Pen/Strep, non-essential amino acids, sodium pyruvate, and a suppressive cytokine cocktail containing: 10ng/ml recombinant IL-6 (Sigma-Aldrich), IL-8 (R&D Systems), and GM-CSF (R&D Systems). In some experiments, human PBMCs were cultured with tumor conditioned media supplemented with 10ng/ml GM-CSF. Tumor conditioned media was RPMI media with the supplements noted above, except IL-6 and IL-8, that had been harvested from tumor cell line cultures and sterile filtered with 0.2 μm membrane. Cytokines, antibodies (anti-Siglec-7 antibodies 4E3 or 10B5, or isotype control antibodies), or rhGM-CSF spiked tumor supernatant were added to human PBMCs every 2-3 days for a week.

[0674] For FACS analysis, suspension and adherent cells were harvested and tested for expression of the indicated receptors by standard FACS procedure. Importantly, dead cells were gated out of the expression analysis, and all MFI values were derived from live cells. Plotted values were calculated as delta MFI compared to isotype treated conditions.

[0675] For T cell proliferation assays, myeloid-derived suppressor cells (MDSCs) were isolated by magnetic-based negative selection using a cocktail of antibodies to CD2, CD3, CD8, CD19, and CD56 (STEMCELL Technologies) after 7 days of culturing. Isolated MDSCs were plated at 50,000 cells per well in a flat-bottom 96-well non-TC plate and treated with the indicated antibodies prior to addition of T cells.

[0676] Non-autologous donor CD3 or CD8 T-cells were isolated from whole blood using RosetteSep selection technology (STEMCELL Technologies), labeled with CFSE (Life Technologies), and activated with 10U/mL IL-2 and 1:1 ratio CD3/CD28 T-Activator Dynabeads (Life Technologies). MDSCs and T cells were co-cultured at a ratio of 1:2 or 50,000: 100,000 cells per well. CFSE was detected on a FACS Canto (BD Biosciences) 3 days post co-culture. Data were analyzed with FlowJo version 10.1 (TreeStar) software.

[0677] As shown in **FIG. 17A** and **FIG.17B**, the anti-Siglec-7 antibodies 10B5 and 4E3 decreased expression of PD-L1 and PD-L2 (PD-1 ligands), B7-H3 (a potent T-cell check point inhibitor), CD200R (an inhibitory signaling receptor), and CD163 and CD206 (M2-type markers) on the surface of MDSCs. These results indicated that anti-Siglec-7 antibody-mediated target engagement, and subsequent downregulation of Siglec-7, led to phenotypic alterations on MDSCs, including reduced expression of suppressive ligands and receptors.

[0678] As shown in **FIG. 17C** and **FIG. 17D**, the anti-Siglec-7 antibodies 10B5 and 4E3 increased T cell proliferation in the presence of MDSCs, allowing for the generation of more tumor-fighting T cells. MDSCs co-cultured with activated T cells suppressed T-cell proliferation by ~25%. In these studies, MDSCs treated with the Siglec-7 antibodies 10B5 or 4E3 induced less suppression of T-cell proliferation (**FIG. 17C** and **FIG. 17D**). An isotype control (mIgG1) antibody did not affect MDSC-dependent suppression of T cell proliferation. Treatment of MDSCs with Siglec-7-targeting antibodies was more effective in alleviating MDSC-mediated T-cell suppression than was a PD-L1 blocking antibody (**FIG. 17C** and **FIG. 17D**).

[0679] Finally, the ability of the anti-Siglec-7 antibodies to induce cell death of MDSCs was tested. Human peripheral blood cells were ficolled, red blood cells were lysed with ACK lysis buffer, and cells were washed 3 times before plating in RPMI with 10% FBS, Pen/Strep, 1mM Glutamine, non-essential amino acids, and sodium pyruvate. Human PBMCs were cultured for one week at 37°C in 5% CO_2 with the following cytokines: 10ng/ml rhGM-CSF (R&D), 10ng/ml rhIL-8 (R&D), and 10ng/ml rhIL-6 (Sigma). To some flasks, mIgG1 (BioXcell) isotype antibody, or the Siglec-7 antibodies 4E3 or 10B5 were added. Every 2-3 days media, cytokines, and antibodies where noted were replenished. After 7 days of culture, cells were harvested by scraping and triterating, and resuspended in PBS with 2% FBS and 1mM EDTA for FACS analysis. For assessment of live and dead cell populations, Live/Dead Fixable Aqua dead cell stain (Thermo Fisher) was diluted 1:500 in PBS with 2% FBS and 1mM EDTA and incubated for 30 minutes on ice. Cells were washed 3 times in buffer and analyzed on a BD FACS Canto (BD Biosciences) for forward and side scatter and AmCyan fluorescence. Data were analyzed with FlowJo (Tree Star Software).

[0680] As shown in **FIG. 18**, the anti-Siglec-7 antibodies 4E3 and 10B5 were capable of inducing cell death in a subset of differentiating MDSCs. Both anti-Siglec-7 antibodies induced an approximately 30% increase in MDSC cell death (**FIG. 18**, middle row) relative to media alone, or isotype-treated cells.

[0681] Taken together, the above studies indicated that the anti-Siglec-7 antibodies 10B5 and 4E3 were capable of phenotypically altering MDSCs (*e.g.*, by reducing expression of suppressive ligands and receptors), effecting downstream MDSC functions (*e.g.*, reducing MDSC-dependent suppression of T-cell proliferation), and inducing cell death of a subset of MDSCs.

CLAIMS

What is claimed is:

1. An isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody decreases cellular levels of Siglec-7.

2. The anti-Siglec-7 antibody of claim 1, wherein the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 without inhibiting interaction between Siglec-7 and one or more Siglec-7 ligands.

3. The anti-Siglec-7 antibody of claim 1, wherein the antibody further inhibits interaction between Siglec-7 and one or more Siglec-7 ligands.

4. An isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 and inhibits interaction between Siglec-7 and one or more Siglec-7 ligands.

5. The anti-Siglec-7 antibody of any one of claims 1-4, wherein the anti-Siglec-7 antibody decreases cell surface levels of Siglec-7, decreases intracellular levels of Siglec-7, decreases total levels of Siglec-7, or any combination thereof.

6. The anti-Siglec-7 antibody of any one of claims 1-5, wherein the anti-Siglec-7 antibody induces Siglec-7 degradation, Siglec-7 cleavage, Siglec-7 internalization, Siglec-7 shedding, downregulation of Siglec-7 expression, or any combination thereof.

7. The anti-Siglec-7 antibody of any one of claims 1-6, wherein the antibody decreases cellular levels of Siglec-7 *in vivo*.

8. The anti-Siglec-7 antibody of any one of claims 1-7, wherein the anti-Siglec-7 antibody inhibits cell surface clustering of Siglec-7.

9. The anti-Siglec-7 antibody of any one of claims 1-8, wherein the anti-Siglec-7 antibody inhibits one or more Siglec-7 activities.

10. The anti-Siglec-7 antibody of claim 9, wherein the one or more Siglec-7 activities are selected from the group consisting of:

(a) Siglec-7 binding to one or more Siglec-7 ligands, optionally wherein the one or more Siglec-7 ligands are selected from the group consisting of sialic acid-containing glycoproteins, sialic acid-containing glycolipids, and any combination thereof;

(b) decreasing proliferation of one or more cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils,

M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia;

(c) inhibiting migration of one or more cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia;

(d) inhibiting one or more functions of one or more cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, macrophages, neutrophils, NK cells, M1 macrophages, M1 neutrophils, M1 NK cells, activated M1 macrophages, activated M1 neutrophils, activated M1 NK cells, M2 macrophages, M2 neutrophils, M2 NK cells, monocytes, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia;

(e) inhibition of one or more types of clearance selected from the group consisting of apoptotic neuron clearance, nerve tissue debris clearance, dysfunctional synapse clearance, non-nerve tissue debris clearance, bacteria clearance, other foreign body clearance, disease-causing protein clearance, disease-causing peptide clearance, and tumor cell clearance; optionally wherein the disease-causing protein is selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides and the tumor cell is from a cancer selected from the group consisting of 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, and thyroid cancer;

(f) inhibition of tumor cell killing by one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells;

(g) inhibiting anti-tumor cell proliferation activity of one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells;

(h) modulated expression of one or more inflammatory receptors, optionally wherein the one or more inflammatory receptors comprise CD86 and the one or more inflammatory receptors are expressed on one or more of microglia, macrophages, neutrophils, NK cells, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells;

(i) promoting or rescuing functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells;

(j) increasing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, tumor-associated NK cells, and regulatory T cells into tumors;

(k) increasing the number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ;

(l) enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC);

(m) decreasing activation of tumor-specific T lymphocytes with tumor killing potential;

(n) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential;

(o) increasing tumor volume;

(p) increasing tumor growth rate; and

(q) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more target proteins selected from the group consisting of PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1,

CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines.

11. The anti-Siglec-7 antibody of any one of claims 1-8, wherein the anti-Siglec-7 antibody exhibits one or more activities selected from the group consisting of:

(a) increasing the number of tumor infiltrating $CD3^+$ T cells;

(b) inhibiting Siglec-7 binding to one or more Siglec-7 ligands;

(c) decreasing cellular levels of Siglec-7 in peripheral immune cells;

(d) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in blood;

(e) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in the tumor;

(f) reducing PD-L1 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(g) reducing PD-L2 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(h) reducing CD11b levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(i) reducing B7-H3 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(j) reducing CD200R levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(k) reducing CD163 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(l) reducing CD206 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(m) decreasing tumor growth rate of solid tumors;

(n) reducing tumor volume;

(o) increasing efficacy of one or more PD-1 inhibitors;

(p) increasing efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, optionally wherein the one or more checkpoint inhibitor therapies and/or immune-modulating therapies target one or more of CTL4, the

adenosine pathway, PD-L1, PD-L2, OX40, TIM3, LAG3, or any combination thereof;

(q) inhibiting differentiation, survival, and/or one or more functions of non-tumorigenic myeloid-derived suppressor cells (MDSC);

(r) inducing cell death of one or more myeloid-derived suppressor cells (MDSC); and

(s) increasing proliferation of T cells in the presence of non-tumorigenic myeloid-derived suppressor cells (MDSC).

12. The anti-Siglec-7 antibody of any one of claims 2-11, wherein the one or more Siglec-7 ligands are selected from the group consisting of Siglec-7 ligands expressed on red blood cells, Siglec-7 ligands expressed on bacterial cells, Siglec-7 ligands expressed on apoptotic cells, Siglec-7 ligands expressed on nerve cells, Siglec-7 ligands expressed on glial cells, Siglec-7 ligands expressed on microglia, Siglec-7 ligands expressed on astrocytes, Siglec-7 ligands expressed on tumor cells, Siglec-7 ligands expressed on viruses, Siglec-7 ligands expressed on dendritic cells, Siglec-7 ligands bound to beta amyloid plaques, Siglec-7 ligands bound to Tau tangles, Siglec-7 ligands on disease-causing proteins, Siglec-7 ligands on disease-causing peptides, Siglec-7 ligands expressed on macrophages, Siglec-7 ligands expressed on neutrophils, Siglec-7 ligands expressed on monocytes, Siglec-7 ligands expressed on natural killer cells, Siglec-7 ligands expressed on T cells, Siglec-7 ligands expressed on T helper cells, Siglec-7 ligands expressed on cytotoxic T cells, Siglec-7 ligands expressed on B cells, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor dendritic cells, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor macrophages, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor neutrophils, Siglec-7 ligands expressed on tumor-imbedded immunosuppressor NK cells, Siglec-7 ligands expressed on myeloid-derived suppressor cells, Siglec-7 ligands expressed on regulatory T cells, secreted mucins, sialic acid, sialic acid-containing glycolipids, sialic acid-containing glycoproteins, alpha-2,8-disialyl containing glycolipids, branched alpha-2,6-linked sialic acid-containing glycoproteins, terminal alpha-2,6-linked sialic acid-containing glycolipids, terminal alpha-2,3-linked sialic acid-containing glycoproteins, and disialogangliosides.

13. The anti-Siglec-7 antibody of any one of claims 1-12, wherein the cellular levels of Siglec-7 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, and wherein the cellular levels of Siglec-7 are measured utilizing an *in vitro* cell assay.

14. The anti-Siglec-7 antibody of any one of claims 1-13, wherein the anti-Siglec-7 antibody does not reduce TREM2 expression.

15. The anti-Siglec-7 antibody of any one of claims 1-14, wherein the anti-Siglec-7 antibody binds a discontinuous Siglec-7 epitope.

16. The anti-Siglec-7 antibody of claim 15, wherein the discontinuous Siglec-7 epitope comprises two or more peptides, three or more peptides, four or more peptides, five or more peptides, six or more peptides, seven or more peptide, eight or more peptides, nine or more peptides, or 10 or more peptides.

17. The anti-Siglec-7 antibody of claim16, wherein each of the peptides comprise five or more, six or more, seven or more, eight or more, nine or more, 10 or more, 11 or more, 12 or more, 13 or more 14 or more, 15 or more, 16 or more, 17 or more, 18 or more, 19 or more, or 20 or more amino acid residues of the amino acid sequence of SEQ ID NO: 1; or five or more, six or more, seven or more, eight or more, nine or more, 10 or more, 11 or more, 12 or more, 13 or more 14 or more, 15 or more, 16 or more, 17 or more, 18 or more, 19 or more, or 20 or more amino acid residues on a mammalian Siglec-7 protein corresponding to the amino acid sequence of SEQ ID NO: 1.

18. The anti-Siglec-7 antibody of any one of claims 1-14, wherein the anti-Siglec-7 antibody binds to a conformational epitope of Siglec-7.

19. The anti-Siglec-7 antibody of any one of claims 1-14, wherein the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 39-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of SEQ ID NO: 1; or within amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 39-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of SEQ ID NO: 1.

20. The anti-Siglec-7 antibody of any one of claims 1-14, wherein the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues selected from the group consisting of:

i. amino acid residues 60-69 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 of SEQ ID NO: 1;
ii. amino acid residues 60-69 and 84-95 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 and 84-95 of SEQ ID NO: 1;
iii. amino acid residues 60-69 and 117-127 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1;
iv. amino acid residues 68-78 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 68-78 of SEQ ID NO: 1;

v. amino acid residues 84-95 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 84-95 of SEQ ID NO: 1;

vi. amino acid residues 111-122 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 111-122 of SEQ ID NO: 1;

vii. amino acid residues 111-122 and 282-291 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 111-122 and 282-291 of SEQ ID NO: 1;

viii. amino acid residues 113-123 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 113-123 of SEQ ID NO: 1;

ix. amino acid residues 113-125 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 113-125 of SEQ ID NO: 1;

x. amino acid residues 117-127 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 117-127 of SEQ ID NO: 1; and

xi. amino acid residues 282-291 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 282-291 of SEQ ID NO: 1.

21. The anti-Siglec-7 antibody of any one of claims 1-14, wherein the anti-Siglec-7 antibody binds to one or more amino acid residues selected from the group consisting of M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian Siglec-7 protein corresponding to an amino acid residue selected from the group consisting of M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1.

22. The anti-Siglec-7 antibody of any one of claims 1-21, wherein the anti-Siglec-7 antibody competes with one or more antibodies selected from the group consisting of 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof for binding to Siglec-7.

23. The anti-Siglec-7 antibody of any one of claims 1-22, wherein the anti-Siglec-7 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain, the heavy chain variable domain, or both comprise at least one, two, three, four, five, or six HVRs selected from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 of a

monoclonal antibody selected from the group consisting of: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8.

24. The anti-Siglec-7 antibody of claim 23, wherein:

(a) the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 7-19 and 476;

(b) the HVR-L2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 20-32 and 477;

(c) the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 33-45 and 478;

(d) the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-58 and 479;

(e) the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 59-71 and 480-482; or

(f) the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 72-84 and 483.

25. The anti-Siglec-7 antibody of claim 23 or 24, wherein:

(a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 7, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 59, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 72;

(b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 60, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 73;

(c) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 62, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 75;

(d) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 37, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 50, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 63, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 76;

(e) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 12, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 25, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 38, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 64, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 77;

(f) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 13, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 39, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 52, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 65, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 78;

(g) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79;

(h) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 480, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74;

(i) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of

SEQ ID NO: 481 and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79;

(j) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 41, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 67, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 80;

(k) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 42, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 68, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 81;

(l) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 82;

(m) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83;

(n) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 476, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 477, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 478, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83;

(o) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid

sequence of SEQ ID NO: 479, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 482, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 483; or

(p) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 84.

26. The anti-Siglec-7 antibody of any one of claims 1-22, wherein the anti-Siglec-7 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises:

(a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7-19 and 476, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 7-19 and 476;

(b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 20-32 and 477, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 20-32 and 477; and

(c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 33-45 and 478, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 33-45 and 478; and

wherein the heavy chain variable domain comprises:

(a) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-58 and 479, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-58 and 479;

(b) an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 59-71 and 480-482, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 59-71 and 480-482; and

(c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 72-84 and 483, or an amino acid sequence with at least about 90%

homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 72-84 and 483.

27. The anti-Siglec-7 antibody of any one of claims 1-26, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 189-318, 449-461, and 484-489; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 319-448, 462-474, and 490-496.

28. The anti-Siglec-7 antibody of any one of claims 1-26, wherein the anti-Siglec-7 antibody comprises a light chain variable domain of a monoclonal antibody selected from the group consisting of: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8; and/or a heavy chain variable domain of a monoclonal antibody selected from the group consisting of: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8.

29. An isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues 39-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of SEQ ID NO: 1; or within amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 39-353, 39-149, 93-104, 95-105, 39-122, 123-149, 150-233, 240-336, 264-273, 295-306, 327-341, or 337-353 of SEQ ID NO: 1.

30. The anti-Siglec-7 antibody of claim 29, wherein the anti-Siglec-7 antibody binds to one or more amino acids within amino acid residues selected from the group consisting of:

i. amino acid residues 60-69 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 of SEQ ID NO: 1;
ii. amino acid residues 60-69 and 84-95 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 and 84-95 of SEQ ID NO: 1;
iii. amino acid residues 60-69 and 117-127 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 60-69 and 117-127 of SEQ ID NO: 1;
iv. amino acid residues 68-78 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 68-78 of SEQ ID NO: 1;
v. amino acid residues 84-95 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 84-95 of SEQ ID NO: 1;

vi. amino acid residues 111-122 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 111-122 of SEQ ID NO: 1;

vii. amino acid residues 111-122 of SEQ ID NO: 1 and 282-291 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 111-122 of SEQ ID NO: 1 and 282-291 of SEQ ID NO: 1;

viii. amino acid residues 113-123 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 113-123 of SEQ ID NO: 1;

ix. amino acid residues 113-125 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 113-125 of SEQ ID NO: 1;

x. amino acid residues 117-127 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 117-127 of SEQ ID NO: 1; and

xi. amino acid residues 282-291 of SEQ ID NO: 1, or amino acid residues on a mammalian Siglec-7 protein corresponding to amino acid residues 282-291 of SEQ ID NO: 1.

31. An isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody binds to one or more amino acid residues selected from the group consisting of M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian Siglec-7 protein corresponding to an amino acid residue selected from the group consisting of M30, Q31, V44, R45, S47, F48, Y50, I72, W74, N81, T103, K104, T107, and R124 of SEQ ID NO: 1.

32. An isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain, the heavy chain variable domain, or both comprise at least one, two, three, four, five, or six HVRs selected from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 of a monoclonal antibody selected from the group consisting of: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8.

33. The anti-Siglec-7 antibody of claim 32, wherein:

(a) the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 7-19 and 476;

(b) the HVR-L2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 20-32 and 477;

(c) the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 33-45 and 478;

(d) the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-58 and 479;

(e) the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 59-71 and 480-482; or

(f) the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 72-84 and 483.

34. The anti-Siglec-7 antibody of claim 32 or 33, wherein:

(a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 7, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 20, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 46, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 59, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 72;

(b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 21, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 34, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 60, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 73;

(c) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 22, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 35, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 48, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 61, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74;

(d) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 36, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 49, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 62, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 75;

(e) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 24, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 37, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 50, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 63, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 76;

(f) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 12, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 25, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 38, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 64, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 77;

(g) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 13, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 39, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 52, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 65, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 78;

(h) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 66, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79;

(i) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 480, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 74;

(j) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 14, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 27, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 40, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 53, the HVR-H2 comprises the amino acid sequence of

SEQ ID NO: 481 and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 79;

(k) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 15, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 41, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 54, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 67, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 80;

(l) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 42, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 68, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 81;

(m) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 43, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 56, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 82;

(n) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83;

(o) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 476, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 477, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 478, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 57, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 70, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 83;

(p) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 18, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 31, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 44, the HVR-H1 comprises the amino acid

sequence of SEQ ID NO: 479, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 482, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 483; or

(q) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 32, the HVR-L3comprises the amino acid sequence of SEQ ID NO: 45, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 58, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 71, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 84.

35. The anti-Siglec-7 antibody of claim 32, wherein the light chain variable domain comprises:

(a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7-19 and 476, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 7-19 and 476;

(b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 20-32 and 477, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 20-32 and 477; and

(c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 33-45 and 478, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 33-45 and 478; and

wherein the heavy chain variable domain comprises:

(a) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-58 and 479, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-58 and 479;

(b) an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 59-71 and 480-482, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 59-71 and 480-482; and

(c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 72-84 and 483, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 72-84 and 483.

36. An isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 189-318, 449-461, and 484-489; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 319-448, 462-474, and 490-496.

37. An isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain of a monoclonal antibody selected from the group consisting of: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8; and/or a heavy chain variable domain of a monoclonal antibody selected from the group consisting of: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8.

38. An isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody competes with one or more antibodies selected from the group consisting of 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, 10G8, and any combination thereof for binding to Siglec-7.

39. An isolated monoclonal anti-Siglec-7 antibody which binds essentially the same Siglec-7 epitope as a monoclonal antibody selected from the group consisting of: 1A12, 1E8, 2G1, 2G4, 3E11, 4A1, 4D7, 4E3, 4E3H1, 4E3H2, 7A3, 7E11, 7F12, 10B5, 10B5L1, 10B5H1, and 10G8.

40. An isolated monoclonal anti-Siglec-7 antibody, wherein the anti-Siglec-7 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises:

(a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7-19 and 476, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 7-19 and 476;

(b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 20-32 and 477, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 20-32 and 477; and

(c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 33-45 and 478, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 33-45 and 478; and/or

wherein the heavy chain variable domain comprises:

(a) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-58 and 479, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-58 and 479;

(b) an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 59-71 and 480-482, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 59-71 and 480-482; and

(c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 72-84 and 483, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 72-84 and 483.

41. The anti-Siglec-7 antibody of any one of claims 1-40, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

42. The anti-Siglec-7 antibody of claim 41, wherein the anti-Siglec-7 antibody has an IgG1, IgG2, IgG3, or IgG4 isotype.

43. The anti-Siglec-7 antibody of claim 42, wherein the antibody binds an inhibitory Fc receptor.

44. The anti-Siglec-7 antibody of claim 43, wherein the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB).

45. The anti-Siglec-7 antibody of claim 44, wherein:

(a) the anti-Siglec-7 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-7 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: 475), 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-7 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-7 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-7 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 or, Kabat numbering.

46. The anti-Siglec-7 antibody of claim 42, wherein:

(a) the anti-Siglec-7 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, N297Q, D270A, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering;

(b) the anti-Siglec-7 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, H268E, V309L, N297A, N297Q, A330S, P331S, C232S, C233S, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or

(c) the anti-Siglec-7 antibody has an IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: E233P, F234V, L234A/F234A, L235A, G237A, E318A, S228P, L236E, S241P,

L248E, T394D, M252Y, S254T, T256E, N297A, N297Q, and any combination thereof, wherein the numbering of the residues is according to EU numbering.

47. The anti-Siglec-7 antibody of claim 46, wherein:

(a) the Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of A330L, L234F; L235E, P331S, and any combination thereof, wherein the numbering of the residues is according to EU numbering;

(b) the Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or

(c) the Fc region further comprises a S228P amino acid substitution according to EU numbering.

48. The anti-Siglec-7 antibody of any one of claims 1-40, wherein the antibody has an IgG4 isotype.

49. The anti-Siglec-7 antibody of claim 48, wherein the anti-Siglec-7 antibody comprises an S228P amino acid substitution at residue position 228, an F234A amino acid substitution at residue position 234, and an L235A amino acid substitution at residue position 235, wherein the numbering of the residue position is according to EU numbering.

50. The anti-Siglec-7 antibody of any one of claims 1-49, wherein the Siglec-7 protein is a mammalian protein or a human protein.

51. The anti-Siglec-7 antibody of any one of claims 1-50, wherein the Siglec-7 protein is a wild-type protein.

52. The anti-Siglec-7 antibody of any one of claims 1-50, wherein the Siglec-7 protein is a naturally occurring variant.

53. The anti-Siglec-7 antibody of any one of claims 1-52, wherein the Siglec-7 protein is expressed on one or more cells selected from the group consisting of human dendritic cells, human macrophages, human neutrophils, human NK cells, human monocytes, human osteoclasts, human T cells, human T helper cell, human cytotoxic T cells, human granulocytes, and human microglia.

54. The anti-Siglec-7 antibody of any one of claims 1-53, wherein the anti-Siglec-7 antibody binds specifically to a mammalian Siglec-7 protein, human Siglec-7 protein, or both.

55. The anti-Siglec-7 antibody of any one of claims 1-54, wherein the anti-Siglec-7 antibody binds Siglec-7 in a pH dependent manner.

56. The anti-Siglec-7 antibody of claim 55, wherein the anti-Siglec-7 antibody binds Siglec-7 at a pH that ranges from 5.5 to 8.0.

57. The anti-Siglec-7 antibody of claim 55, wherein the anti-Siglec-7 antibody dissociates from Siglec-7 at a pH of less than 5.0.

58. The anti-Siglec-7 antibody of any one of claims 1-57, wherein the anti-Siglec-7 antibody is an antibody fragment that binds to an epitope comprising amino acid residues on human Siglec-7 or a mammalian Siglec-7 protein.

59. The anti-Siglec-7 antibody of any one of claims 1-57, wherein the anti-Siglec-7 antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human Siglec-7, a naturally occurring variant of human Siglec-7, and a disease variant of human Siglec-7.

60. The anti-Siglec-7 antibody of claim 58 or claim 59, wherein the antibody fragment is cross-linked to a second antibody fragment that binds to one or more human proteins selected from the group consisting of human Siglec-7, a naturally occurring variant of human Siglec-7, and a disease variant of human Siglec-7.

61. The anti-Siglec-7 antibody of any one of claims 58-60, wherein the fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv, or scFv fragment.

62. The anti-Siglec-7 antibody of any one of claims 1-61, wherein the anti-Siglec-7 antibody is a murine antibody.

63. The anti-Siglec-7 antibody of any one of claims 1-62, wherein the anti-Siglec-7 antibody is a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody.

64. The anti-Siglec-7 antibody of any one of claims 1-63, wherein the anti-Siglec-7 antibody is a bispecific antibody recognizing a first antigen and a second antigen.

65. The anti-Siglec-7 antibody of claim 64, wherein the first antigen is Siglec-7 and the second antigen is:

(a) an antigen facilitating transport across the blood-brain-barrier;

(b) an antigen facilitating transport across the blood-brain-barrier selected from the group consisting of transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1

and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopep peptide, and ANG1005;

(c) a disease-causing agent selected from the group consisting of disease-causing peptides or proteins or, disease-causing nucleic acids, wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides; and

(d) ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from the group consisting of PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, and phosphatidylserine; and

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

66. The anti-Siglec-7 antibody of any one of claims 1-65, wherein the anti-Siglec-7 antibody is a conjugated antibody.

67. The anti-Siglec-7 antibody of claim 66, wherein the anti-Siglec-7 antibody is conjugated to a detectable marker, a toxin, or a therapeutic agent.

68. The anti-Siglec-7 antibody of claim 67, wherein the anti-Siglec-7 antibody is conjugated to a toxin selected from the group consisting of ricin, ricin A-chain, doxorubicin, daunorubicin, a maytansinoid, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin, diphtheria toxin, *Pseudomonas* exotoxin (PE) A, PE40, abrin, abrin A chain, modeccin A chain, alpha-sarcin, gelonin, mitogellin, retstrictocin, phenomycin, enomycin, curicin, crotin, calicheamicin, *Saponaria officinalis* inhibitor, glucocorticoid,

auristatin, auromycin, yttrium, bismuth, combrestatin, duocarmycins, dolastatin, cc1065, and a cisplatin.

69. The anti-Siglec-7 antibody of any one of claims 1-68, wherein the anti-Siglec-7 antibody is used in combination with one or more antibodies that specifically bind a disease-causing agent selected from the group consisting of disease-causing peptides, disease-causing proteins, amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and any combination thereof; or with one or more antibodies that bind an immunomodulatory protein selected from the group consisting of: PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, TREM1, TREM2, CD33, Siglec-5, Siglec-9, Siglec-11, phosphatidylserine, disease-causing nucleic acids, antisense GGCCCC (G2C4) repeat-expansion RNA, and any combination thereof.

70. The anti-Siglec-7 antibody of any one of the preceding claims, wherein the anti-Siglec-7 antibody has a dissociation constant (K_D) for human Siglec-7 and mammalian Siglec-7 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 25°C.

71. The anti-Siglec-7 antibody of any one of the preceding claims, wherein the anti-Siglec-7 antibody has a dissociation constant (K_D) for human Siglec-7 that ranges from about 9.5 nM to about 17 pM, or less than 17 pM, wherein the K_D is determined at a temperature of approximately 25°C.

72. The anti-Siglec-7 antibody of any one of the preceding claims, wherein the anti-Siglec-7 antibody binds to human dendritic cells with an EC_{50} that ranges from 2 nM to100 pM, wherein the EC_{50} is determined at a temperature of approximately 4°C.

73. The anti-Siglec-7 antibody of any one of the preceding claims, wherein the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 with an EC_{50} that ranges from 500 pM to 18 pM, wherein the EC_{50} is determined at a temperature of approximately 37°C.

74. An isolated nucleic acid comprising a nucleic acid sequence encoding the anti-Siglec-7 antibody of any one of the preceding claims.

75. A vector comprising the nucleic acid of claim 74.

76. An isolated host cell comprising the vector of claim 75.

77. A method of producing an anti-Siglec-7 antibody, comprising culturing the host cell of claim 76 so that the anti-Siglec-7 antibody is produced.

78. The method of claim 77, further comprising recovering the anti-Siglec-7 antibody produced by the host cell.

79. An isolated anti-Siglec-7 antibody produced by the method of claim 77 or claim 78.

80. A pharmaceutical composition comprising the anti-Siglec-7 antibody of any one of claims 1-73, and a pharmaceutically acceptable carrier.

81. A method of preventing, reducing risk, 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, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both.

82. The method of claim 81, wherein the disease, disorder, or injury is cancer, and wherein the agent inhibits one or more Siglec-7 activities selected from the group consisting of:

(a) promoting proliferation, maturation, migration, differentiation, and/or functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated suppressor neutrophils, tumor-associated suppressor NK cells, and regulatory T cells;

(b) enhancing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated suppressor neutrophils, tumor-associated suppressor NK cells, and regulatory T cells into tumors;

(c) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ;

(d) enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC);

(e) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10;

(f) increasing tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes;

(g) decreasing activation of tumor-specific T lymphocytes with tumor killing potential;

(h) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential;

(i) decreasing infiltration of tumor-specific NK cells with tumor killing potential;

(j) decreasing the tumor killing potential of NK cells;

(k) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response;

(l) increasing tumor volume;

(m) increasing tumor growth rate;

(n) increasing metastasis;

(o) increasing rate of tumor recurrence;

(p) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more target proteins selected from the group consisting of PD1/PDL1, CTLA4, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, and any combination thereof, or one or more cancer vaccines;

(q) inhibition of PLCγ/PKC/calcium mobilization; and

(r) inhibition of PI3K/Akt, Ras/MAPK signaling.

83. The method of claim 82, wherein the cancer expresses Siglec-7 or one or more Siglec-7 ligands.

84. The method of any one of claims 81-83, wherein the cancer is selected from the group consisting of 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), and multiple myeloma.

85. The method of any one of claims 81-84, wherein the agent exhibits one or more activities selected from the group consisting of:

(a) increasing the number of tumor infiltrating $CD3^+$ T cells;

(b) inhibiting Siglec-7 binding to one or more Siglec-7 ligands;

(c) decreasing cellular levels of Siglec-7 in peripheral immune cells

(d) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in blood;

(e) reducing the number of non-tumorigenic $CD14^+$ myeloid cells, optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic $CD14^+$ myeloid cells are present in the tumor;

(f) reducing PD-L1 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(g) reducing PD-L2 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(h) reducing CD11b levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(i) reducing B7-H3 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(j) reducing CD200R levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(k) reducing CD163 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(l) reducing CD206 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC);

(m) decreasing tumor growth rate of solid tumors;

(n) reducing tumor volume;

(o) increasing efficacy of one or more PD-1 inhibitors;

(p) increasing efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, optionally wherein the one or more checkpoint inhibitor therapies and/or immune-modulating therapies target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, LAG3, or any combination thereof;

(q) inhibiting differentiation, survival, and/or one or more functions of non-tumorigenic myeloid-derived suppressor cells (MDSC);

(r) inducing cell death of one or more myeloid-derived suppressor cells (MDSC);

(s) increasing proliferation of T cells in the presence of non-tumorigenic myeloid-derived suppressor cells (MDSC).

86. A method of inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof, comprising administering

to the individual a therapeutically effective amount of an agent that decreases cellular levels of Siglec-7, inhibits interaction between Siglec-7 and one or more Siglec-7 ligands, or both.

87. The method of claim 86, wherein the one or more immune cells are selected from the group consisting of dendritic cells, macrophages, neutrophils, NK cells, microglia, T cells, T helper cells, cytotoxic T cells, and any combination thereof.

88. The method of any one of claims 81-87, wherein the agent is selected from the group consisting of an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide.

89. The method of any one of claims 81-87, wherein the agent is an isolated anti-Siglec-7 antibody.

90. The method of claim 89, wherein the anti-Siglec-7 antibody is the anti-Siglec-7 antibody of any one of claims 1-73.

91. A method of decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an agent that binds or interacts with Siglec-7.

92. The method of claim 91, wherein the agent is an isolated anti-Siglec-7 antibody or anti-Siglec-7 antibody conjugate.

93. The method of claim 92, wherein the anti-Siglec-7 antibody is the anti-Siglec-7 antibody of any one of claims 1-73.

94. A method of decreasing cellular levels of Siglec-7 on one or more cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated anti-Siglec-7 antibody.

95. The method of claim 94, wherein the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 *in vivo*.

96. The method of claim 94 or claim 95, wherein the anti-Siglec-7 antibody decreases cellular levels of Siglec-7 with an EC_{50} that ranges from 500 pM to 18 pM, wherein the EC_{50} is determined at a temperature of approximately 37°C.

97. The method of any one of claims 94-96, wherein the anti-Siglec-7 antibody has a dissociation constant (K_D) for human Siglec-7 that ranges from about 10 nM to 10 pM, or less than 10 pM, wherein the K_D is determined at a temperature of approximately 25°C.

98. The method of any one of claim 94-97, wherein the anti-Siglec-7 antibody binds to human dendritic cells with an EC_{50} that ranges from 2 nM to100 pM, wherein the EC_{50} is determined at a temperature of approximately 4°C.

99. The method of any one of claim 94-98, wherein the anti-Siglec-7 antibody is the anti-Siglec-7 antibody of any one of claims 1-73.

100. The method of any one of claims 81-99, further comprising administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or one or more standard or investigational anti-cancer therapies.

101. The method of claim 100, wherein the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the anti-Siglec-7 antibody.

102. The method of claim 100 or claim 101, wherein the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from the group consisting of an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti- B- and T-lymphocyte attenuator (BTLA) antibody, an anti-Killer inhibitory receptor (KIR) antibody, an anti-GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, an anti-TNFa antibody, an anti-CD33 antibody, an anti-Siglec-5 antibody, an anti-Siglec-9 antibody, an anti-Siglec-11 antibody, an antagonistic anti-TREM1 antibody, an antagonistic anti-TREM2 antibody, and any combination thereof.

103. The method of claim 100, wherein the one or more standard or investigational anti-cancer therapies are selected from the group consisting of radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib therapy, trastuzumab therapy, etanercept therapy, adoptive cell transfer (ACT) therapy, chimeric antigen receptor T cell transfer (CAR-T) therapy, vaccine therapy, and cytokine therapy.

104. The method of any one of claims 81-103, further comprising administering to the individual at least one antibody that specifically binds to an inhibitory cytokine.

105. The method of claim 104, wherein the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the anti-Siglec-7 antibody.

106. The method of claim 104 or claim 105, wherein the at least one antibody that specifically binds to an inhibitory cytokine is selected from the group consisting of an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof.

107. The method of any one of claims 81-106, further comprising administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein.

108. The method of claim 107, wherein the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the anti-Siglec-7 antibody.

109. The method of claim 107 or claim 108, wherein the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from the group consisting of an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonistic anti-TREM1 antibody, an agonistic anti-TREM2 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, and any combination thereof.

110. The method of any one of claims 81-109, further comprising administering to the individual at least one stimulatory cytokine.

111. The method of claim 110, wherein the at least one stimulatory cytokine is administered in combination with the anti-Siglec-7 antibody.

112. The method of claim 110 or claim 111, wherein the at least one stimulatory cytokine is selected from the group consisting of IFN-a4, IFN-b, IL-1β, TNF-α, IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, IL-33, MCP-1, MIP-1-beta, and any combination thereof.

113. A method of assessing responsiveness of an individual in need thereof to an agent that binds or interacts with Siglec-7, the method comprising:

a. measuring the expression levels of $CD45^+$ and $CD14^+$ on non-tumorigenic myeloid cells in a blood sample obtained from the individual prior to administering to the individual an agent that binds or interacts with Siglec-7;
b. administering to the individual a therapeutically effective amount of the agent; and
c. measuring the expression levels of $CD45^+$ and $CD14^+$ on non-tumorigenic myeloid cells in a blood sample obtained from the individual after administration of the agent,

wherein a reduction in the levels of $CD45^+$ $CD14^+$ on non-tumorigenic myeloid cells after administration of the anti-Siglec-7 antibody indicates the individual is responsive to the agent.

114. The method of claim 113, further comprising administering one or more additional therapeutically effective amounts of the agent.

115. The method of claim 112 or claim 113, wherein the agent is selected from the group consisting of an antibody, a soluble Siglec-7 receptor, a Siglec-7-Fc fusion protein, a Siglec-7 immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide.

116. The method of claim 112 or claim 113, wherein the agent is an isolated anti-Siglec-7 antibody or anti-Siglec-7 antibody conjugate.

117. The method of claim 112 or claim 113, wherein the anti-Siglec-7 antibody is the anti-Siglec-7 antibody of any one of claims 1-73.

```
Human Siglec-7                --MLLLLLLPLLWGRERVEGQKSNRKDYSLTMQSSVTVQEGMCVHVRCSFSYPVDSQTDS   58
Chimpanzee Siglec-7           -MLLLLLLPPLLWGRERVEGQKSNRKDYSLTMQSSVTVQEGMCVHVRCSFSYPVDSQTDS   59
Pygmy Chimpanzee Siglec-7     -MLLLLLLIPLLWGRERVEGQKSNRKDYSLTMQSSVTVQEGMCVHVRCSFSYPVDSQTDS   59
Orangutan Siglec-7            MLLLLLLFLPLLWGRERVEGQKNNRKDYSLMMQSSVTVQEGLCVHVQCSFSYPVDSQTDS   60
Gorilla Siglec-7              -MLLLLLLIPLLWGRERVEGQKSKRKDYSLTMQSSVTVQEGMCVHVRCSFSYPVDSQTDS   59
Gibbon Siglec-7               -MLLLLLLIPLLWGRERVEGQKSNQKNYPLMMQSSVTVQEGLCVHVRCSFSYPVDSQTDS   59
                                :*****: ********************.:::*:* * ********************:*****:**********

Human Siglec-7                DPVHGYWFRAGNDISWKAPVATNNPAWAVQEETRDRFHLLGDPQTKNCTLSIRDARMSDA   118
Chimpanzee Siglec-7           DPVHGYWFWAENDISWKAPVATNNPARAVREETRDRFHLLGDPQTKNCTLSIRDARMSDA   119
Pygmy Chimpanzee Siglec-7     DPVHGYWFRAENDISWKAPVATNNPARAVREETRDRFHLLGDPQTKNCTLSIRDARMSDA   119
Orangutan Siglec-7            DPVHGYWFRAGDDISWKAPVATNNPAQAVREETRDRFHLLGDPQTKNCTLSIRDARMSDA   120
Gorilla Siglec-7              DPVHGYWFRAENDISWKAPVATNDPARAVREETRDRFHLLGDPQTKNCTLSIRDARMSDA   119
Gibbon Siglec-7               DPVHGYWFRAGDDISWKTPVATNNRARAVREETRDRFHLLGDPQTKNCTLSIRDARMSDA   119
                              ********** * :******:******: * **:**********************************

Human Siglec-7                GRYFFRMEKGNIKWNYKYDQLS----------------------------------------   140
Chimpanzee Siglec-7           GRYFFRMEKGNIKWNYKHDQLSVNVTASQAPLSRYRLEVLELVTVQEGXCVSVPCSVLXP   179
Pygmy Chimpanzee Siglec-7     GRYFFRMEKGNIKWNYKYDQLS----------------------------------------   141
Orangutan Siglec-7            GRYFFRMERGNIKWNYKYDRLSVNVTASQAPPSRYRLEVPESVTVQEGLCVSVPCSVLXP   180
Gorilla Siglec-7              GRYFFRMEKGNIKWNYKYDQLS----------------------------------------   141
Gibbon Siglec-7               GTYFYRMERGKIKWNYKYHQLS----------------------------------------   141
                              * **:***:*:*******:.:**

Human Siglec-7                ----------------------------------------------------------------   140
Chimpanzee Siglec-7           YYNXTDSSPVHGCWFKKGINIQWNNPVATNIPNGKVQETRGRFHLLGDLKTNNCSLSIRD   239
Pygmy Chimpanzee Siglec-7     ----------------------------------------------------------------   141
Orangutan Siglec-7            YYNWTDSSPVHGCWFKKGINIQWNNPVATNIPNGKVEETRGRFHLLGDLKTNNCSLSIRD   240
Gorilla Siglec-7              ----------------------------------------------------------------   141
Gibbon Siglec-7               ----------------------------------------------------------------   141

Human Siglec-7                ----------------------------------VNVTALTHRPNILIPGTLESGCFQNLTCSVPW   172
Chimpanzee Siglec-7           ARKGDLGNYYFQVERGQIRWNYKTKQLSVNVTALTHRPNILIPGTLESGCFQNLTCSVPW   299
Pygmy Chimpanzee Siglec-7     ----------------------------VNVTALTHRPNILIPGTLESGCFQNLTCSVPW   173
Orangutan Siglec-7            ARKGDLGNYYFQVERGXIRWNYKMKQLSVNVTALTHRPNILIPGTLESGCFQNLTCSVPW   300
Gorilla Siglec-7              ----------------------------VNVTALTHRPNILIPSTLESGCFQNLTCSVPW   173
Gibbon Siglec-7               ----------------------------VHVTALTHRPNIVIPGTLESGCFQNLTCSVPW   173
                                                           *.**********:**.**********************

Human Siglec-7                ACEQGTPPMISWMGTSVS-PLHPSTTRSSVLTLIPQPQHHGTSLTCQVTLPGAGVTTNRT   231
Chimpanzee Siglec-7           ACEQGTPPMISWMGTSVS-PLHPSTTRSSVLTLIPQPQHHGTSLTCQVTLPGAGVTTNRT   358
Pygmy Chimpanzee Siglec-7     ACEQGTPPMISWMGTSVS-PLHPSTTRSSVLTLIPQPQHHGTSLTCQVTLPGAGVTTNRT   232
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FIG. 1A

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Orangutan Siglec-7   ACEQGTPPMISWMGTSVSTHLHPSTTRSSVLTLIPQXEDHGTNFTLQYVLTPAYVTVCSI  360
Gorilla Siglec-7     ACEQGTPPMISWMGTSVS-PLHPSTTRSSVLTLIPQPQHHGTSLTCQVTLPGAGVTTNRT  232
Gibbon Siglec-7      ACEQGTPPMISWMGTSLS-PLHPSTTRSSVLTLIPQPQDHGTSLTCQVTLPGAGVTTNRT  232
                     ********************;*  ********************  :.***.:* * .* *  **.

Human Siglec-7       -IQLNVSYPPQNL--TVTVFQGEGTASTALGNSSSLSVLEGQSLRLVCAVDSNPPARLSW  288
Chimpanzee Siglec-7  -IQLNVSYPPQNL--TVTVFQGEGTASTALGNSSSLSVLEGQSLRLVCAVDSNPPARLSW  415
Pygmy Chimpanzee Siglec-7 -IQLNVSYPPQNL--TVTVFQGEGTASTALGNSSSLSVLEGQSLRLVCAVDSNPPARLSW  289
Orangutan Siglec-7   PQSHSVSFLPVSITTLSLXPFNFFSTASTALGNSSSLSVLEGQSLRLVCAVDSNPPARLSW  420
Gorilla Siglec-7     -IQLNVSYPPQNL--TVTIFQGEGTASTALGNSSSLSVLEGQSLRLVCAVDSNPPARLSW  289
Gibbon Siglec-7      -IRLNVSYPPQNL--TVTVFQGEGTASTALGNSSSLSVLEGQSLRLVCAVDSNPPARLSW  289
                        .**: * .: ::  *:  .**********************************

Human Siglec-7       TWRSLTLYPSQPSNPLVLELQVHLGDEGEFTCRAQNSLGSQHVSLNLSLQQEYTGKMRPV  348
Chimpanzee Siglec-7  TWRSLTLYPSQPSNPLVLELQVHLGDEGEFTCRAQNSLGSQHVSLNLSLQHEYTGKMRPV  475
Pygmy Chimpanzee Siglec-7 TWRSLTLYPSQPSNPLVLELQVHLGDEGEFTCRAQNSLGSQHVSLNLSLQHEYTGKMRPV  349
Orangutan Siglec-7   TWRSLTLYPSQPSNPLVLELRVHLGDEGECICRAQNSLGSQHVSLNLSLQHEYTGKMRPV  480
Gorilla Siglec-7     TWRSLTLYPSQPSNPLVLELQVHLGDEGEFTCRAQNSLGSQHVSLNLSLQHEYTGKMRPV  349
Gibbon Siglec-7      TWRSLTLYPSQPSNPLVLELRVHLGDEGEFTCRARNSLGSQHFSLNLSLQHEYTGKMRPV  349
                     **********************;*********  ***:*********.**********:**********

Human Siglec-7       SGVLLGAVGGAGATALVFLSFCVIFIVVRSCRKKSARPAADVGDIGMKDANTIRGSASQG  408
Chimpanzee Siglec-7  SGVLLGAVGGAGATALVFLSFCVIFIVVRSCRKKSARPAADVGDTGMEDANTIRGSASQG  535
Pygmy Chimpanzee Siglec-7 SGVLLGAVGGAGATALVFLSFCVIFIVVRSCRKKSARPAADVGDTGMEDANTIRGSASQG  409
Orangutan Siglec-7   SGVMLGAVGGAGATALVFLSFCVIFIVVRSCRKKSARPAADVGDTGMEDANTVRGSASQG  540
Gorilla Siglec-7     SGVLLGAVGGAGATALVFLSFCVIFIVVRSCRKKSARPAADVGDTGMEDANTIRGSASQG  409
Gibbon Siglec-7      SGVTLGAVGGAGATALVFLSFCVIFIVVRSYRKKSARPAAGVGDTGMEDANAIRGSASQG  409
                     *** ********************************** ********** *** **:****:********

Human Siglec-7       NLTESWADDNPRHHGLAAHSSGEEREIQYAPLSFHKGEPQDLSGQEATNNEYSEIKIPK-  467
Chimpanzee Siglec-7  TLTESWAYDNPRHHGLAAPSSGEEREVQYAPLSFHKGEPQDLSGQEATNNEYSEIKIPK-  594
Pygmy Chimpanzee Siglec-7 TLTESWAYDNPRHHGLAAPSSGEEREVQYAPLSFHKGEPQDLSGQEATNNEYSEIXIPKX  469
Orangutan Siglec-7   TLIESWADDNPRHLGLAAPSSGEEREIQYASLSFHKGEPQDLSRQEATNNEYSEIKIPK-  599
Gorilla Siglec-7     TLTESWADDNPRHYGLAAPSSGEEREVQYAPLSFHKGEPQDLSGQEATNNEYSEIKIPK-  468
Gibbon Siglec-7      TMIESWADDNPRHHGLAAPSSGEEGEIQYASVSFHKVEPQDLSGQEATNNEYSEIKIPK-  468
                     .: ***** ***** ***** ****** *:**** :**** ******* ************ ***

Human Siglec-7       ----------------------------  467
Chimpanzee Siglec-7  ----------------------------  594
Pygmy Chimpanzee Siglec-7 ENAEARACLRVHDPSSKGVRG  490
Orangutan Siglec-7   ----------------------------  599
Gorilla Siglec-7     ----------------------------  468
Gibbon Siglec-7      ----------------------------  468
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FIG. 1A (Cont)

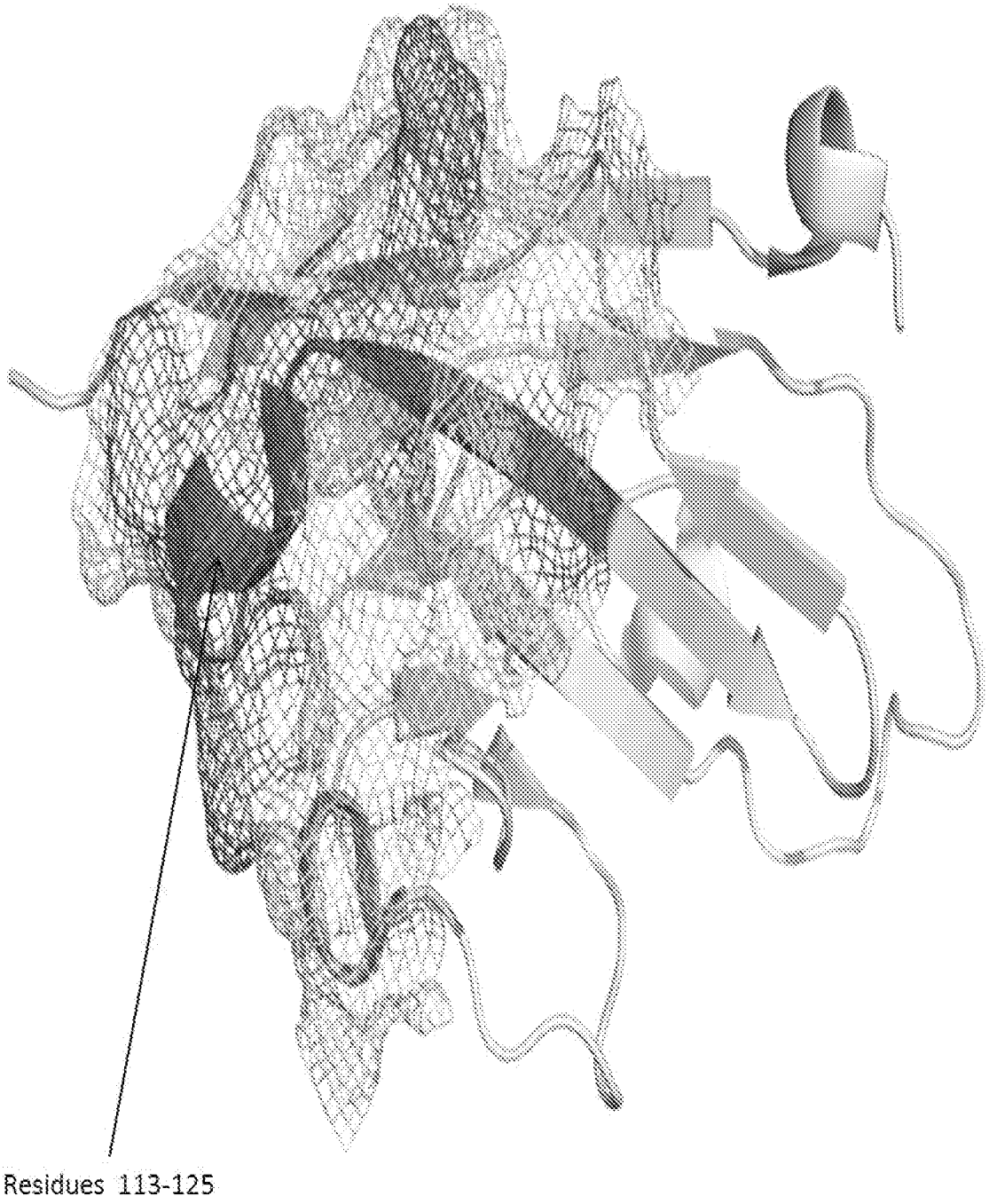


FIG. 1B

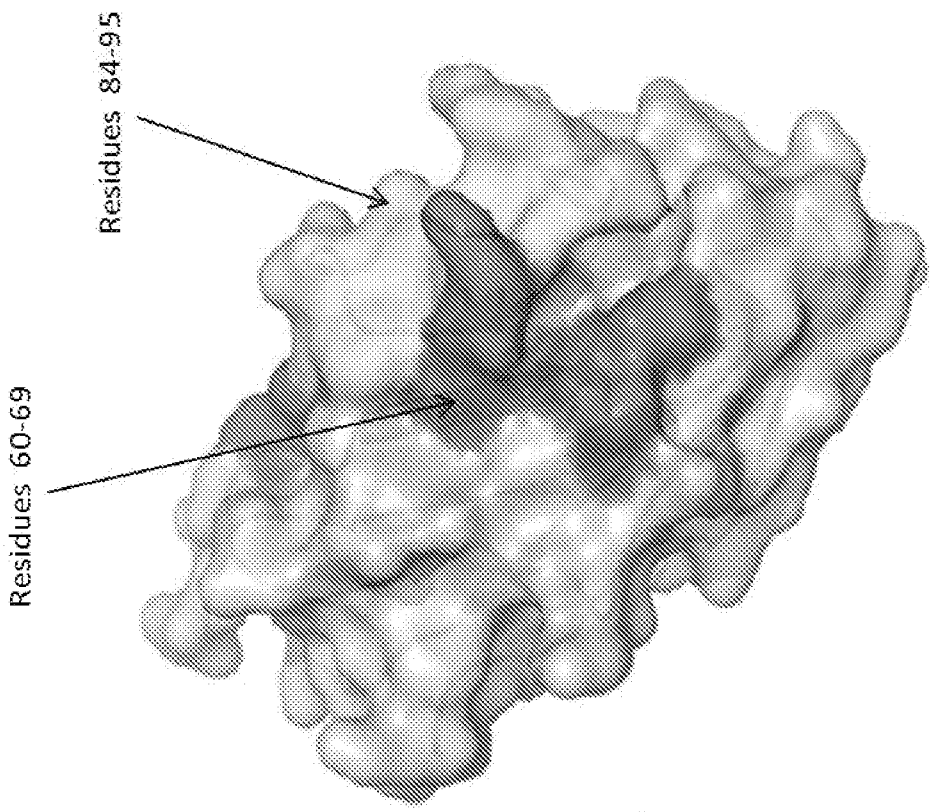

Residues 84-95
Residues 60-69

FIG. 1D

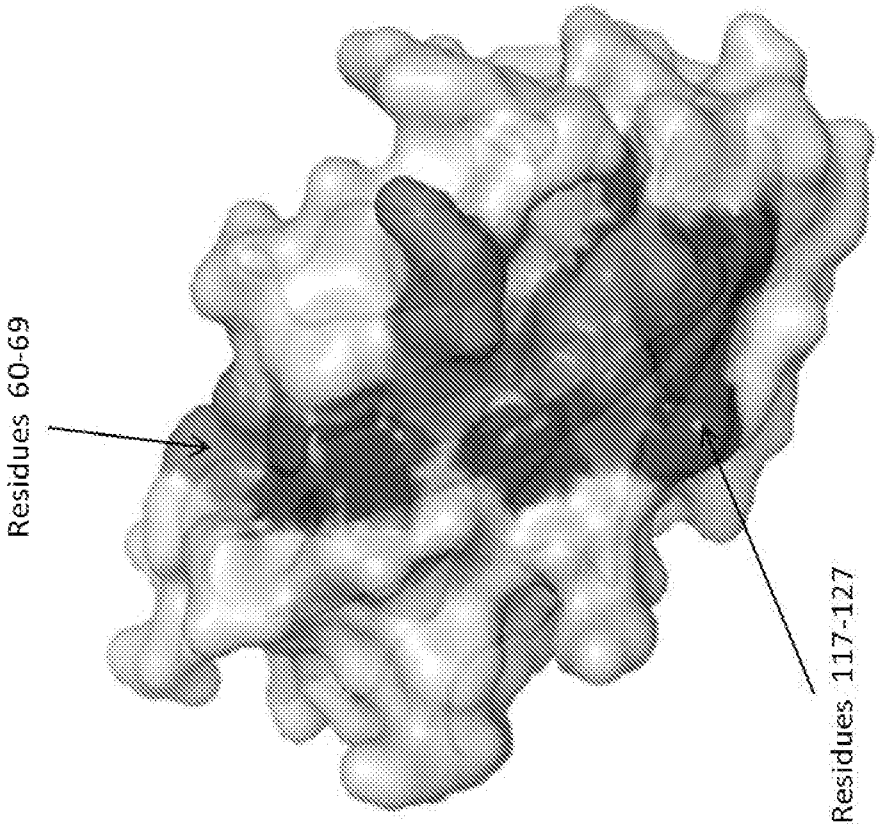

Residues 60-69
Residues 117-127

FIG. 1C

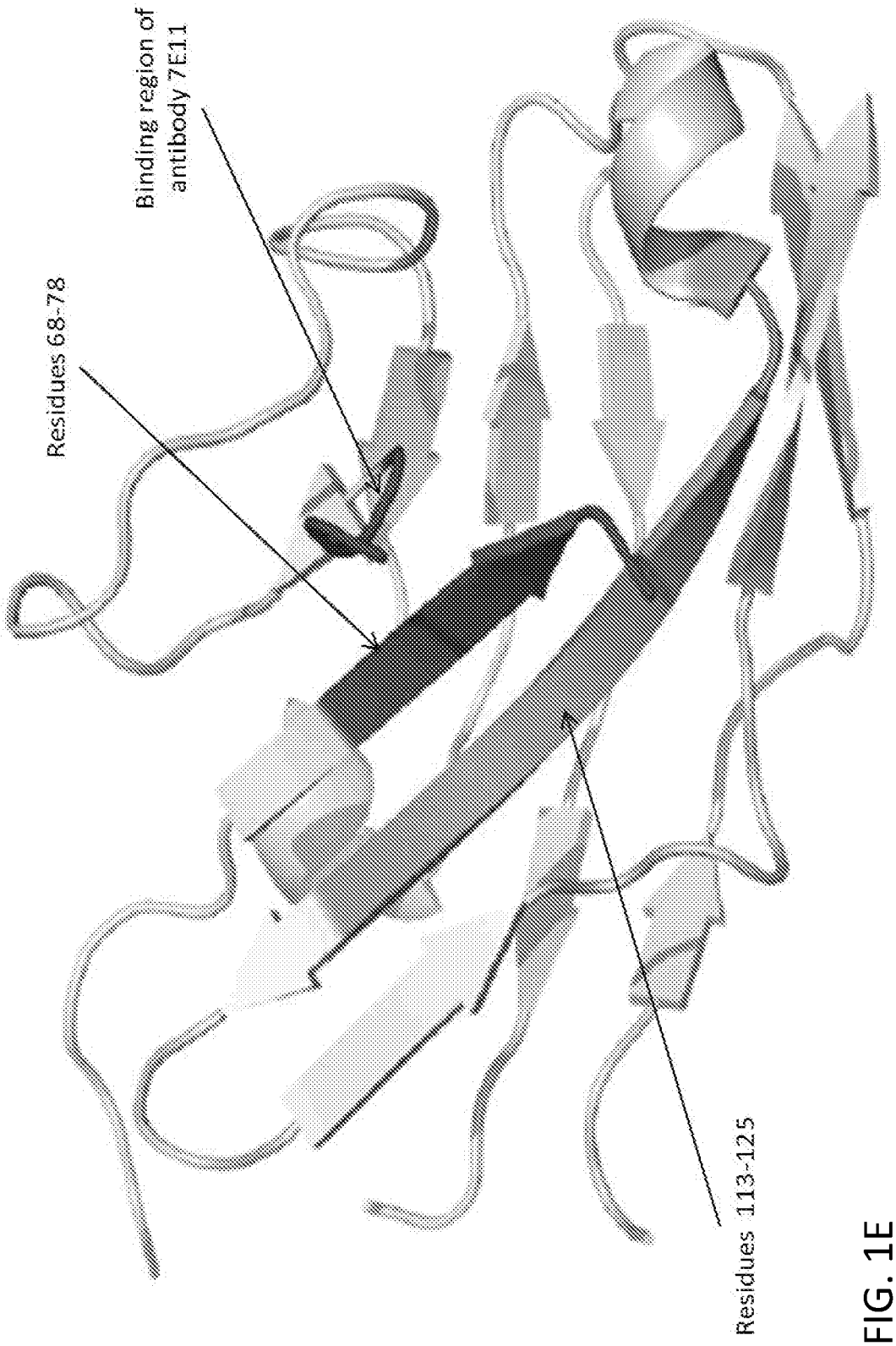

Binding region of antibody 7E11
Residues 68-78
Residues 113-125

FIG. 1E

Binding Reactivity (% WT)					
Mutation	4E3 Fab	10B5 MAb	10B5 Fab	6-434 MAb	57.7 MAb
M30A	122.9 (79)	89.9 (29)	20.1 (12)	84.8 (6)	100.0 (6)
Q31A	111.5 (46	108.0 (11)	18.2 (13)	100.8 (22)	109.7 (42)
V44A	115.0 (12)	93.9 (27)	13.3 (7)	68.0 (43)	89.3 (8)
R45A	129.1 (25)	37.3 (2)	1.6 (3)	111.6 (48)	125.9 (92)
S47A	103.4 (14)	81.7 (5)	1.5 (1)	101.1 (17)	117.9 (21)
F48A	145.5 (28)	158.7 (76)	13.9 (5)	112.9 (17)	157.8 (13)
Y50A	139.2 (77)	108.5 (75)	18.2 (3)	97.9 (58)	142.3 (26)
I72A	26.5 (12)	130.1 (86)	92.8 (9)	64.2 (11)	100.7 (7)
W74A	25.7 (16)	101.0 (67)	79.8 (39)	74.9 (28)	83.7 (25)
N81A	22.0 (13)	153.1 (23)	137.7 (73)	111.6 (20)	5.6 (6)
T103A	138.9 (25)	96.3 (52)	6.3 (4)	77.5 (33)	105.7 (39)
K104A	115.0 (60)	13.6 (1)	-2.0 (5)	83.8 (7)	115.1 (67)
T107A	124.2 (105)	83.8 (17)	0.4 (10)	66.8 (8)	129.2 (9)
R124A	1.0 (4)	149.9 (22)	81.1 (42)	126.0 (48)	115.2 (4)
M185A	91.6 (62)	29.1 (5)	-2.2 (8)	69.3 (3)	74.3 (9)

FIG. 1F

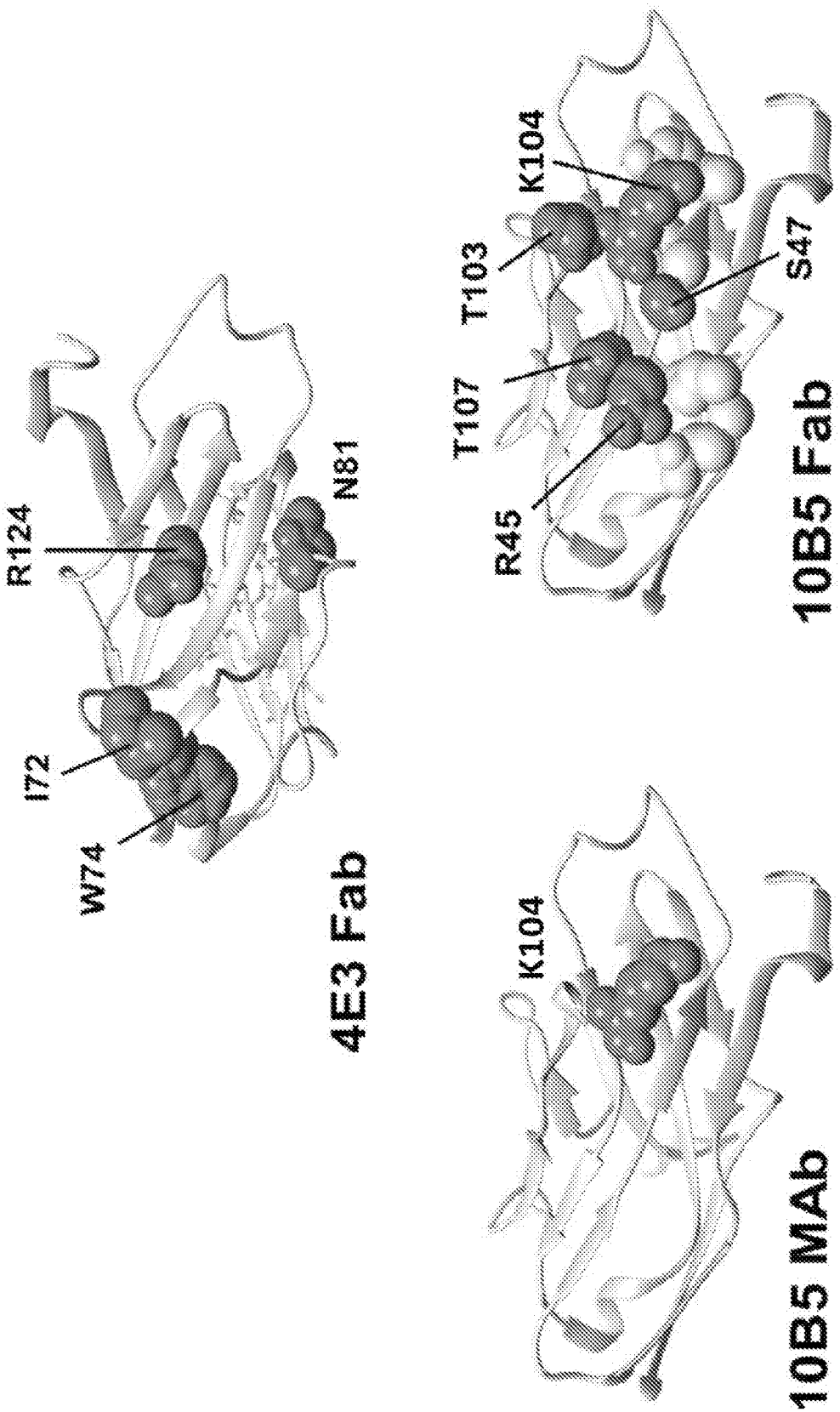

R124
N81
I72
W74
4E3 Fab
T107
T103
K104
R45
S47
10B5 Fab
K104
10B5 MAb

FIG. 1G

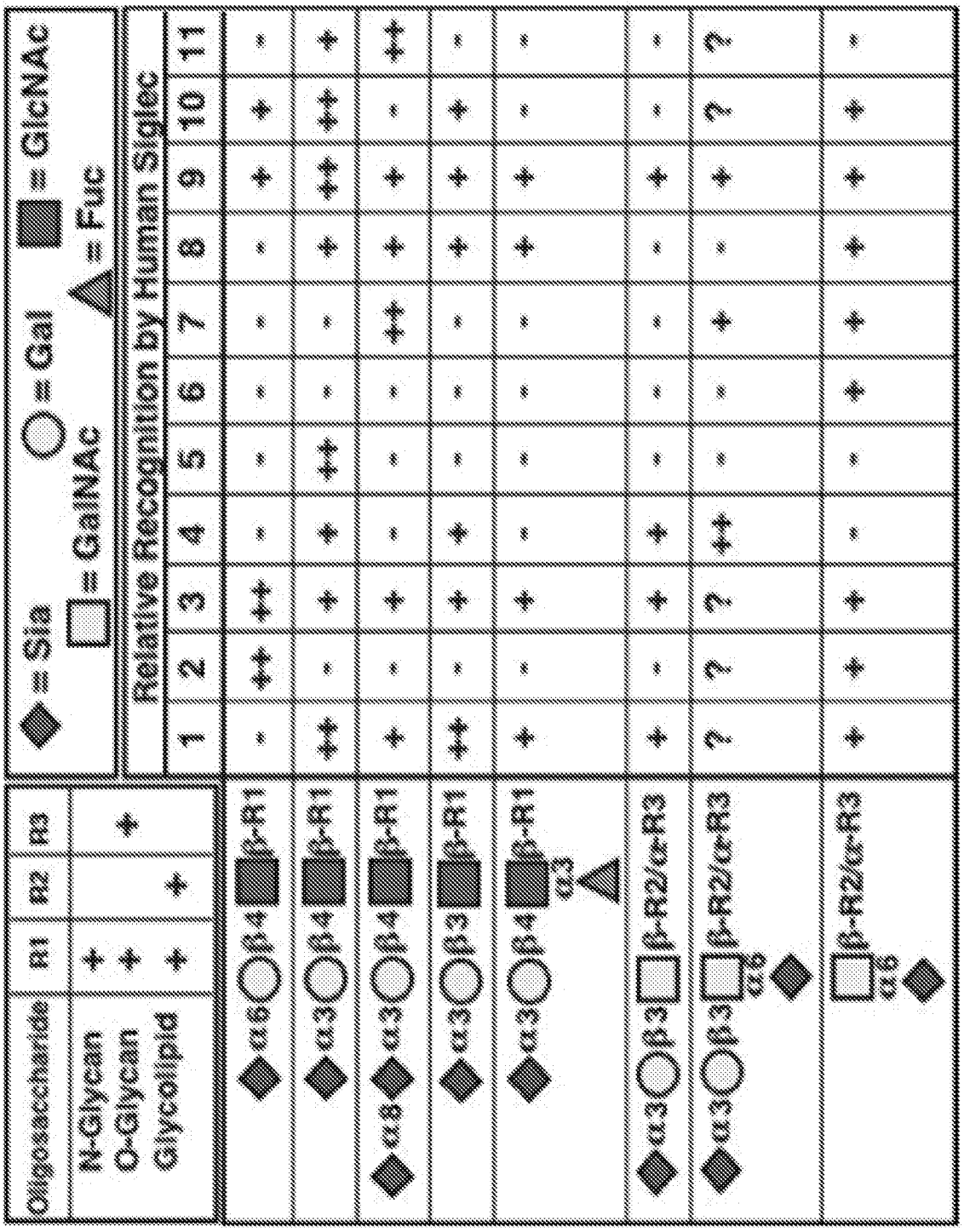

◆ = Sia
○ = Gal
■ = GlcNAc
□ = GalNAc
△ = Fuc
Oligosaccharide
R1
R2
R3
N-Glycan
O-Glycan
Glycolipid
Relative Recognition by Human Siglec
1 2 3 4 5 6 7 8 9 10 11
◆α6○β4■β-R1
◆α3○β4■β-R1
◆α8◆α3○β4■β-R1
◆α3○β3■β-R1
◆α3○β4■β-R1 α3
◆α3○β3□β-R2/α-R3
◆α3○β3□α6 β-R2/α-R3
□α6 β-R2/α-R3

FIG. 2

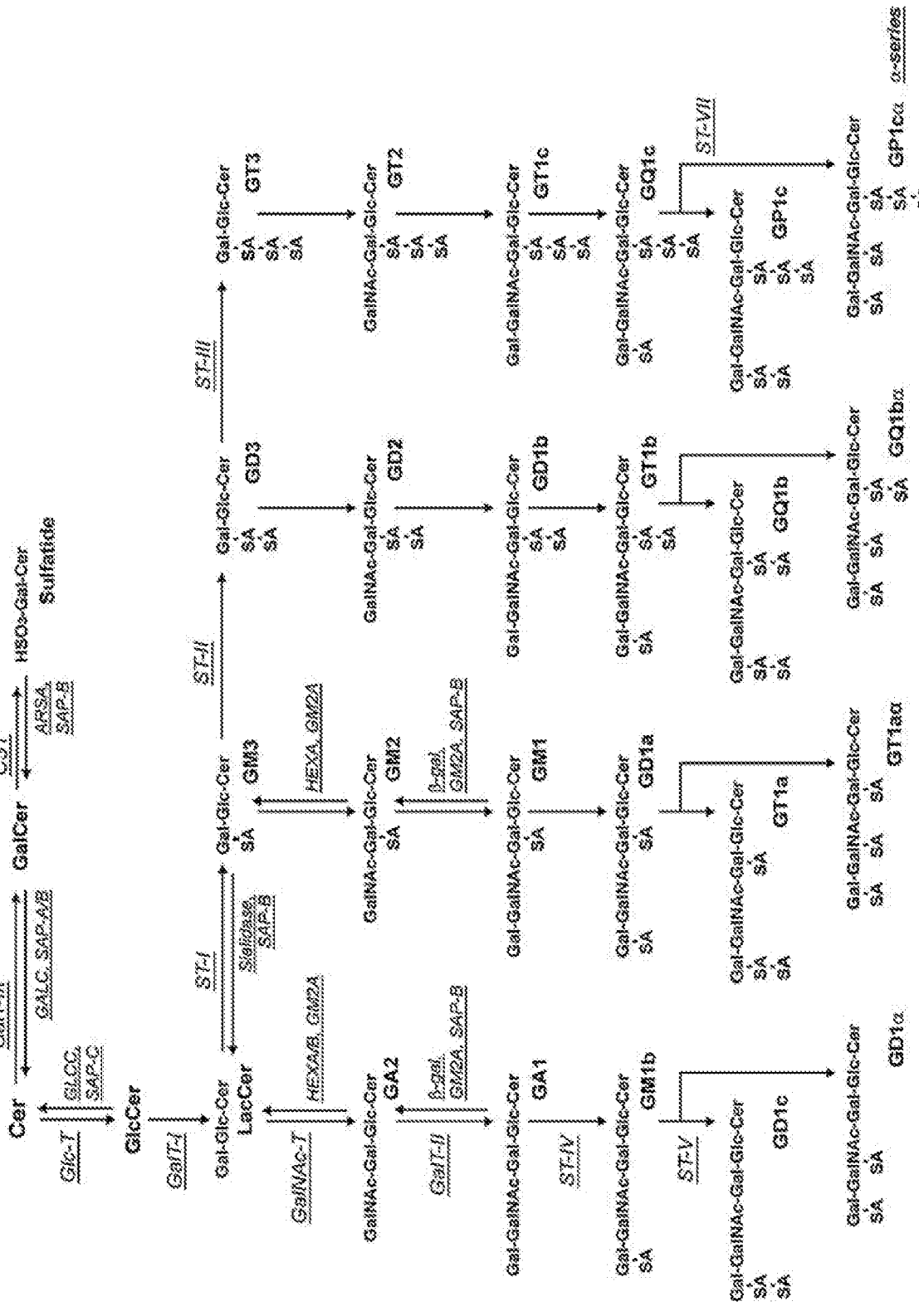

Cer
GalCer
HSO3-Gal-Cer
Sulfatide
GalT-III
GALC, SAP-A/B
CST
ARSA, SAP-B
Glc-T
GLCC, SAP-C
GlcCer
GalT-I
Gal-Glc-Cer
LacCer
ST-I
Sialidase, SAP-B
ST-II
ST-III
GM3
GD3
GT3
GalNAc-T
HEXA/B, GM2A
GA2
GM2
GD2
GT2
GalT-II
b-gal, GM2A, SAP-B
GA1
GM1
GD1b
GT1c
ST-IV
GM1b
GD1a
GT1b
GQ1c
ST-V
GD1c
GT1a
GQ1b
ST-VII
GD1α
GT1aα
GQ1bα
GP1c
GP1cα
asialo-series
a-series
b-series
c-series
α-series

FIG. 3

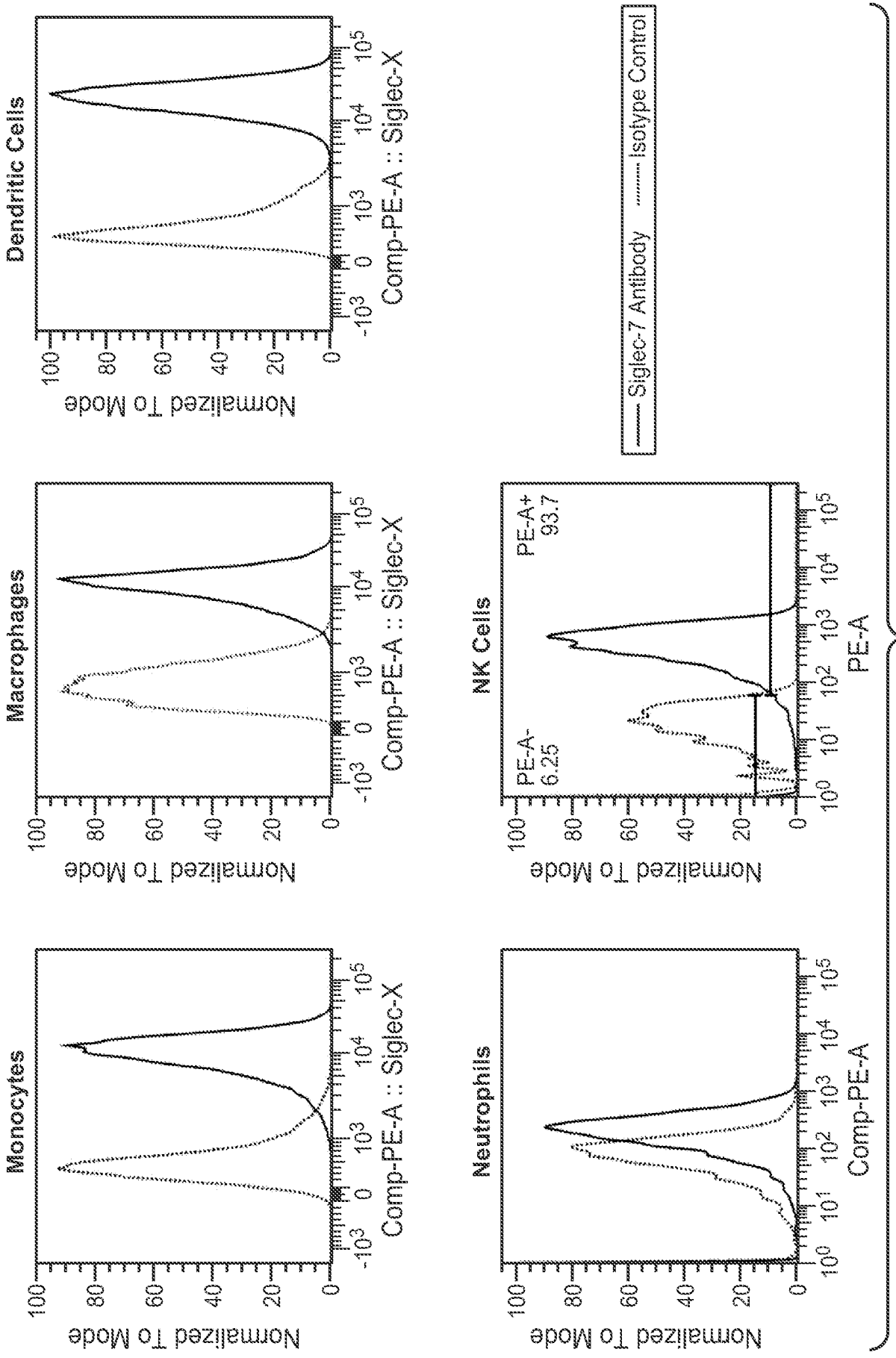

Dendritic Cells
Macrophages
Monocytes
NK Cells
Neutrophils
Normalized To Mode
Comp-PE-A :: Siglec-X
Comp-PE-A
PE-A
PE-A-
6.25
PE-A+
93.7
Siglec-7 Antibody
Isotype Control

FIG. 4

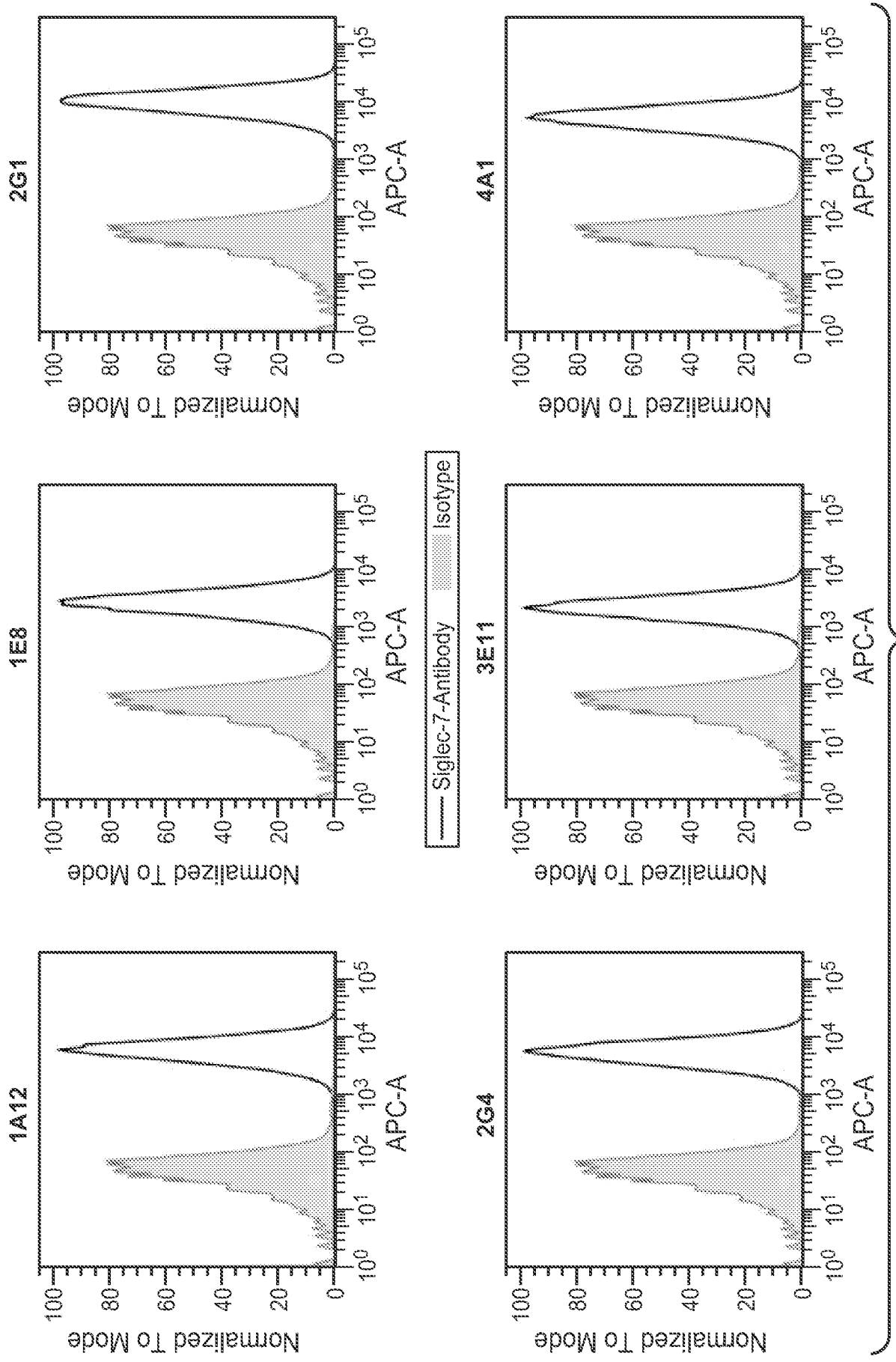

2G1
4A1
1E8
3E11
1A12
2G4
Siglec-7-Antibody
Isotype
Normalized To Mode
APC-A

FIG. 5A

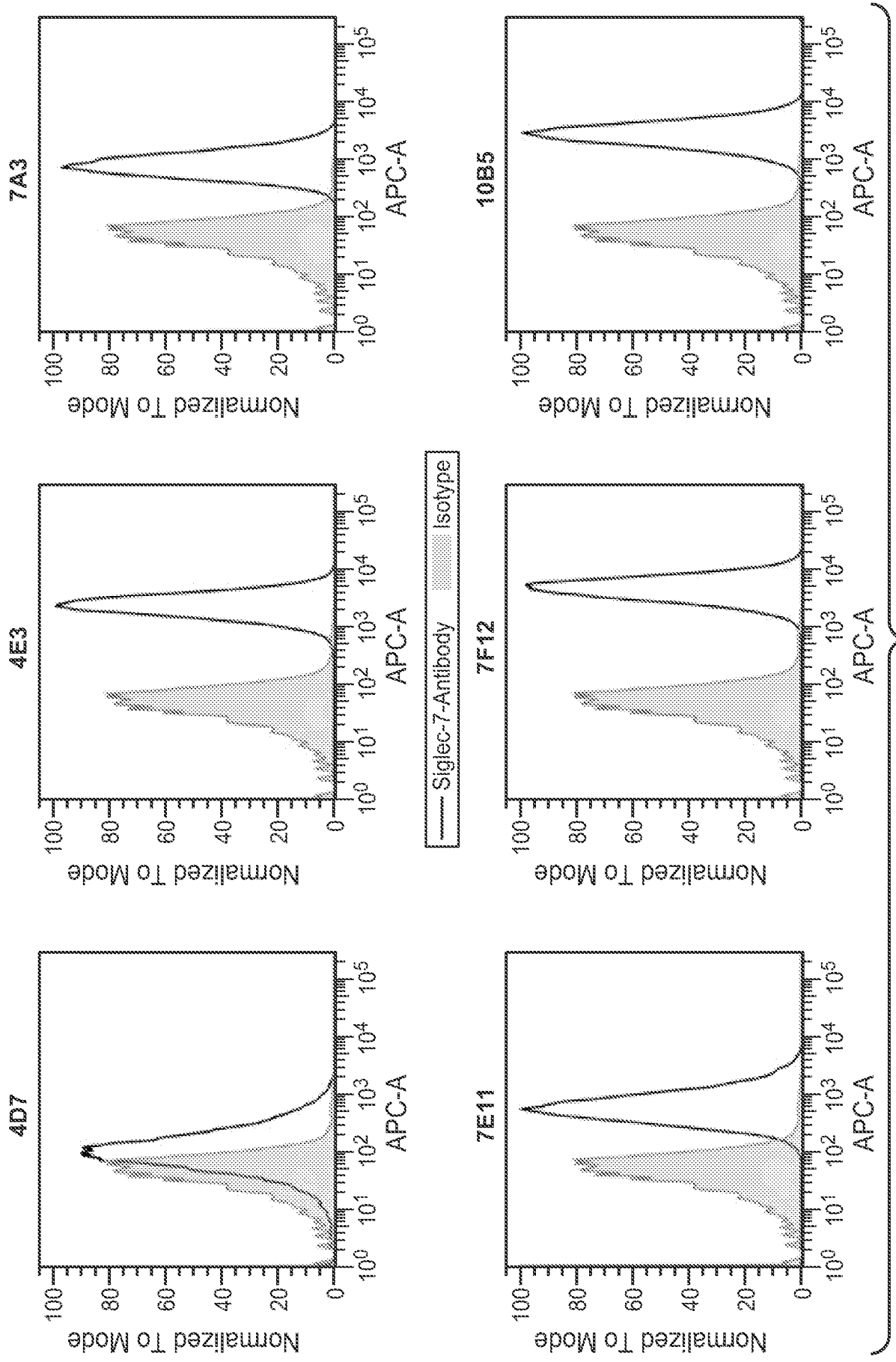

7A3
10B5
4E3
7F12
4D7
7E11
Siglec-7-Antibody
Isotype
Normalized To Mode
APC-A

FIG. 5A (Cont.)

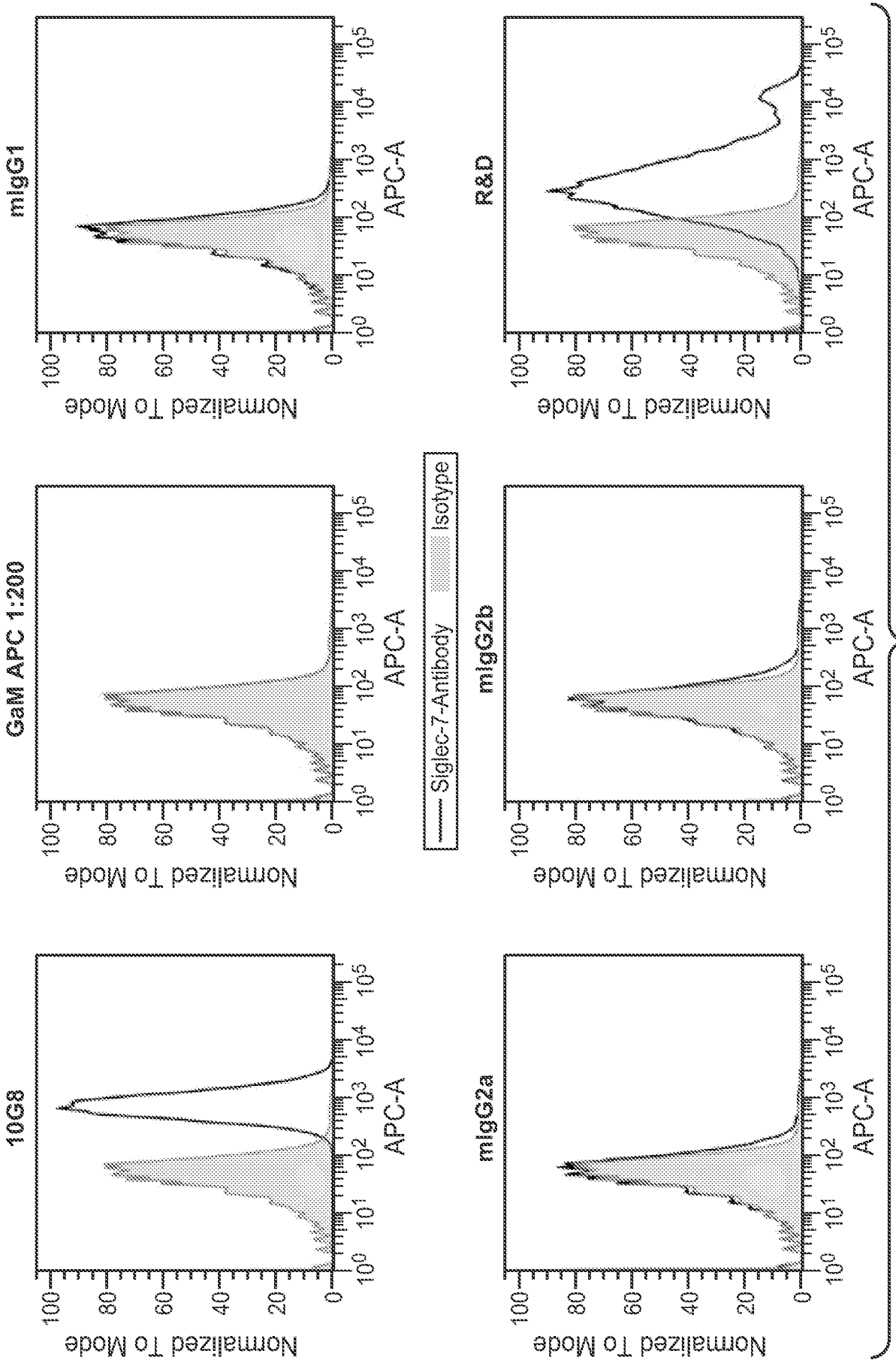

mIgG1
R&D
GaM APC 1:200
mIgG2b
10G8
mIgG2a
Siglec-7-Antibody
Isotype
Normalized To Mode
APC-A
0
20
40
60
80
100
10^0
10^1
10^2
10^3
10^4
10^5

FIG. 5A (Cont.)

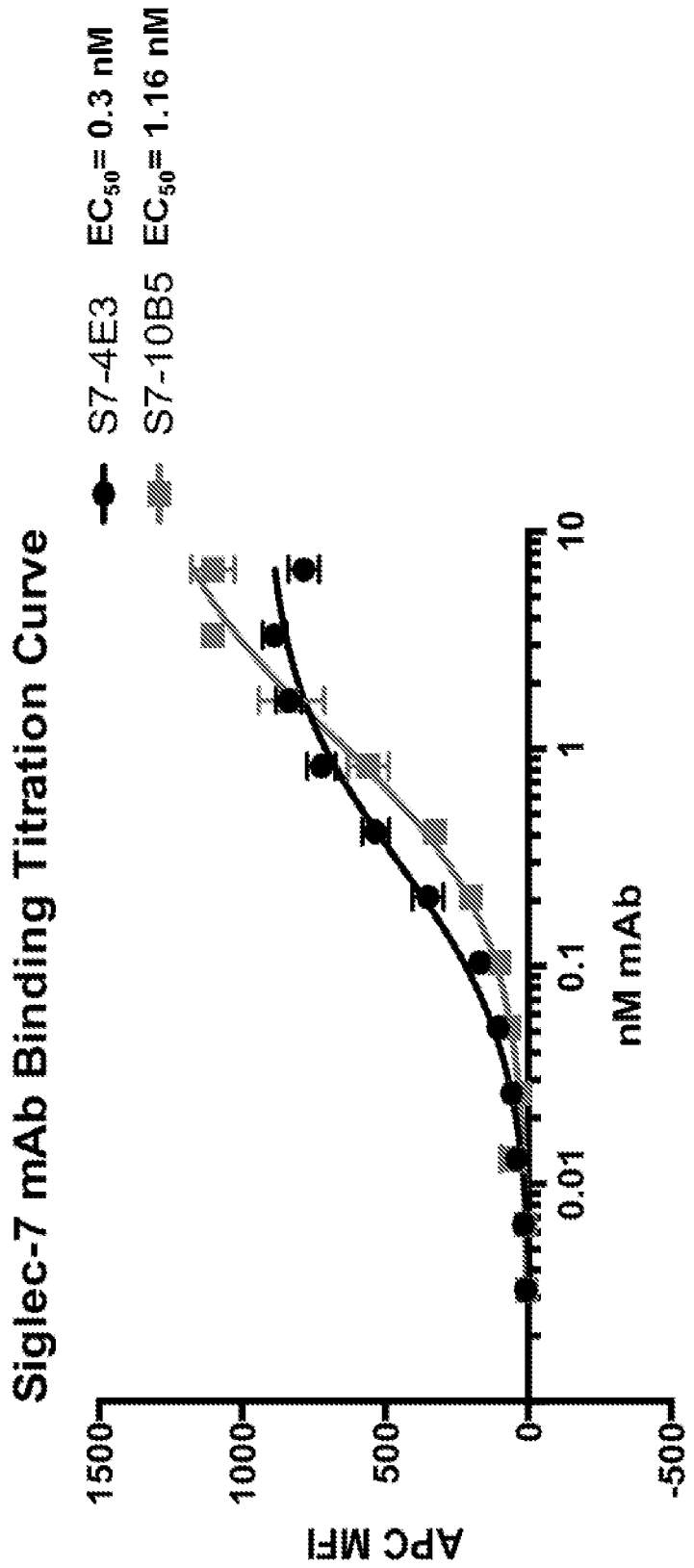

Siglec-7 mAb Binding Titration Curve
S7-4E3 EC50= 0.3 nM
S7-10B5 EC50= 1.16 nM
APC MFI
1500
1000
500
0
-500
0.01
0.1
1
10
nM mAb

FIG. 5B

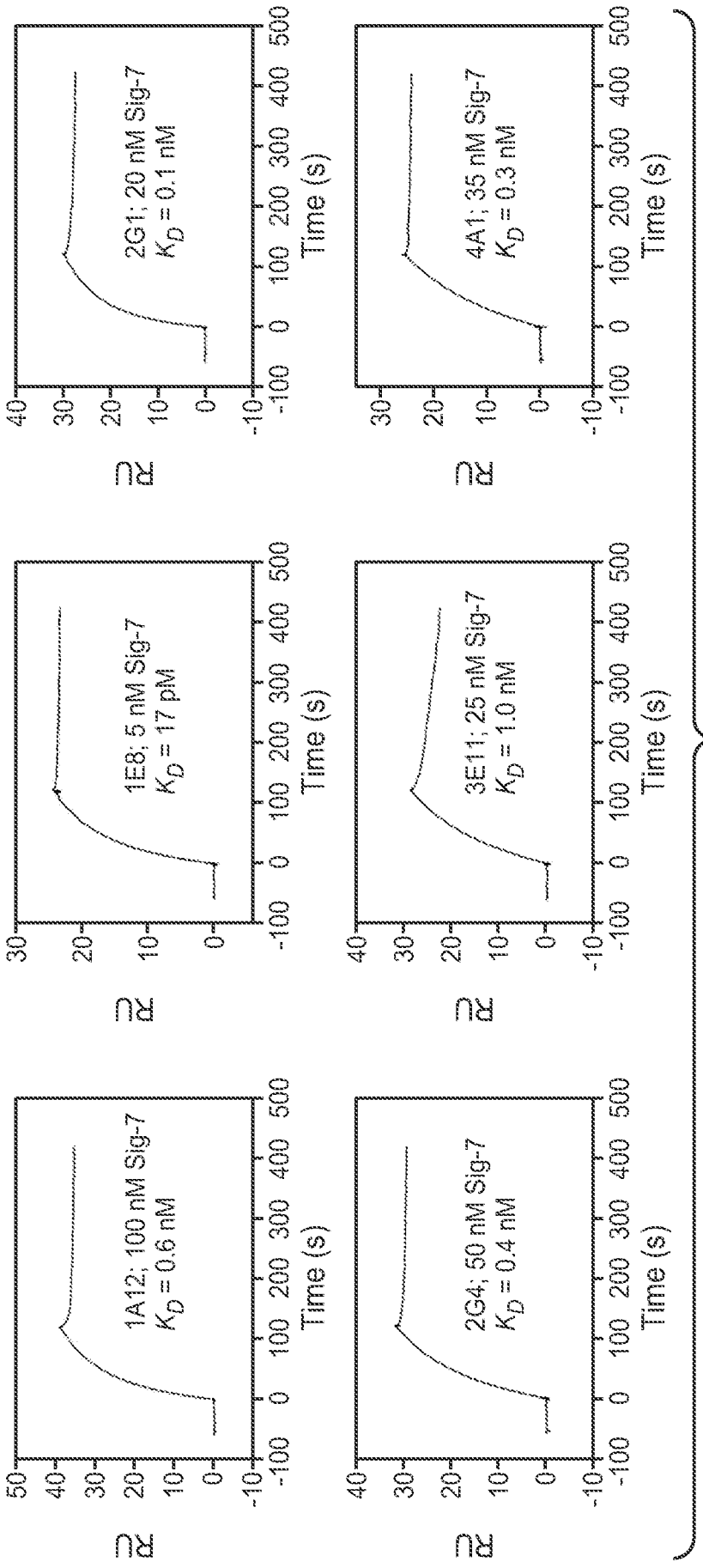

1A12; 100 nM Sig-7
K_D = 0.6 nM
1E8; 5 nM Sig-7
K_D = 17 pM
2G1; 20 nM Sig-7
K_D = 0.1 nM
2G4; 50 nM Sig-7
K_D = 0.4 nM
3E11; 25 nM Sig-7
K_D = 1.0 nM
4A1; 35 nM Sig-7
K_D = 0.3 nM
RU
Time (s)

FIG. 6A

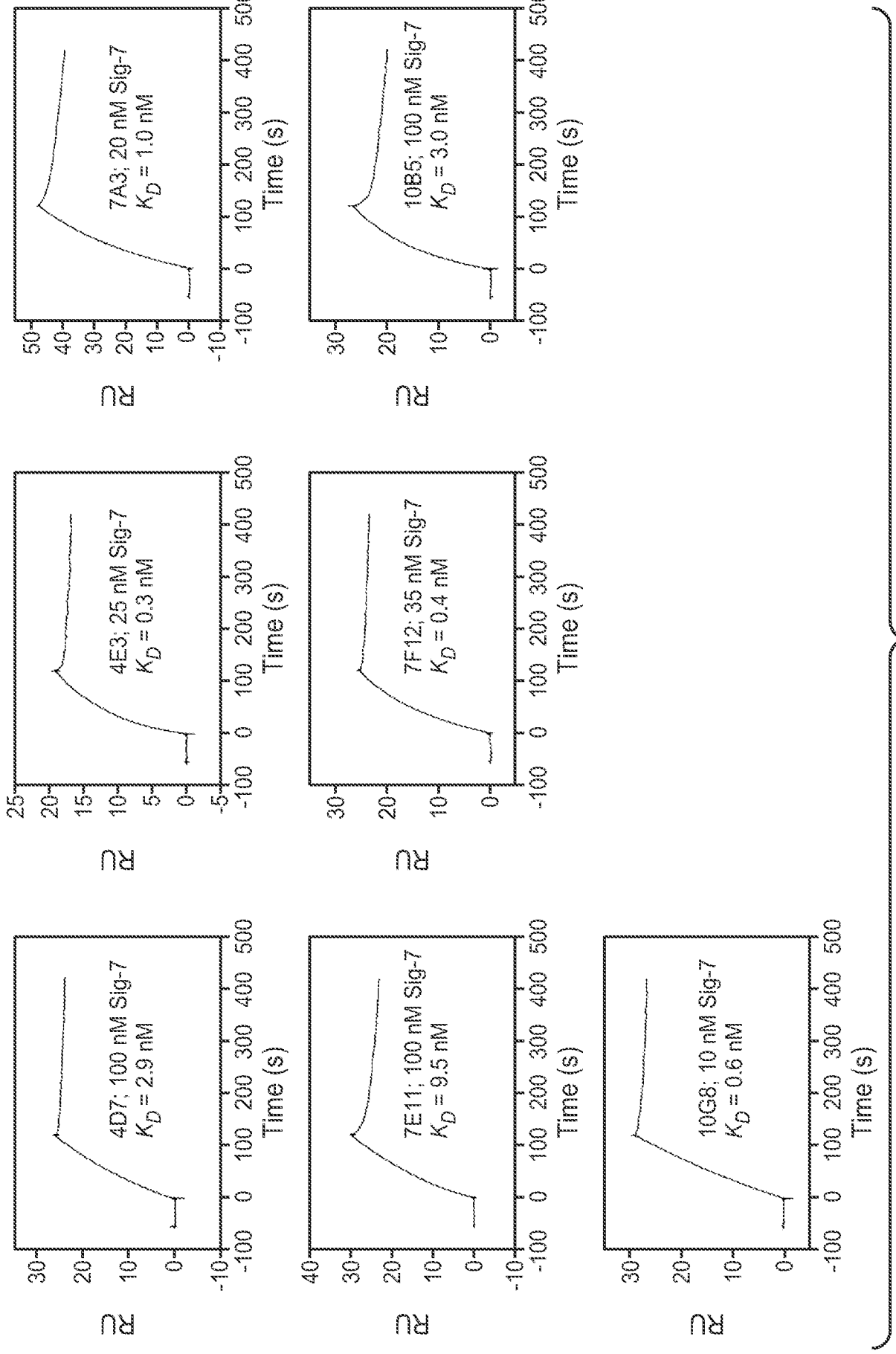

RU
Time (s)
4D7; 100 nM Sig-7
K_D = 2.9 nM
4E3; 25 nM Sig-7
K_D = 0.3 nM
7A3; 20 nM Sig-7
K_D = 1.0 nM
7E11; 100 nM Sig-7
K_D = 9.5 nM
7F12; 35 nM Sig-7
K_D = 0.4 nM
10B5; 100 nM Sig-7
K_D = 3.0 nM
10G8; 10 nM Sig-7
K_D = 0.6 nM

FIG. 6A (Cont.)

```
Potential humanized sequence based on IMGT IGKV3-11*01 acceptor framework (AbM CDR definition)
IGKV3-11*01 EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRAT
            GIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPP
Joining region  IMGT J00242|IGKJ2*01|YTFGQGTKLEIK

seq                 10        20        30         40         50
AbM                 10        20        30        40         50
             b b b    p p     b b b  b   b  bi bi i    ii ibbi      i
S7-4E3      QIVLTQSPAILSASPGEKVTMTC SANSSFTYMY WYQQKPGSSPRLLIF DTSNLAS
            *         *  *    ** **                        **     *
3-11*01     EIVLTQSPATLSLSPGERATLSC RASQSVSSYLAWYQQKPGQAPRLLIY DASNRAT
h4E3-L1     EIVLTQSPATLSLSPGERATLSC SANSSFTYMY WYQQKPGQAPRLLIY DTSNLAS
h4E3-L2     EIVLTQSPATLSLSPGERVTMSC SANSSFTYMY WYQQKPGQAPRLLIY DTSNLAS
h4E3-L3     EIVLTQSPATLSLSPGERVTMSC SANSSFTYMY WYQQKPGQAPRLLIF DTSNLAS
                       A              #                  S         #

seq           60        70        80         90        100
AbM           60        70        80        90        100
             b   b         b b b  b    ib bib  ibi iib  i   b b b
S7-4E3      GVPIRFSGSGSGTSYSLTISRMEAEDTATYYC QQWSSSPLT FGAGTKLELK
             * *          ***    ** *  * *                *     *
3-11*01     GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC QQRSNWPP  FGQGTKLEIK
h4E3-L1     GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC QQWSSSPLT FGQGTKLEIK
h4E3-L2     GVPARFSGSGSGTDYTLTISSMEPEDFAVYYC QQWSSSPLT FGQGTKLEIK
h4E3-L3     GVPARFSGSGSGTDYTLTISSMEPEDFAVYYC QQWSSSPLT FGQGTKLELK
                                  T        ^

# deamidation substitutions: Q/S/A/D
^ tryptophan oxidation substitutions: H/Y/F

h4E3-L1 is a "CDR-swap" with no changes to human framework. Subsequent sequences alter framework
changes shown in red (compared to sequence above it).
```

FIG. 6B

```
Potential humanized sequence based on IMGT IGHV3-21*01 acceptor framework (AbM CDR definition)
IGHV3-21*01 EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIY
            YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARX
Joining region   IMGT J00256|IGHJ4*01|YFDYWGQGTLVTVSS

seq                 10        20        30        40        50
AbM                 10        20        30        40        50  a
           b b b     p     b b b b   b b    b  bi i     i ibb  b
S7-4E3     EVQLVESGGALVKPGGSLKISCAVS GFIFSNYDMS WVRQNPEKRLEWVA TISSGGGYTY
                   *        **   *                  * * *    *
3-21*01    EVQLVESGGGLVKPGGSLRLSCAAS GFTFSSYSMN WVRQAPGKGLEWVS SISSSSSYIY
h4E3-H1    EVQLVESGGGLVKPGGSLRLSCAAS GFIFSNYDMS WVRQAPGKGLEWVS TISSGGGYTY
h4E3-H2    EVQLVESGGGLVKPGGSLRLSCAVS GFIFSNYDMS WVRQAPGKGLEWVA TISSGGGYTY
h4E3-H3    EVQLVESGGGLVKPGGSLRISCAVS GFIFSNYDMS WVRQAPGKGLEWVA TISSGGGYTY
                                     #

seq       60        70        80          90        100       110         120
AbM        60        70        80  abc     90                          110
            i  b    b b b x    b b b  b     bibibb                i   b b b
S7-4E3     YPDSVKGRFTISRDNAKNALYLQMSSLRSEDTALYYCTR HGYGNYDWYFDV WGAGATVTVSS
            *                  *     *   *    *   *                  * *
3-21*01    YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR                WGQGTLVTVSS
h4E3-H1    YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR HGYGNYDWYFDV WGQGTLVTVSS
h4E3-H2    YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCTR HGYGNYDWYFDV WGQGTLVTVSS
h4E3-H3    YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCTR HGYGNYDWYFDV WGQGALVTVSS
            P                                  L         #  ^

# deamidation substitutions: Q/S/A/D
^ tryptophan oxidation substitutions: H/Y/F

h4E3-H1 is a "CDR-swap" with no changes to human framework. Subsequent sequences alter framework
changes shown in red (compared to sequence above it).
```

FIG. 6C

```
Potential humanized sequence based on IMGT IGKV1-39*01 acceptor framework (AbM CDR definition)
IGKV1-39*01 DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS
            GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPP
Joining region  IMGT J00242|IGKJ2*01|YTFGQGTKLEIK

seq                 10        20        30        40        50
AbM                 10        20        30        40        50
           b b b    p p     b b b  b   b   bi bi i    ii ibbi      i
S7-10B5.1 DVQMTQTTSSLSASLGDRVTISC RASQDINTYLN WYQQKPDGTVKLLIY YTSRLHS
           *    **       *       *                      ****
1-39*01   DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQQKPGKAPKLLIY AASSLQS
h10B5-L1  DIQMTQSPSSLSASVGDRVTITC RASQDINTYLN WYQQKPGKAPKLLIY YTSRLHS
h10B5-L2  DIQMTQSPSSLSASVGDRVTITC RASQDINTYLN WYQQKPGKAPKLLIY YTSRLHS
h10B5-L3  DVQMTQSPSSLSASVGDRVTITC RASQDINTYLN WYQQKPGKAPKLLIY YTSRLHS
                                    #           TV

seq       60        70        80        90        100
AbM       60        70        80        90        100
           b   b        b b b  b    ib bib  ibi iib  i   b b b
S7-10B5.1 GVPSRFSGSGSGTDYSLTISNLEQEDIATYFC QQGNTLPWT FGGGTKLEIK
                     **    * **  *   *              *
1-39*01   GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYSTPP  FGQGTKLEIK
h10B5-L1  GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGNTLPWT FGQGTKLEIK
h10B5-L2  GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QQGNTLPWT FGQGTKLEIK
h10B5-L3  GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QQGNTLPWT FGQGTKLEIK
                                  I   F     #

# deamidation substitutions: Q/S/A/D

h10B5-L1 is a "CDR-swap" with no changes to human framework. Subsequent sequences alter framework
changes shown in red (compared to sequence above it).
```

FIG. 6D

```
Potential humanized sequence based on IMGT IGHV1-46*01 acceptor framework (AbM CDR definition)
IGHV1-46*01 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTS
            YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
Joining region   IMGT J00256|IGHJ4*01|YFDYWGQGTLVTVSS

seq                10        20        30        40        50
AbM                10        20        30        40        50  a
          b b b     p     b b b b   b b    b  bi i     i ibb  b
S7-10B5.1 QVHLQQSGPELVKPGASVKISCKAS GYAFTNCWMN WVRQRPGKGLDWIG RIFPGNGHTN
            * *   * **       *                      *  *  * *
1-46*01   QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYYMH WVRQAPGQGLEWMG IINPSGGSTS
h10B5-H1  QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNCWMN WVRQAPGQGLEWMG RIFPGNGHTN
h10B5-H2  QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNCWMN WVRQAPGQGLEWIG RIFPGNGHTN
h10B5-H3  QVQLVQSGAEVKKPGASVKISCKAS GYAFTNCWMN WVRQAPGQGLEWIG RIFPGNGHTN
h10B5-H4  QVQLVQSGAEVKKPGASVKISCKAS GYAFTNCWMN WVRQAPGQGLEWIG RIFPGNGHTN
                    V                   #x^                       @   #

seq       60        70        80        90        100       110
AbM        60        70        80  abc       90                  110
            i  b    b b b x    b b b  b     bibibb           i   b b b
S7-10B5.1 YSGKFKDKATLTEDKSSSTAYMQLSSLTSEDSAVYFCAR DYSDYYFDY WGQGTTLTVSS
           **  **** * * * *  *  *    *   *   *                 **
1-46*01   YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR           WGQGTLVTVSS
h10B5-H1  YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR DYSDYYFDY WGQGTLVTVSS
h10B5-H2  YAQKFQGRVTMTEDTSTSTVYMELSSLRSEDTAVYYCAR DYSDYYFDY WGQGTLVTVSS
h10B5-H3  YAQKFQGRATLTEDTSTSTAYMELSSLRSEDTAVYYCAR DYSDYYFDY WGQGTLLTVSS
h10B5-H4  YAQKFQGRATLTEDKSTSTAYMELSSLRSEDTAVYYCAR DYSDYYFDY WGQGTLLTVSS
           S                        F
# deamidation substitutions: Q/S/A
@ isoaspartate substitutions: Q/S/A
^ tryptophan oxidation substitutions: H/Y/F

h10B5-H1 is a "CDR-swap" with no changes to human framework. Subsequent sequences alter framework
changes shown in red (compared to sequence above it).
```

FIG. 6E

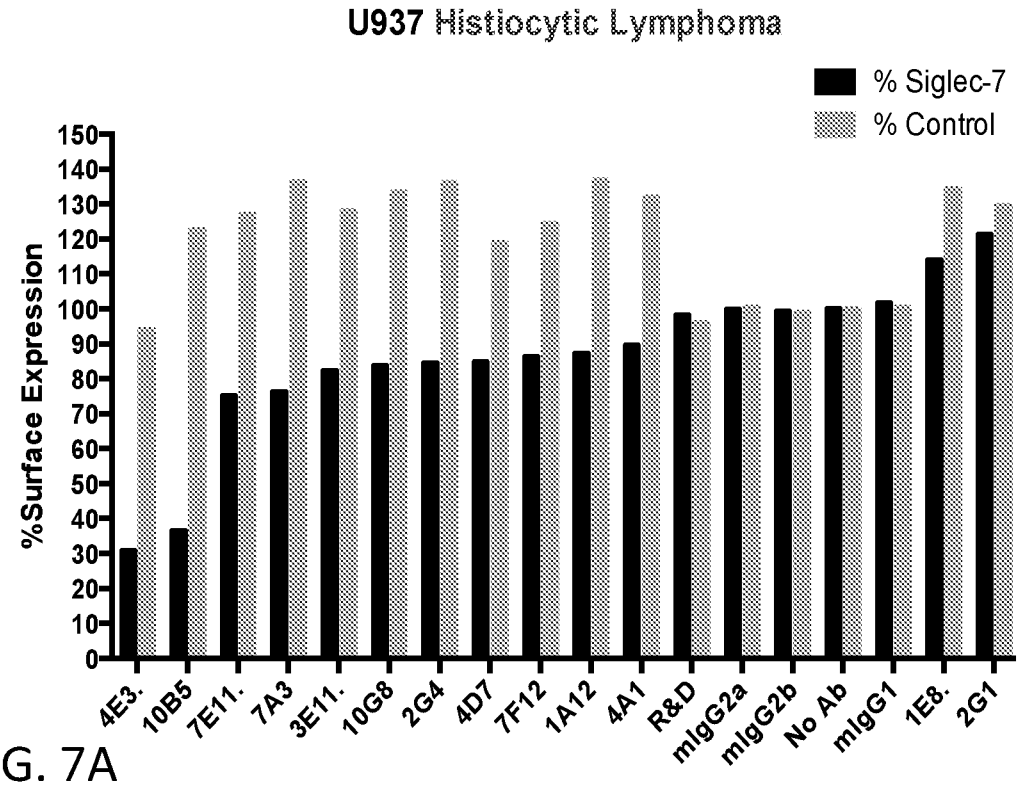

U937 Histiocytic Lymphoma
% Siglec-7
% Control
%Surface Expression
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
4E3.
10B5
7E11.
7A3
3E11.
10G8
2G4
4D7
7F12
1A12
4A1
R&D
mIgG2a
mIgG2b
No Ab
mIgG1
1E8.
2G1

FIG. 7A

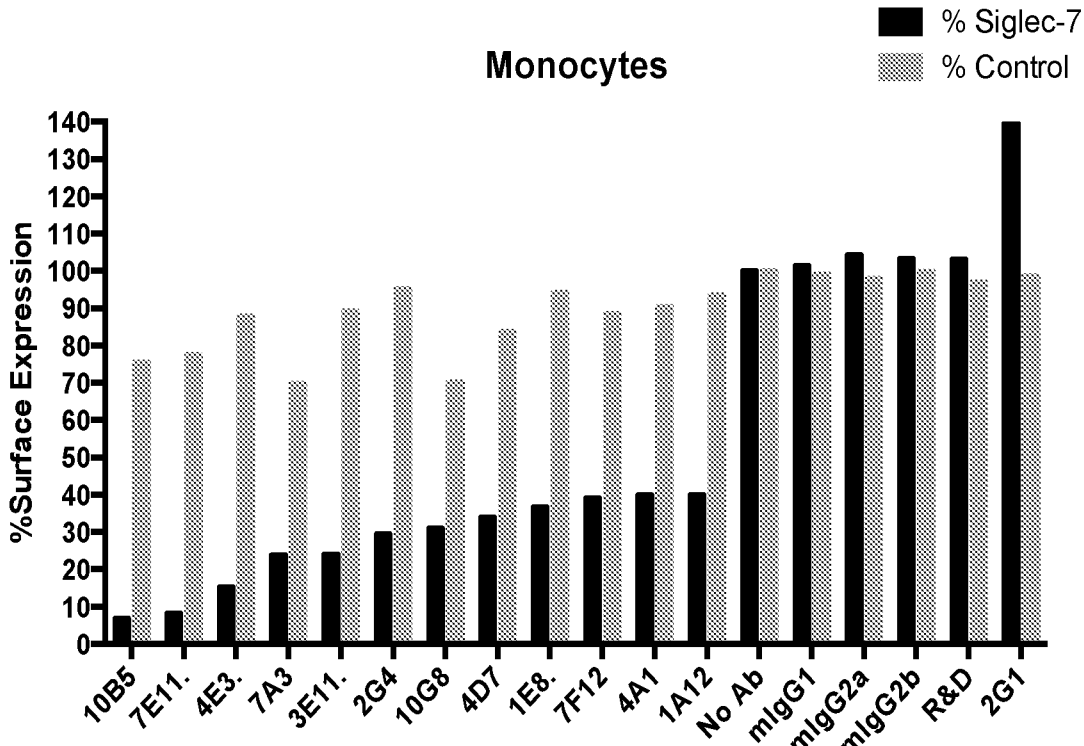

% Siglec-7
% Control
Monocytes
%Surface Expression
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
10B5
7E11.
4E3.
7A3
3E11.
2G4
10G8
4D7
1E8.
7F12
4A1
1A12
No Ab
mIgG1
mIgG2a
mIgG2b
R&D
2G1

FIG. 7B

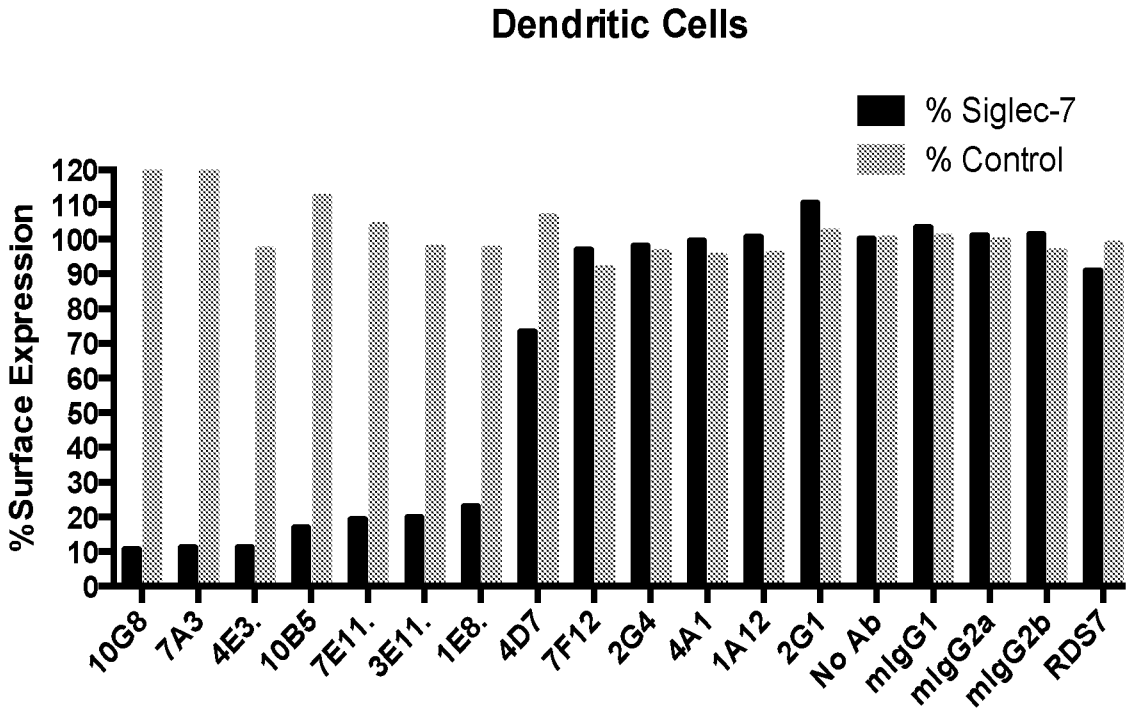

Dendritic Cells
% Siglec-7
% Control
%Surface Expression
120
110
100
90
80
70
60
50
40
30
20
10
0
10G8
7A3
4E3.
10B5
7E11.
3E11.
1E8.
4D7
7F12
2G4
4A1
1A12
2G1
No Ab
mIgG1
mIgG2a
mIgG2b
RDS7

FIG. 7C

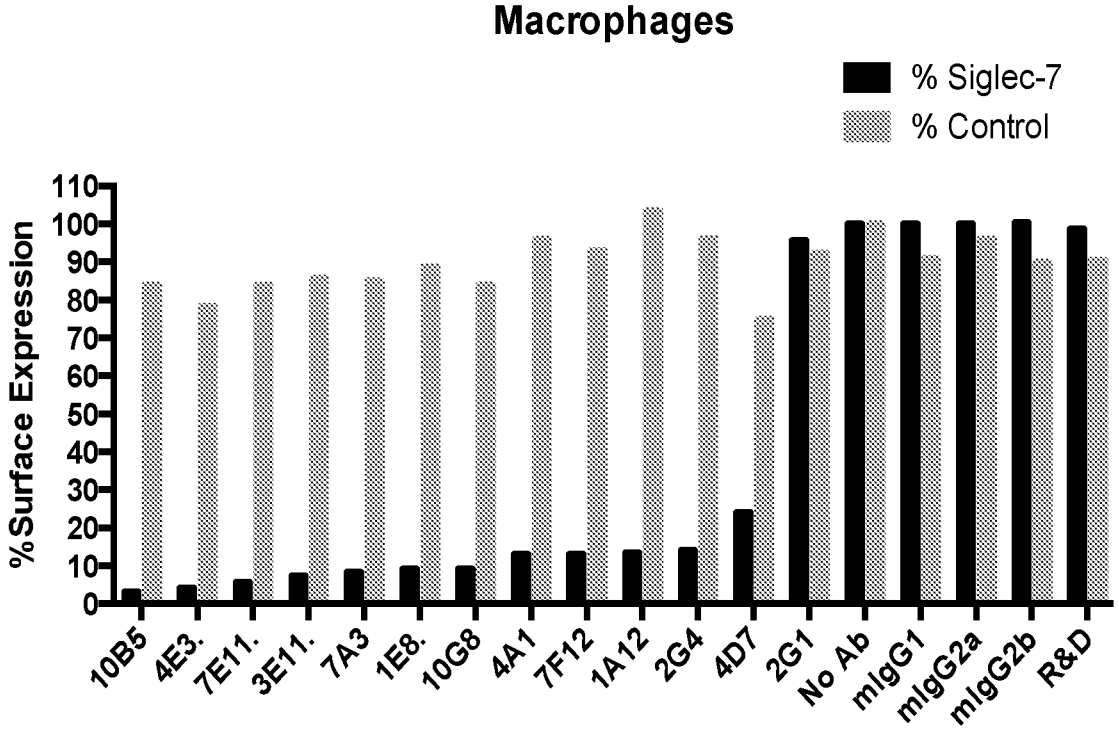

Macrophages
% Siglec-7
% Control
%Surface Expression
110
100
90
80
70
60
50
40
30
20
10
0
10B5
4E3.
7E11.
3E11.
7A3
1E8.
10G8
4A1
7F12
1A12
2G4
4D7
2G1
No Ab
mIgG1
mIgG2a
mIgG2b
R&D

FIG. 7D

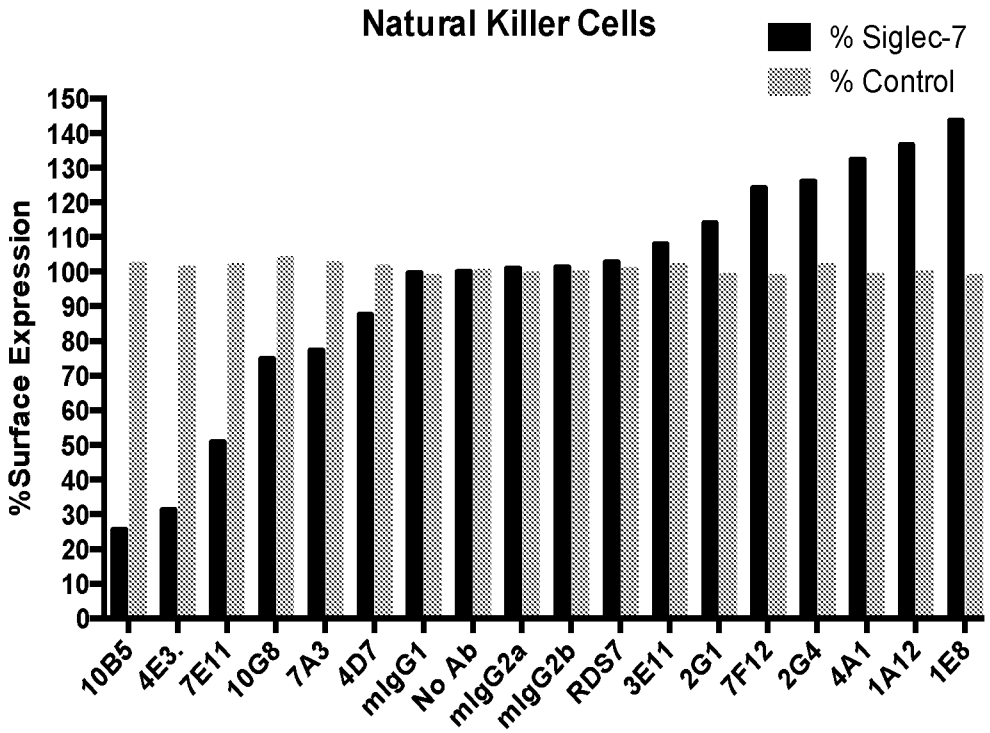

Natural Killer Cells
% Siglec-7
% Control
%Surface Expression
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
10B5
4E3.
7E11
10G8
7A3
4D7
mIgG1
No Ab
mIgG2a
mIgG2b
RDS7
3E11
2G1
7F12
2G4
4A1
1A12
1E8
1.0ug/ml Antibody

FIG. 7E

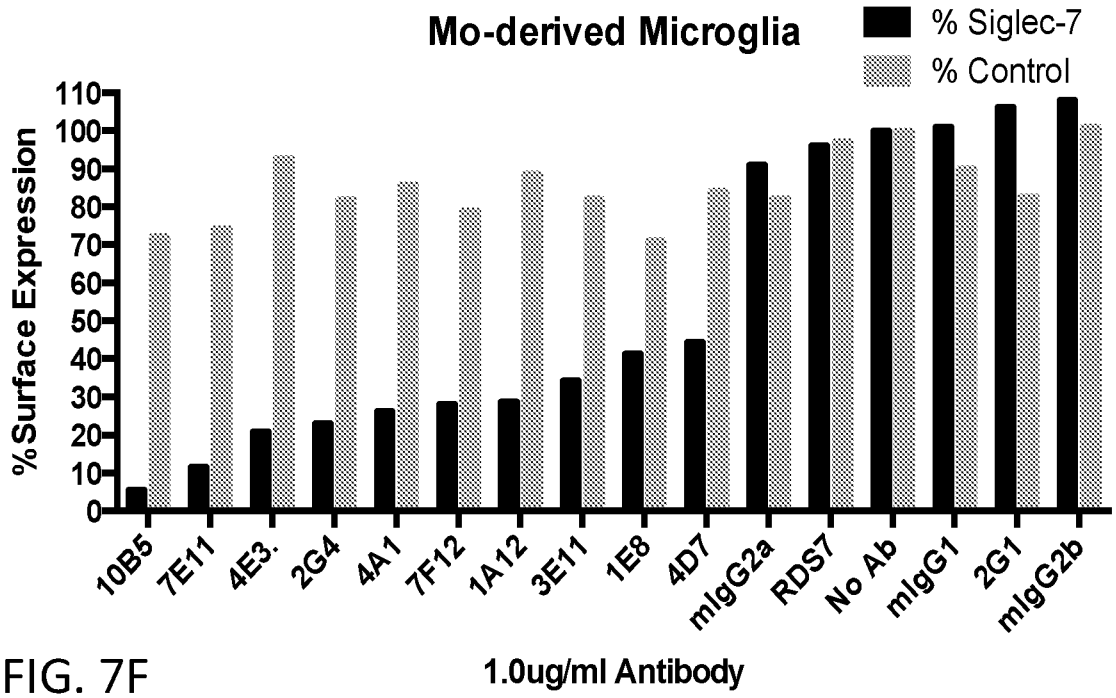

Mo-derived Microglia
% Siglec-7
% Control
%Surface Expression
110
100
90
80
70
60
50
40
30
20
10
0
10B5
7E11
4E3.
2G4
4A1
7F12
1A12
3E11
1E8
4D7
mIgG2a
RDS7
No Ab
mIgG1
2G1
mIgG2b
1.0ug/ml Antibody

FIG. 7F

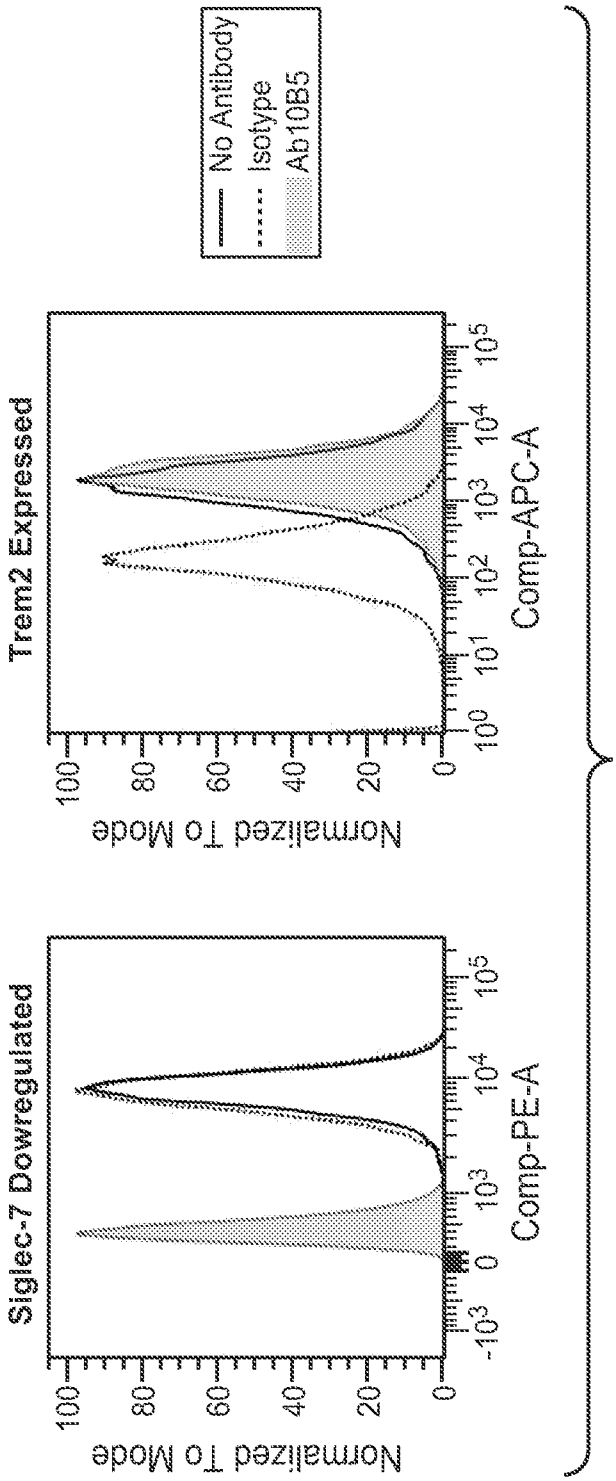

No Antibody
Isotype
Ab10B5
Trem2 Expressed
Normalized To Mode
Comp-APC-A
Siglec-7 Dowregulated
Normalized To Mode
Comp-PE-A

FIG. 7G

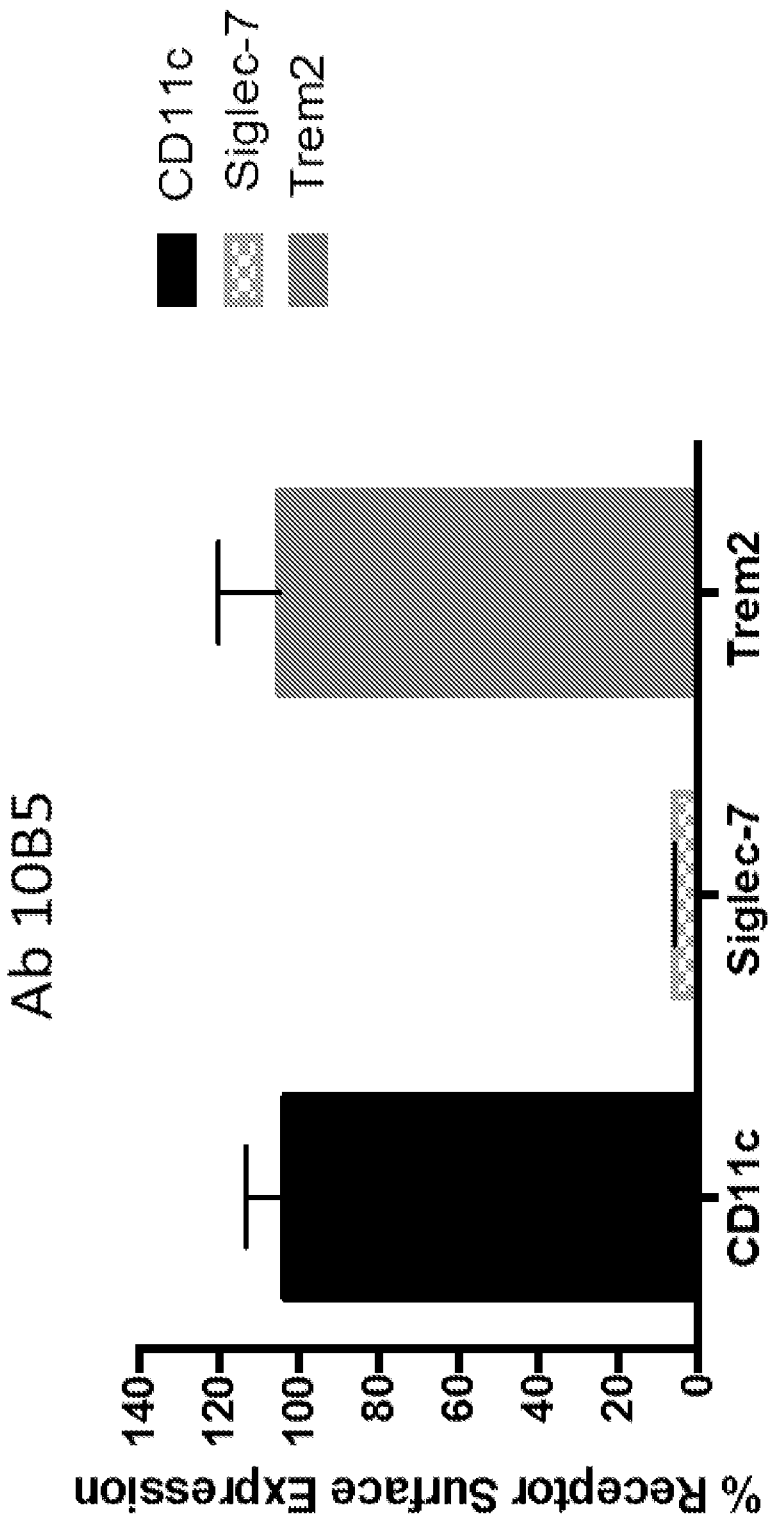

CD11c
Siglec-7
Trem2
Ab 10B5
% Receptor Surface Expression
0
20
40
60
80
100
120
140
CD11c
Siglec-7
Trem2

FIG. 7H

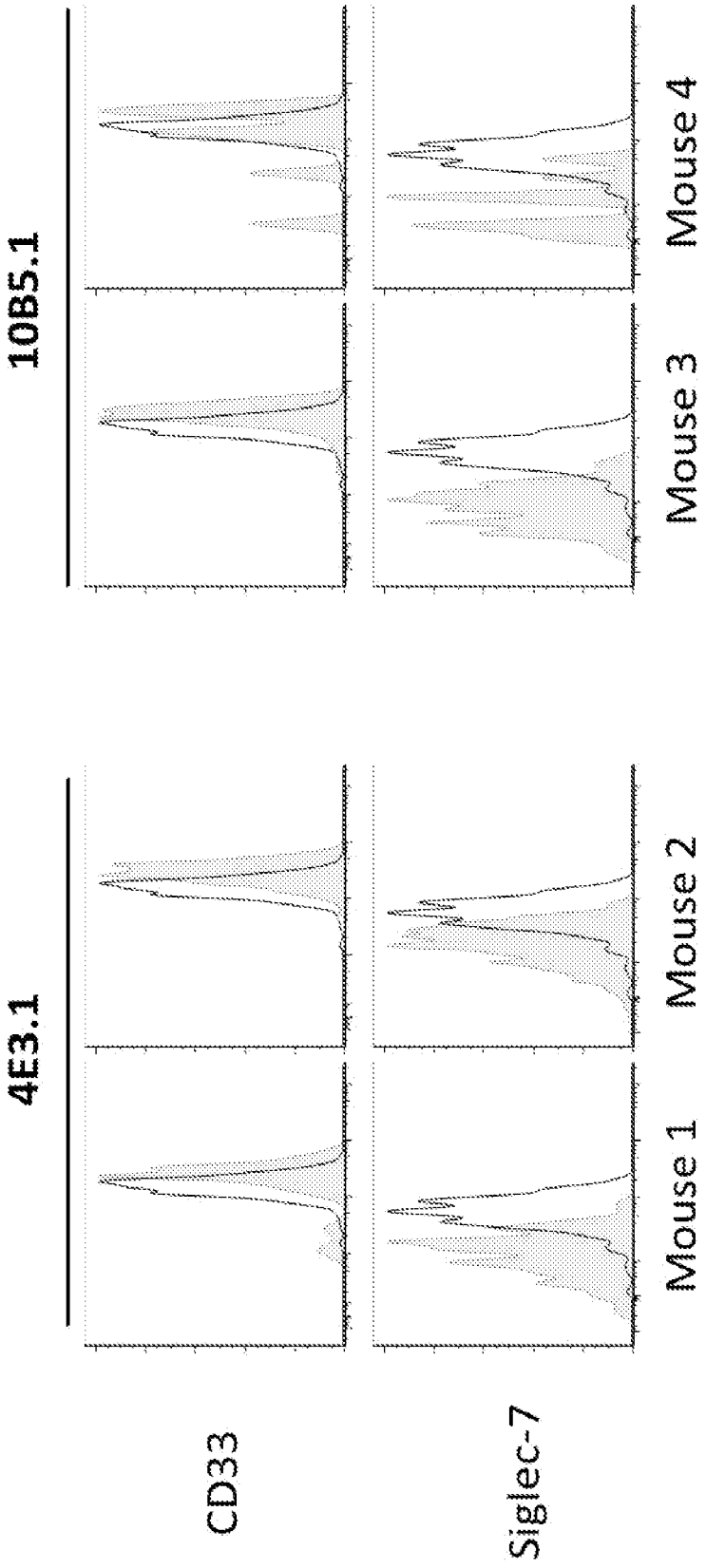

4E3.1
10B5.1
CD33
Siglec-7
Mouse 1
Mouse 2
Mouse 3
Mouse 4
Gray Filled: Siglec-7 antibody treated
Black Line: MOPC21-treated

FIG. 7I

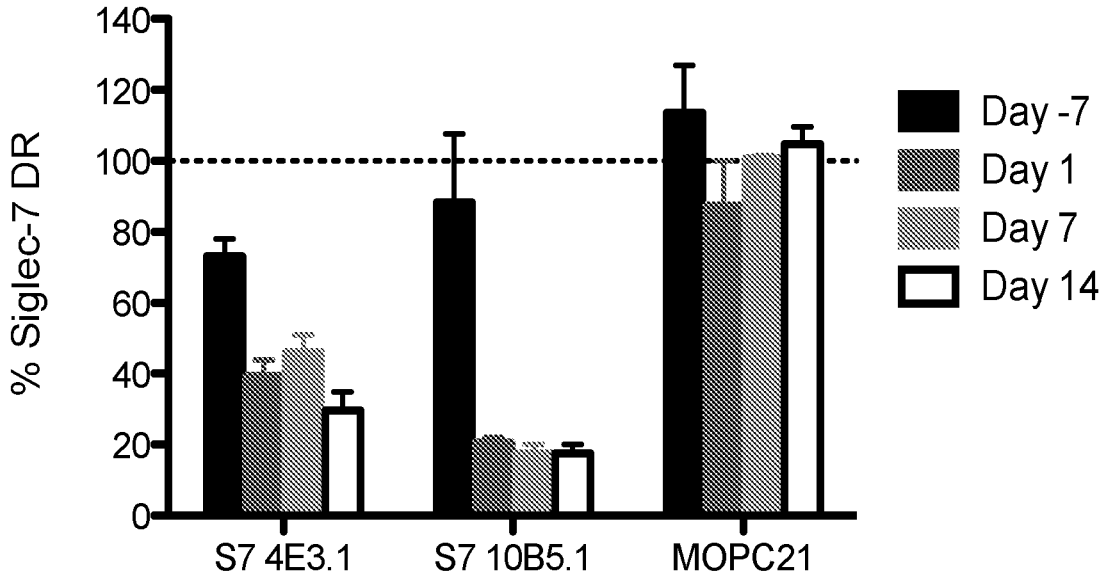

% Siglec-7 DR
140
120
100
80
60
40
20
0
S7 4E3.1
S7 10B5.1
MOPC21
Day -7
Day 1
Day 7
Day 14

FIG. 7J

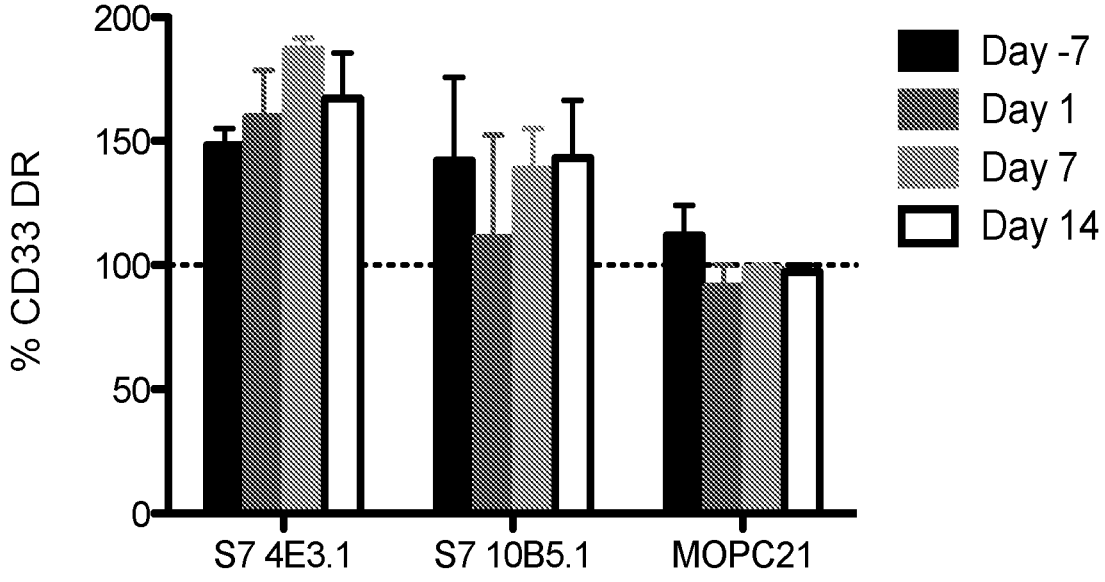

% CD33 DR
200
150
100
50
0
S7 4E3.1
S7 10B5.1
MOPC21
Day -7
Day 1
Day 7
Day 14

FIG. 7K

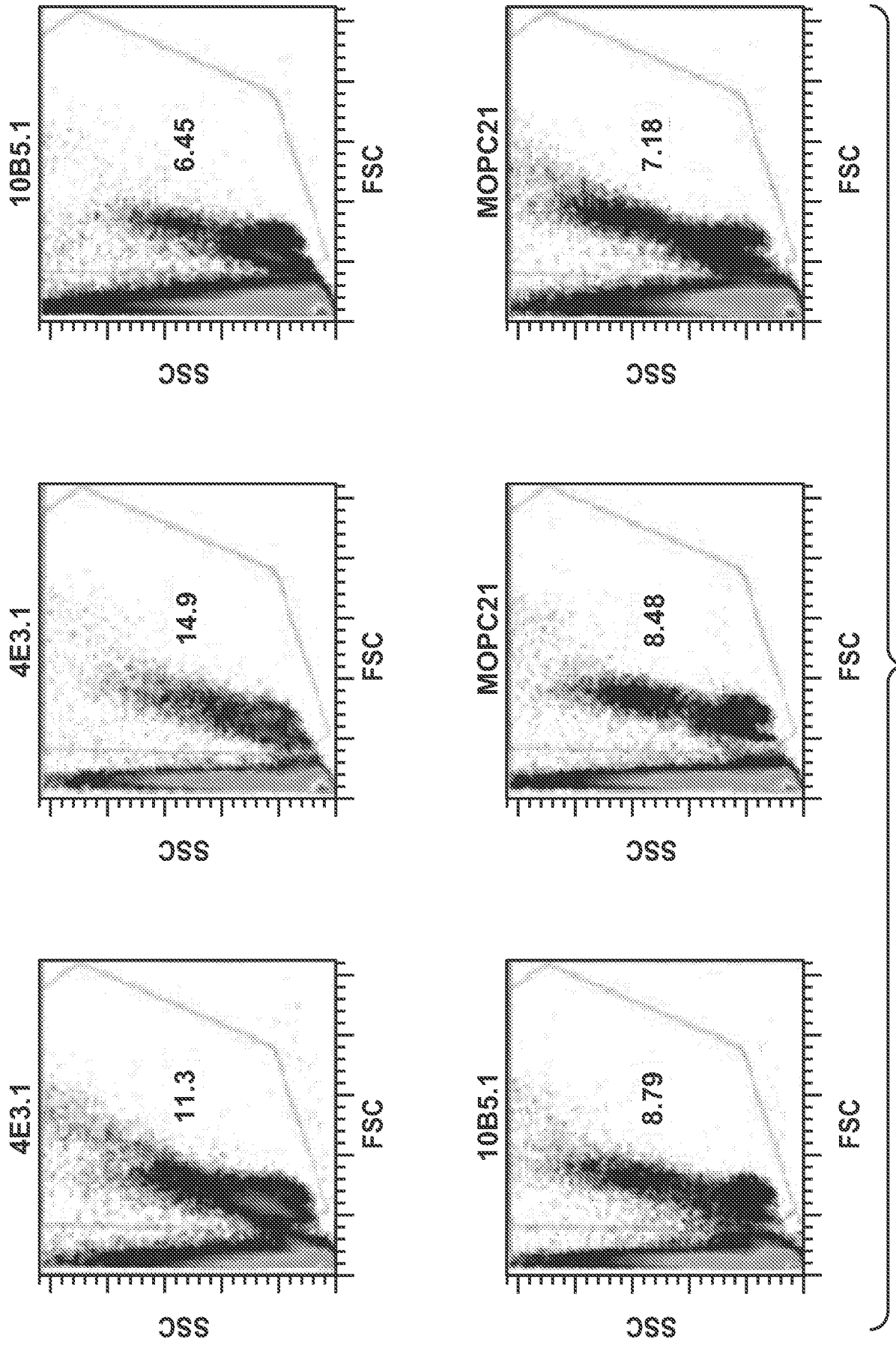

10B5.1
6.45
SSC
FSC
MOPC21
7.18
SSC
FSC
4E3.1
14.9
SSC
FSC
MOPC21
8.48
SSC
FSC
4E3.1
11.3
SSC
FSC
10B5.1
8.79
SSC
FSC

FIG. 7L

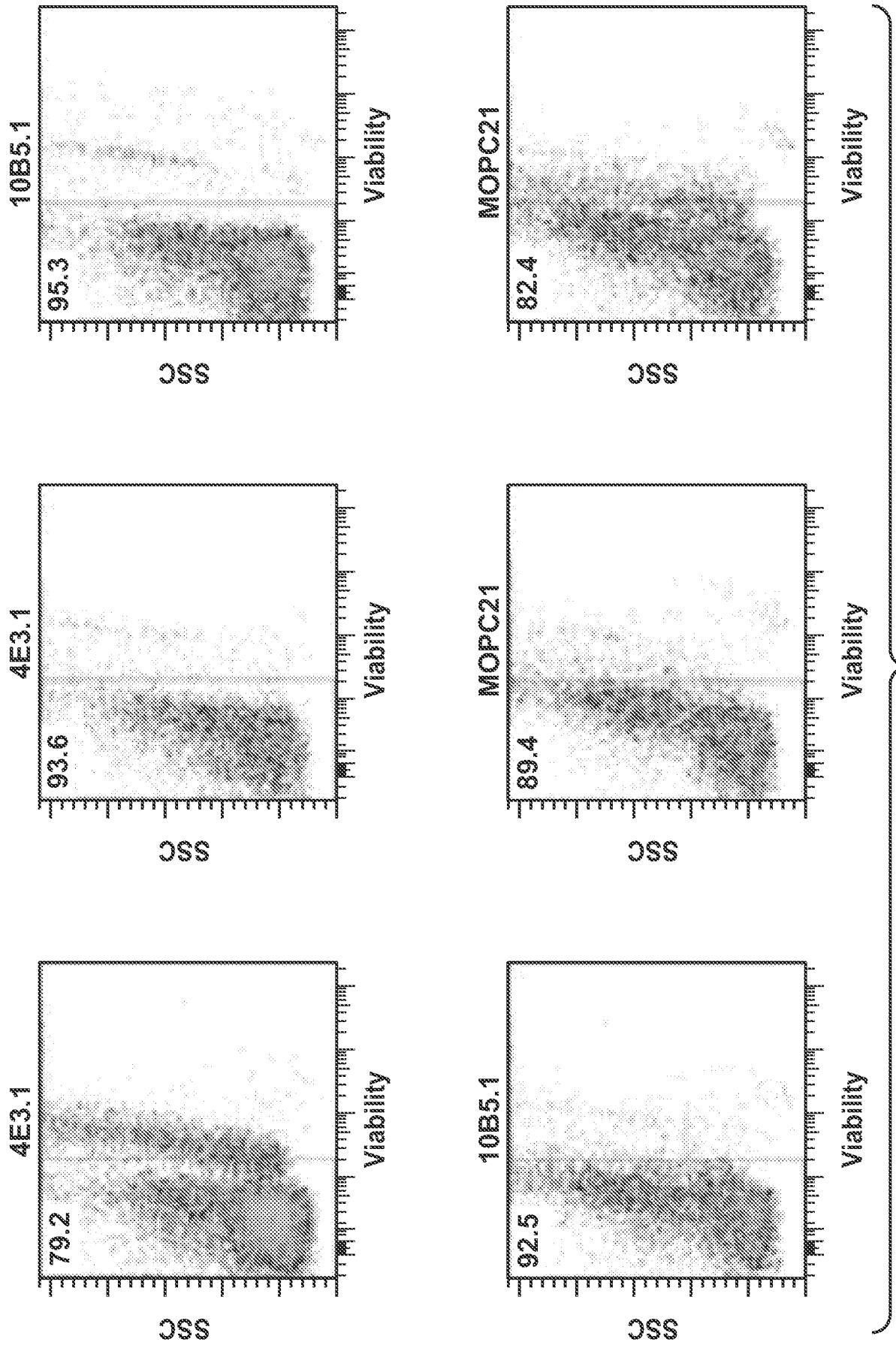

10B5.1
95.3
SSC
Viability
MOPC21
82.4
SSC
Viability
4E3.1
93.6
SSC
Viability
MOPC21
89.4
SSC
Viability
4E3.1
79.2
SSC
Viability
10B5.1
92.5
SSC
Viability

FIG. 7L (Cont.)

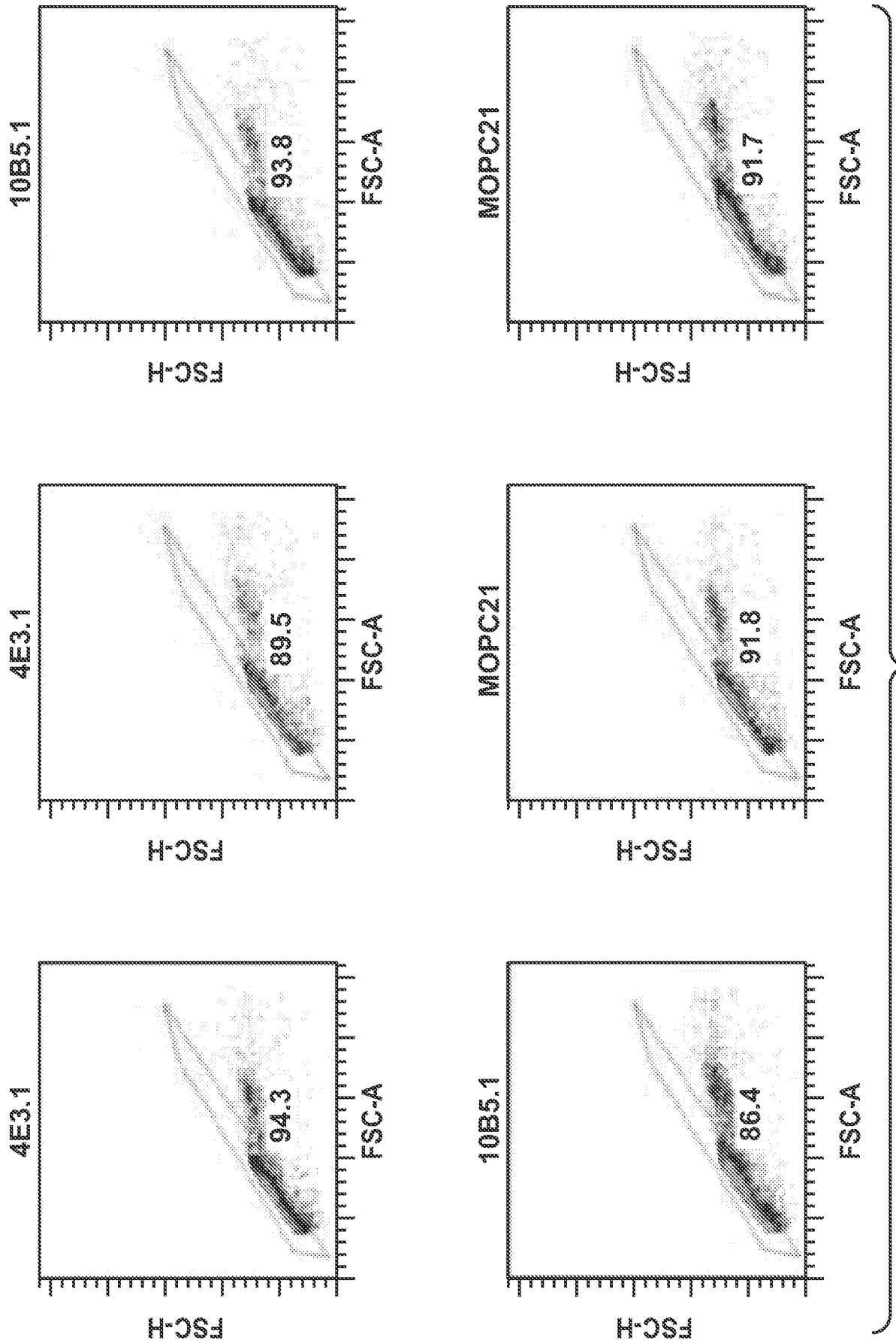

10B5.1
93.8
FSC-H
FSC-A
MOPC21
91.7
FSC-H
FSC-A
4E3.1
89.5
FSC-H
FSC-A
MOPC21
91.8
FSC-H
FSC-A
4E3.1
94.3
FSC-H
FSC-A
10B5.1
86.4
FSC-H
FSC-A

FIG. 7L (Cont.)

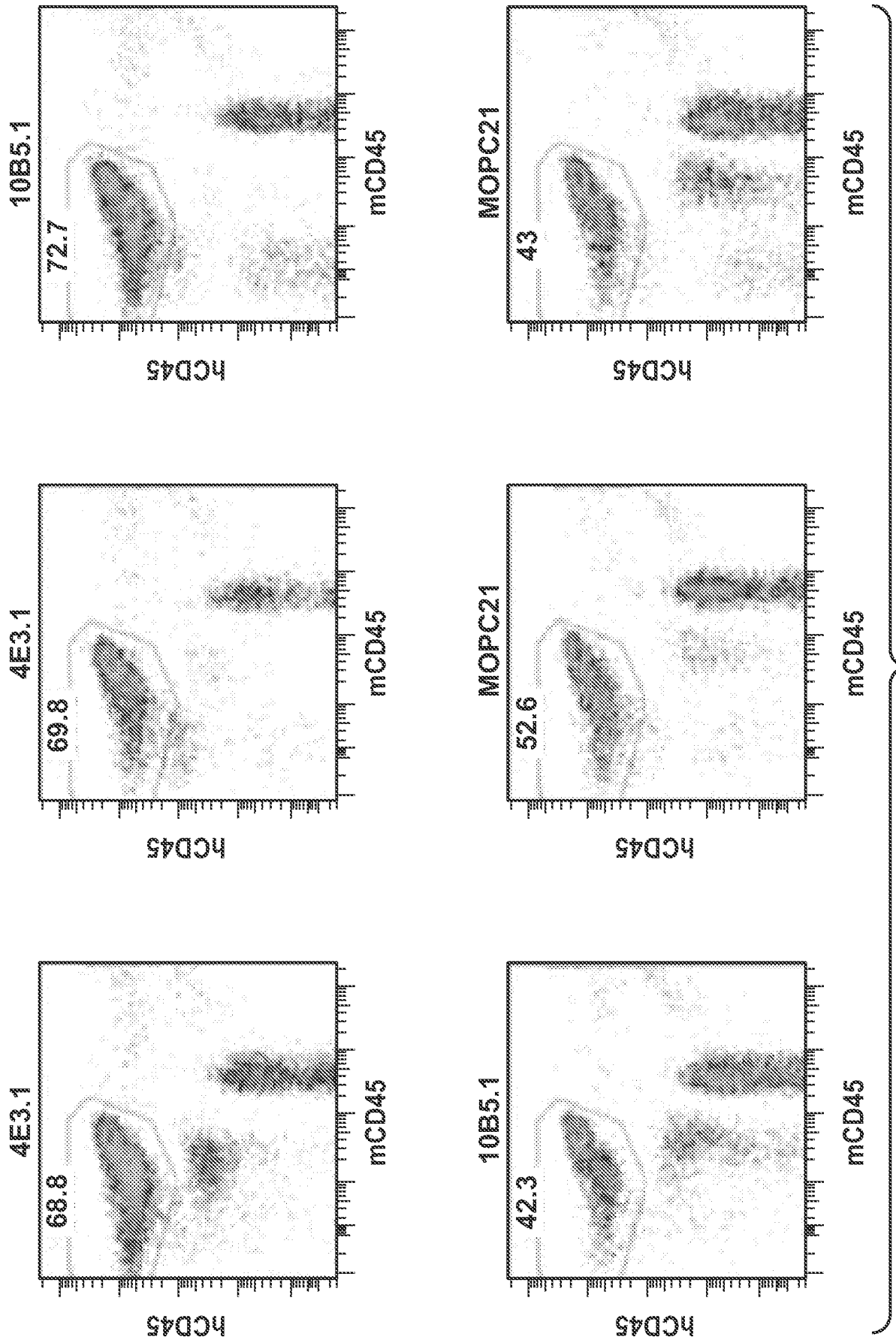

10B5.1
72.7
hCD45
mCD45
MOPC21
43
hCD45
mCD45
4E3.1
69.8
hCD45
mCD45
MOPC21
52.6
hCD45
mCD45
4E3.1
68.8
hCD45
mCD45
10B5.1
42.3
hCD45
mCD45

FIG. 7L (Cont.)

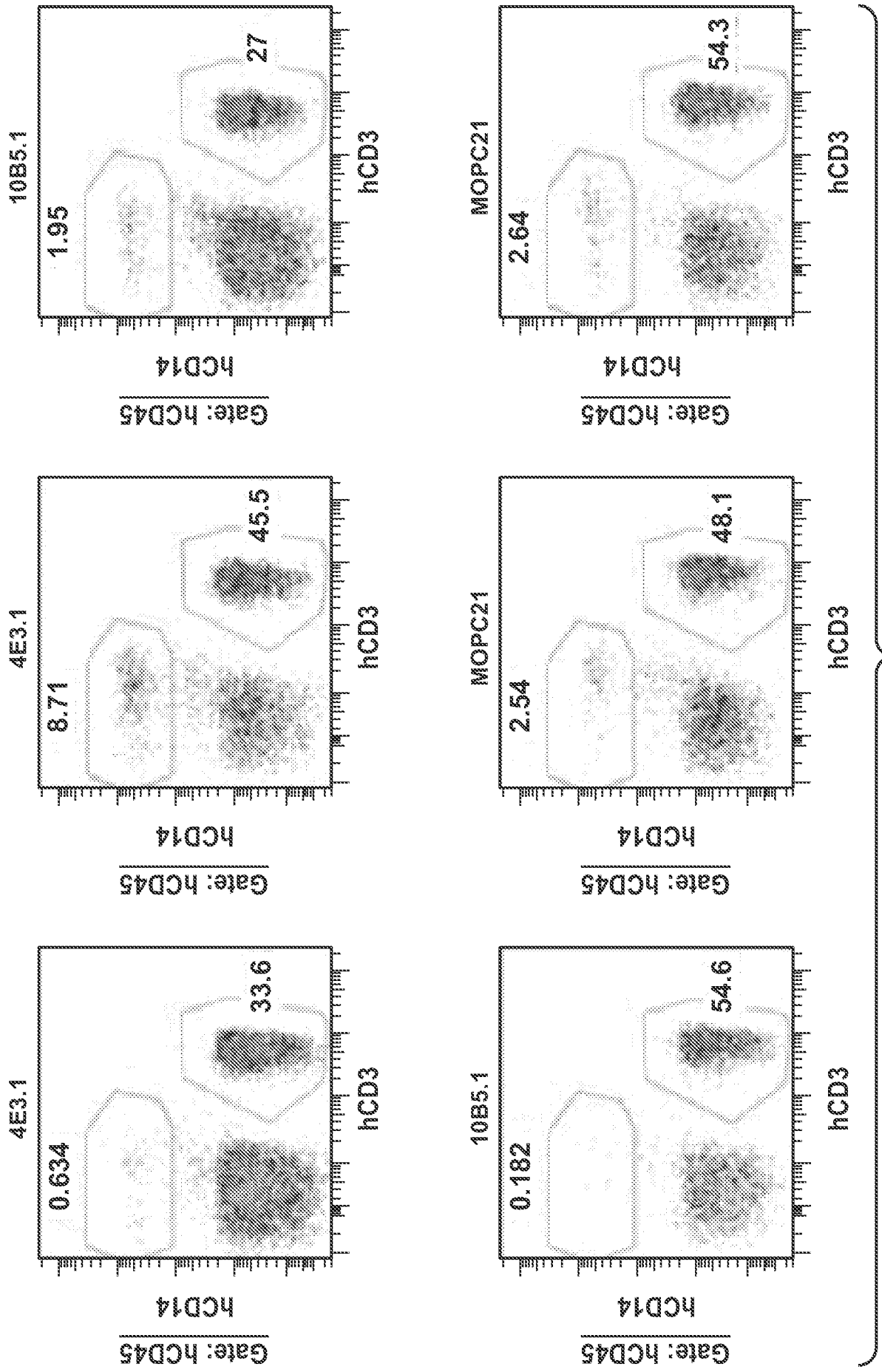

Gate: hCD45
hCD14
hCD3
4E3.1
0.634
33.6
4E3.1
8.71
45.5
10B5.1
1.95
27
MOPC21
2.54
48.1
MOPC21
2.64
54.3
10B5.1
0.182
54.6

FIG. 7L (Cont.)

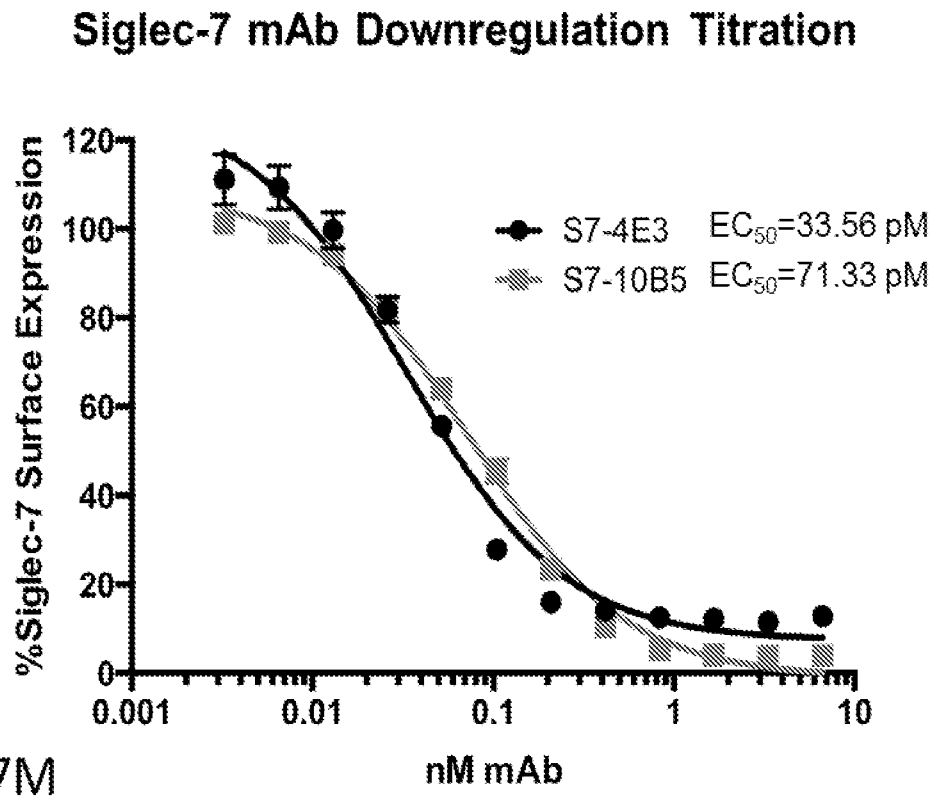

Siglec-7 mAb Downregulation Titration
%Siglec-7 Surface Expression
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
nM mAb
S7-4E3 EC50=33.56 pM
S7-10B5 EC50=71.33 pM

FIG. 7M

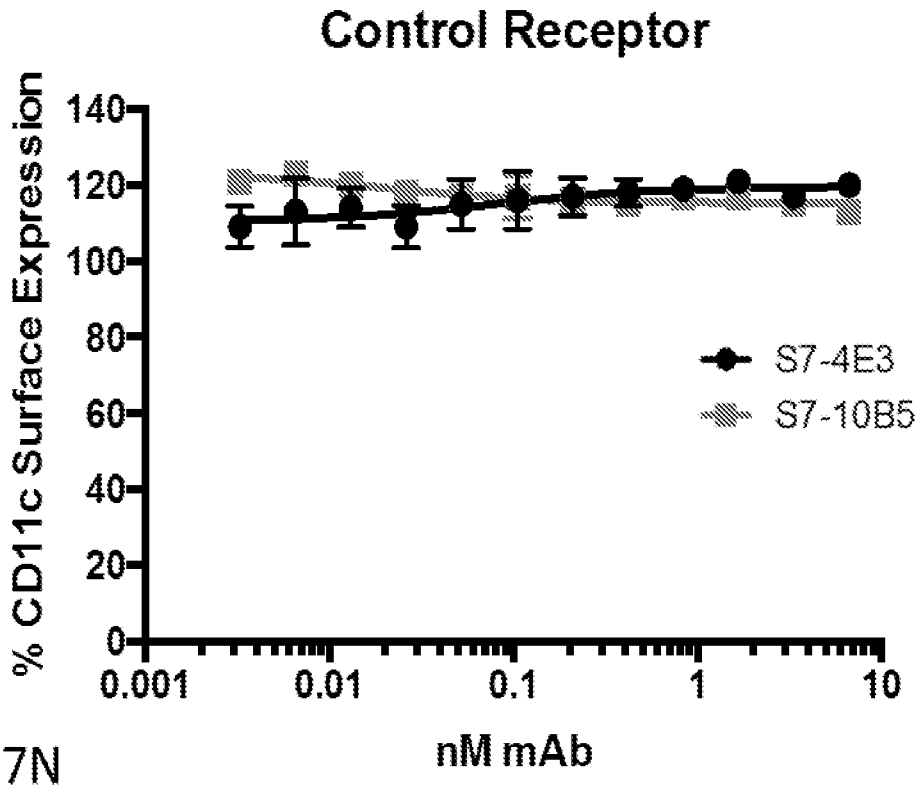

Control Receptor
% CD11c Surface Expression
140
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
nM mAb
S7-4E3
S7-10B5

FIG. 7N

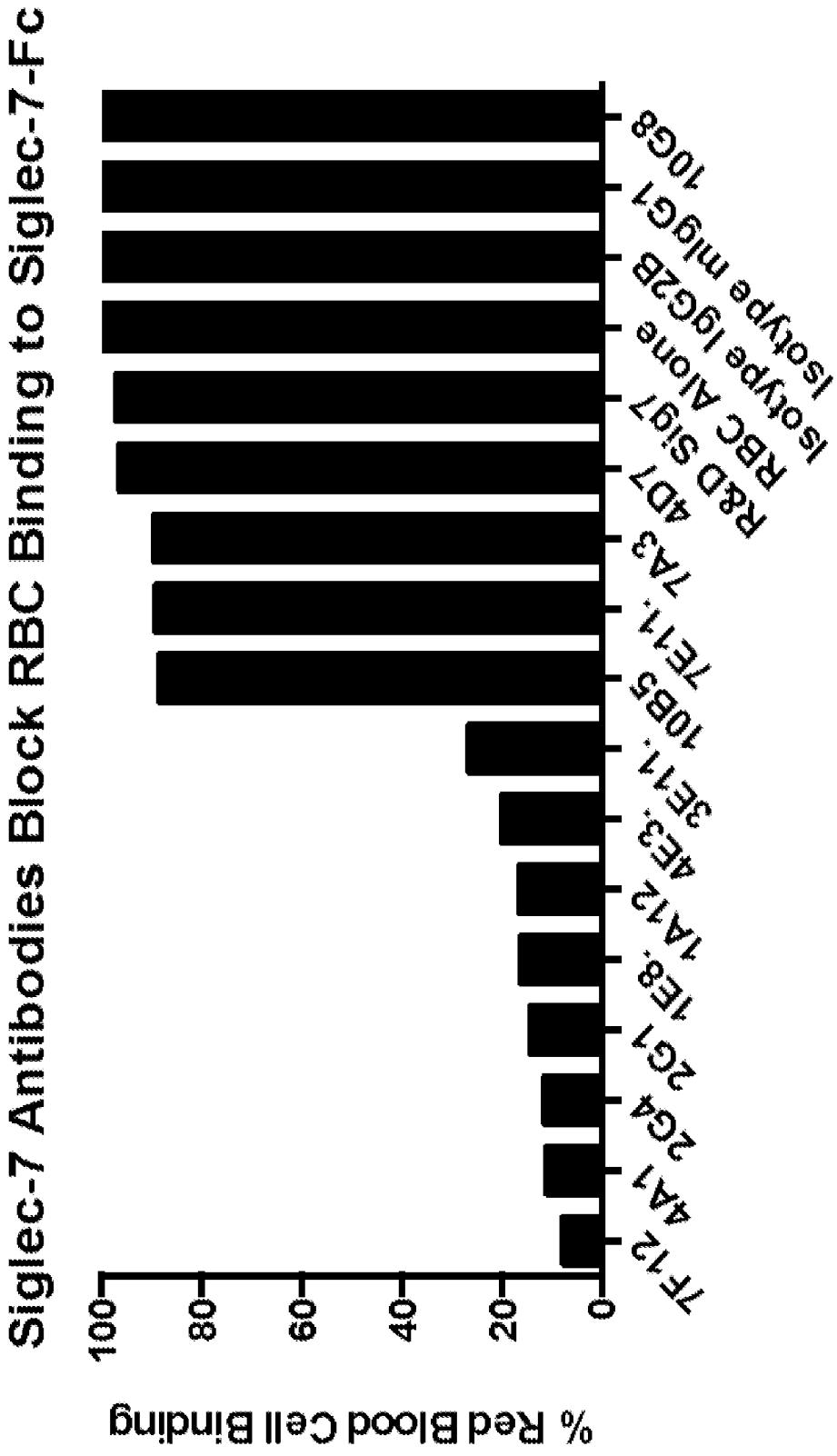

Siglec-7 Antibodies Block RBC Binding to Siglec-7-Fc
% Red Blood Cell Binding
100
80
60
40
20
0
7F12
4A1
2G4
2G1
1E8.
1A12
4E3.
3E11.
10B5
7E11.
7A3
4D7
R&D Sig7
RBC Alone
Isotype IgG2B
Isotype mIgG1
10G8
1.0ug/ml Antibody

FIG. 8

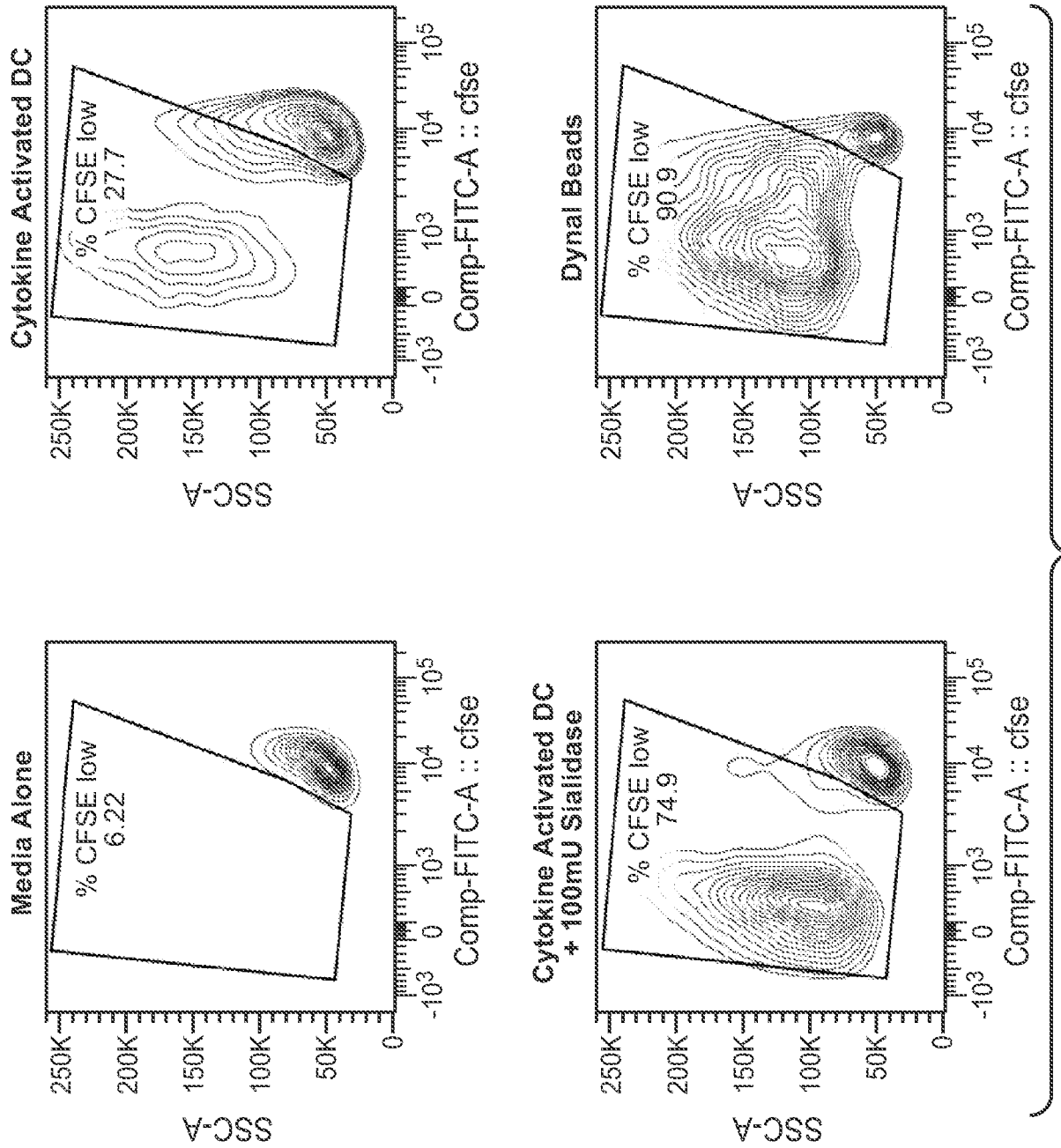

Media Alone
% CFSE low
6.22
Cytokine Activated DC
% CFSE low
27.7
Cytokine Activated DC
+ 100mU Sialidase
% CFSE low
74.9
Dynal Beads
% CFSE low
90.9
SSC-A
Comp-FITC-A :: cfse
250K
200K
150K
100K
50K
0
-10^3
0
10^3
10^4
10^5

FIG. 9

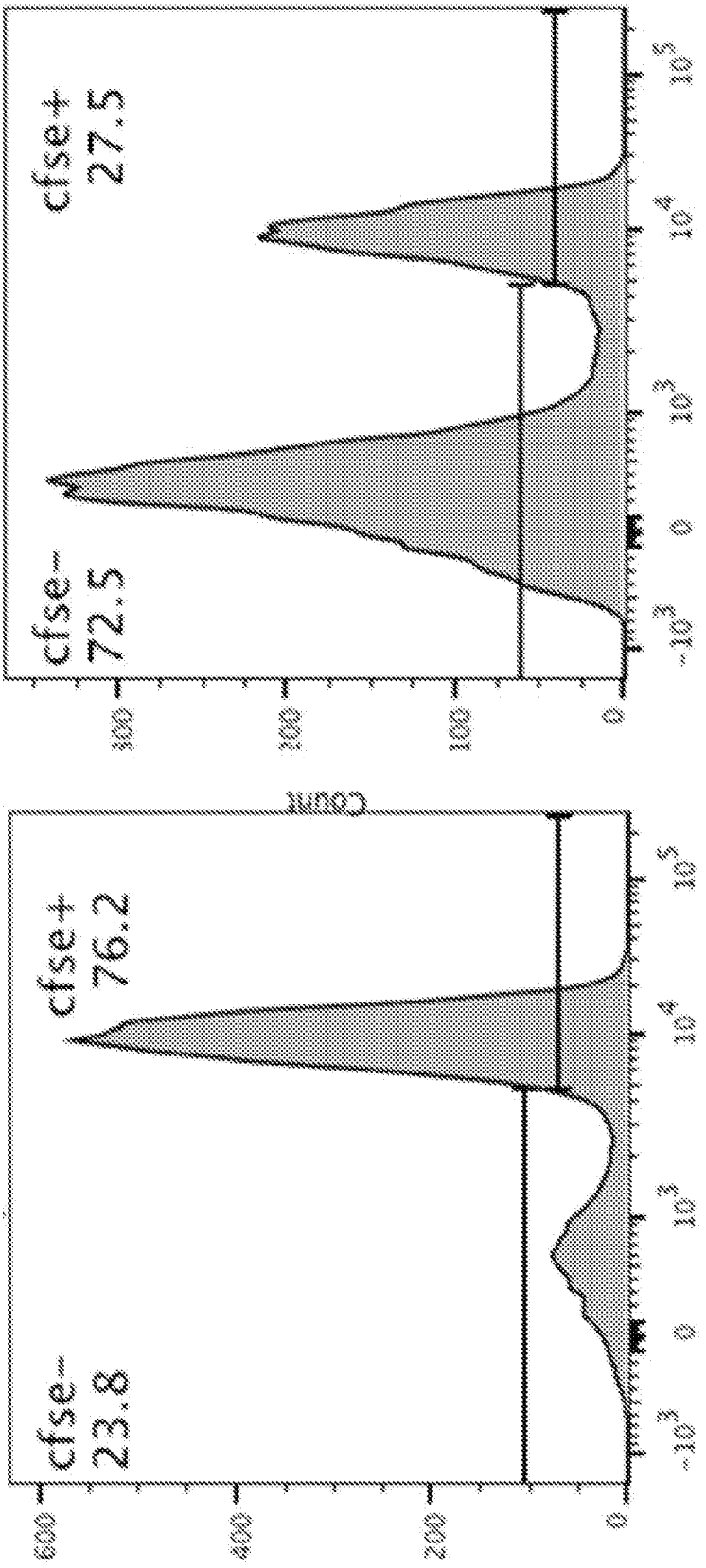

cfse+
27.5
cfse-
72.5
cfse+
76.2
cfse-
23.8
Count
0
100
200
400
600
-10^3
0
10^3
10^4
10^5

FIG. 10

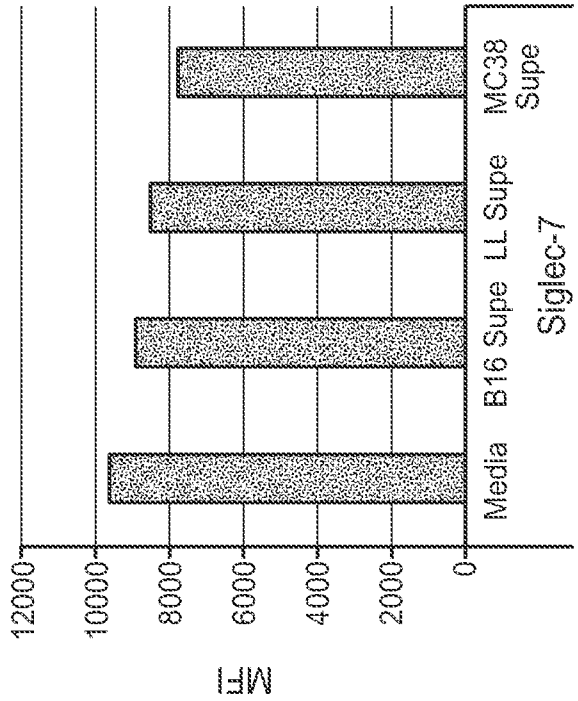

MFI
12000
10000
8000
6000
4000
2000
0
Media
B16 Supe
LL Supe
MC38 Supe
Siglec-7

FIG. 11A

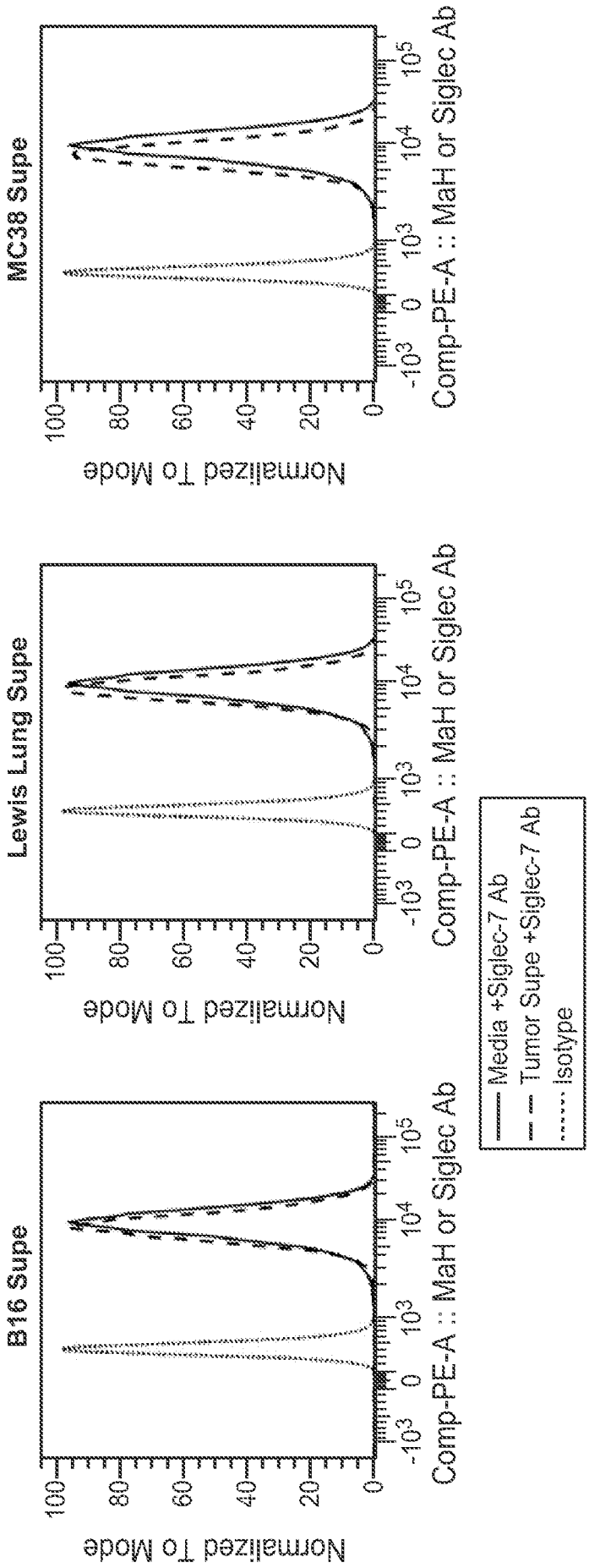

B16 Supe
Lewis Lung Supe
MC38 Supe
Normalized To Mode
Comp-PE-A :: MaH or Siglec Ab
Media +Siglec-7 Ab
Tumor Supe +Siglec-7 Ab
Isotype

FIG. 11B

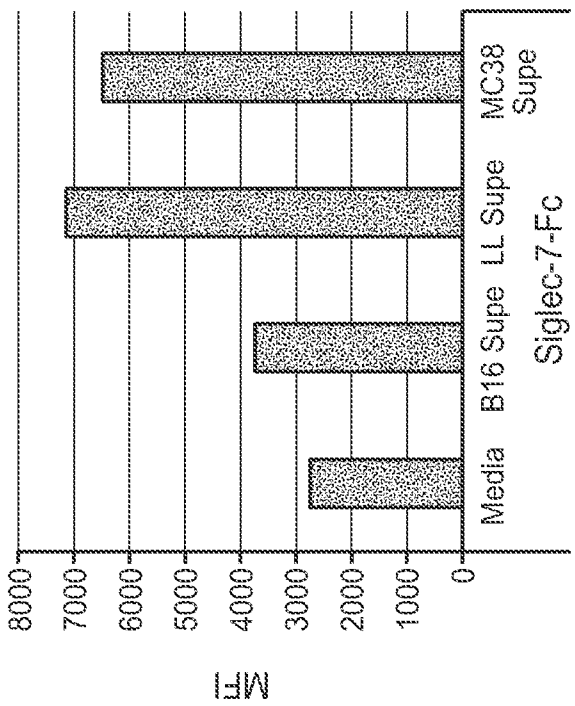

MFI
8000
7000
6000
5000
4000
3000
2000
1000
0
Media
B16 Supe
LL Supe
MC38 Supe
Siglec-7-Fc

FIG. 11C

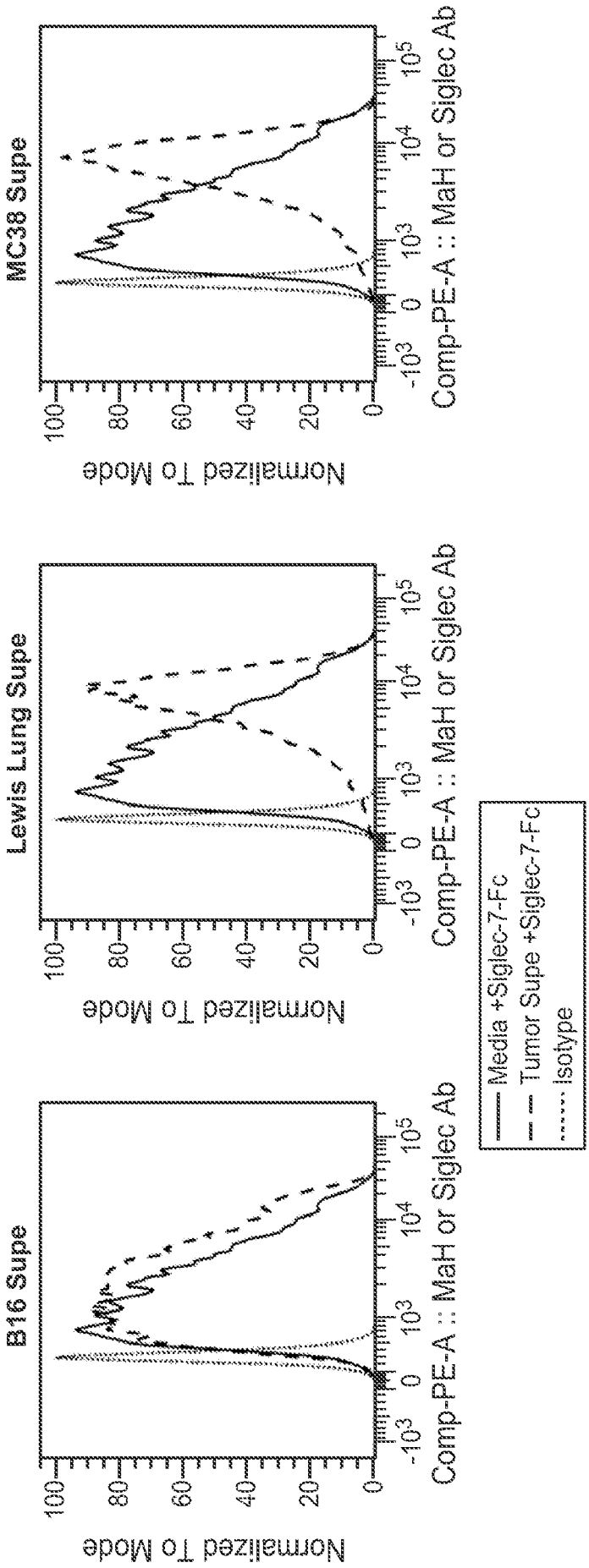

B16 Supe
Lewis Lung Supe
MC38 Supe
Normalized To Mode
Comp-PE-A :: MaH or Siglec Ab
Media +Siglec-7-Fc
Tumor Supe +Siglec-7-Fc
Isotype

FIG. 11D

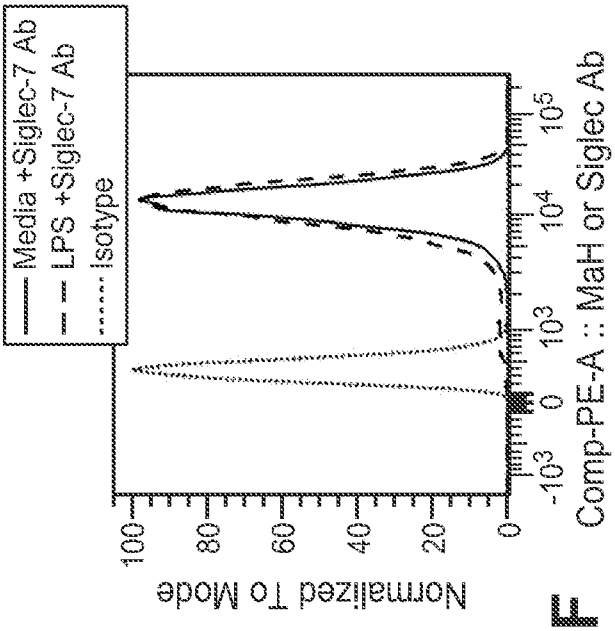


FIG. 11F

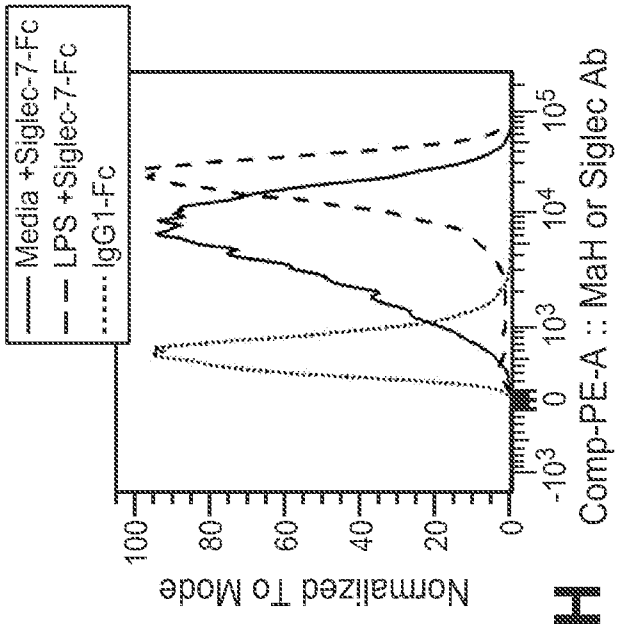


FIG. 11H

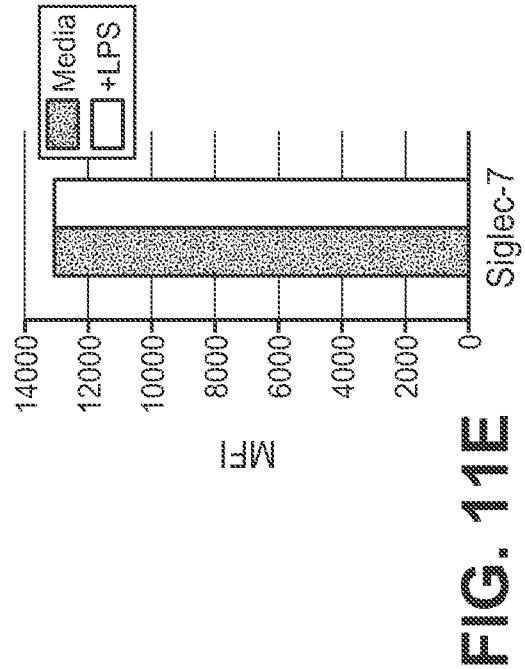


FIG. 11E

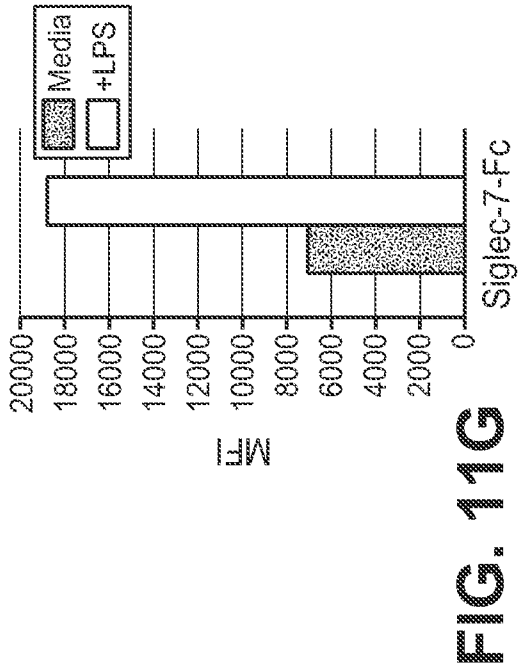


FIG. 11G

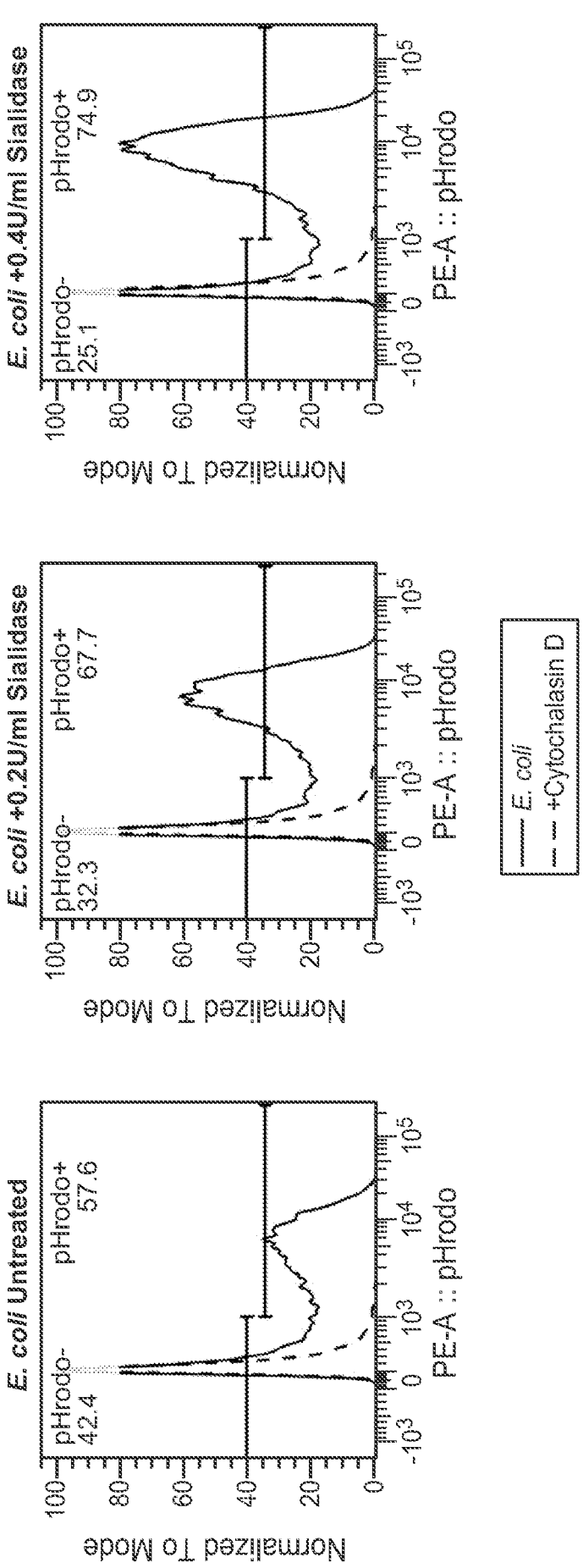

E. coli Untreated
pHrodo- 42.4
pHrodo+ 57.6
E. coli +0.2U/ml Sialidase
pHrodo- 32.3
pHrodo+ 67.7
E. coli +0.4U/ml Sialidase
pHrodo- 25.1
pHrodo+ 74.9
Normalized To Mode
PE-A :: pHrodo
E. coli
+Cytochalasin D

FIG. 12

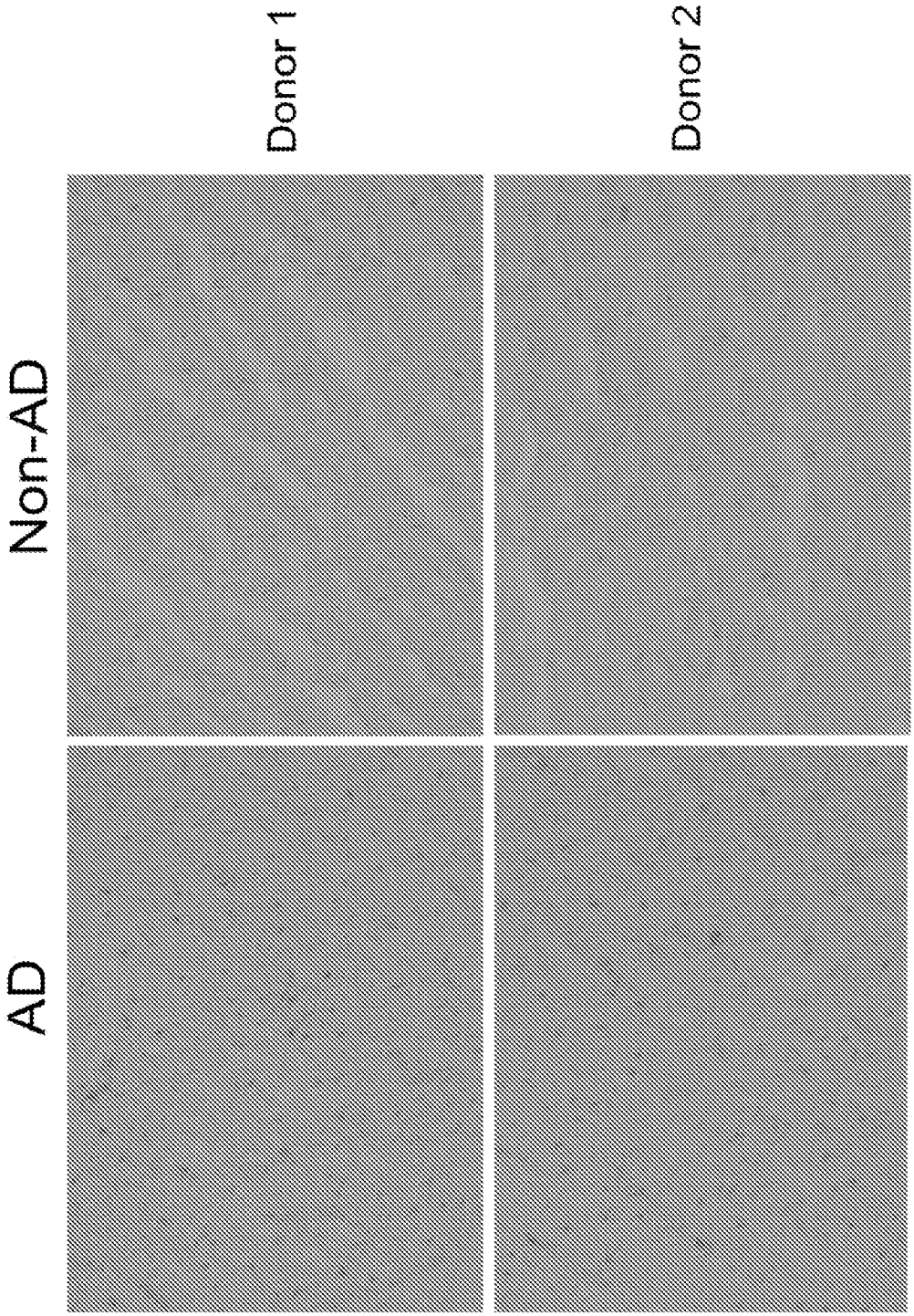


FIG. 13A

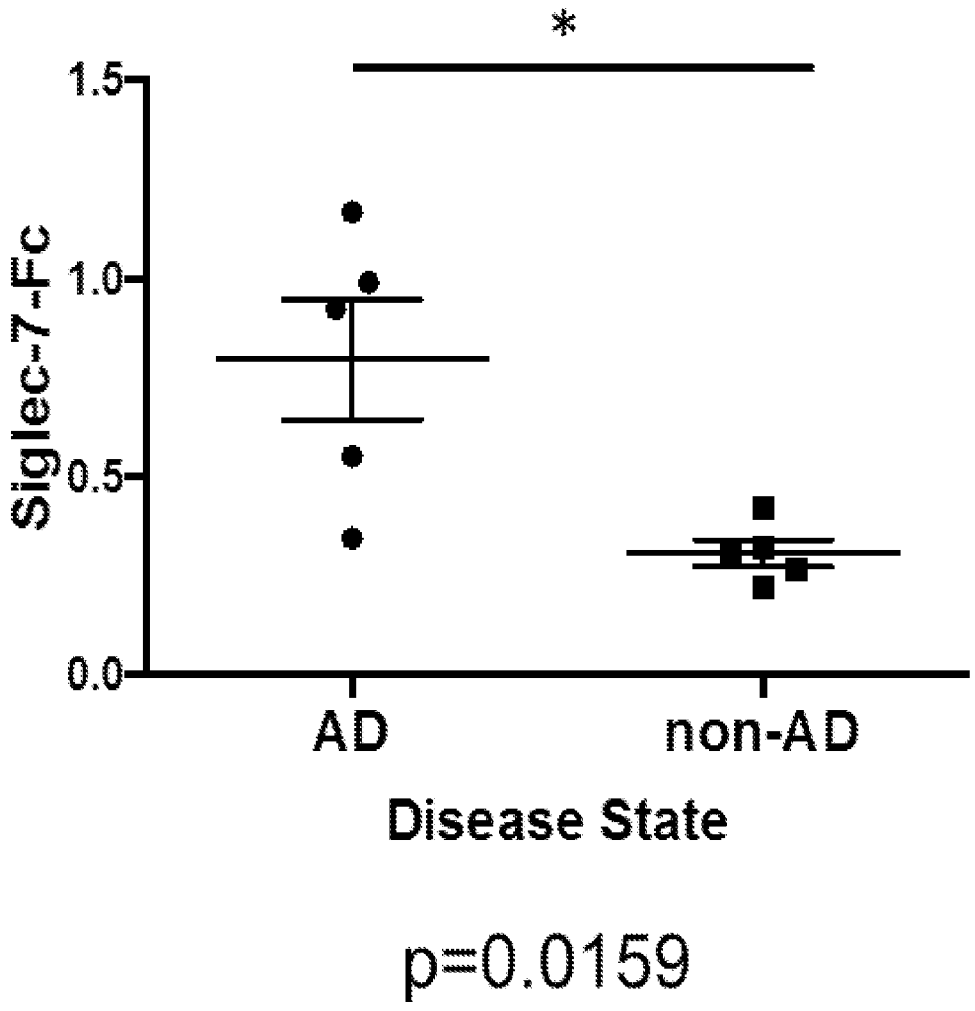


FIG. 13B

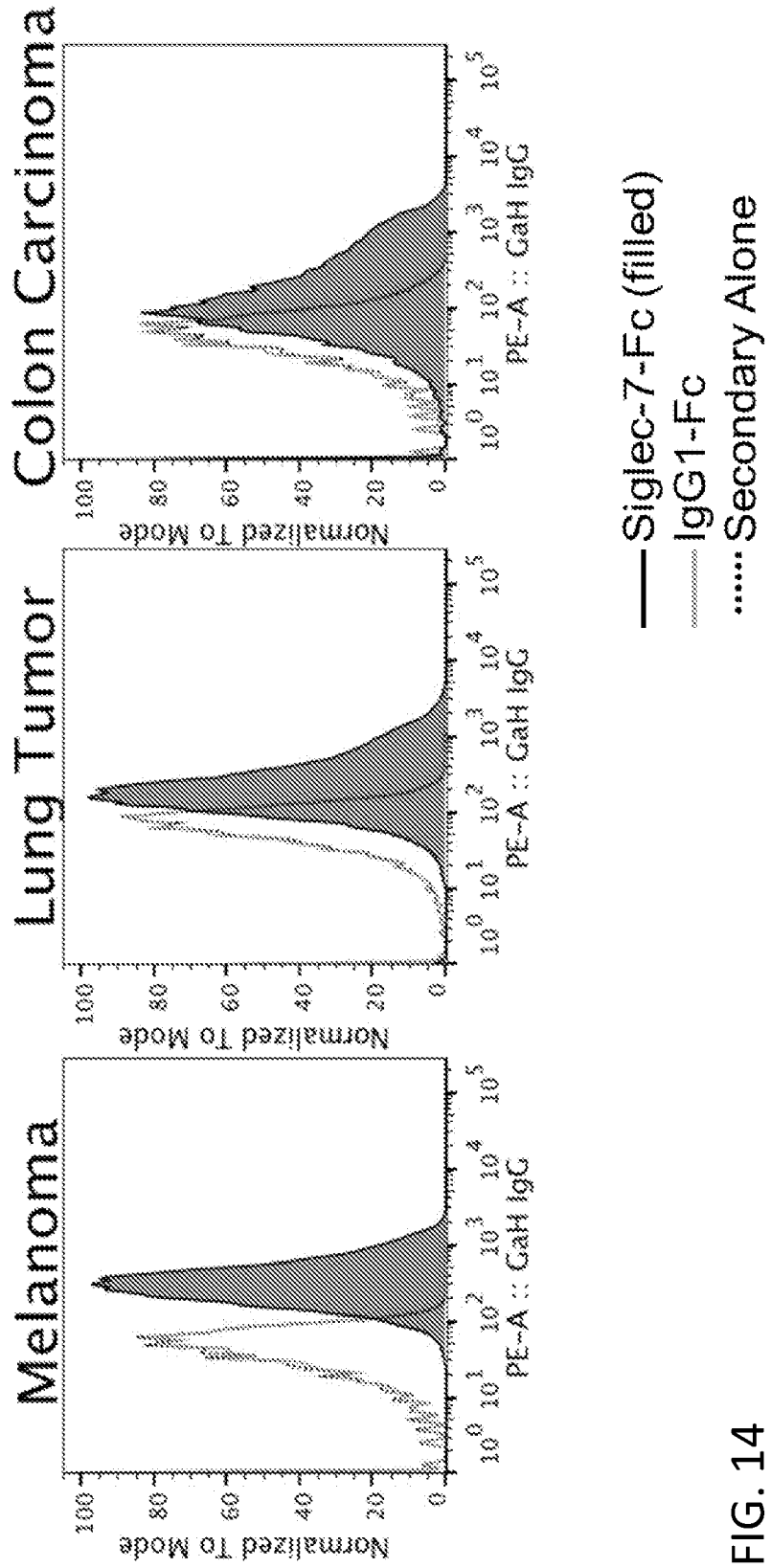

Melanoma
Lung Tumor
Colon Carcinoma
Normalized To Mode
PE-A :: GaH IgG
Siglec-7-Fc (filled)
IgG1-Fc
Secondary Alone

FIG. 14

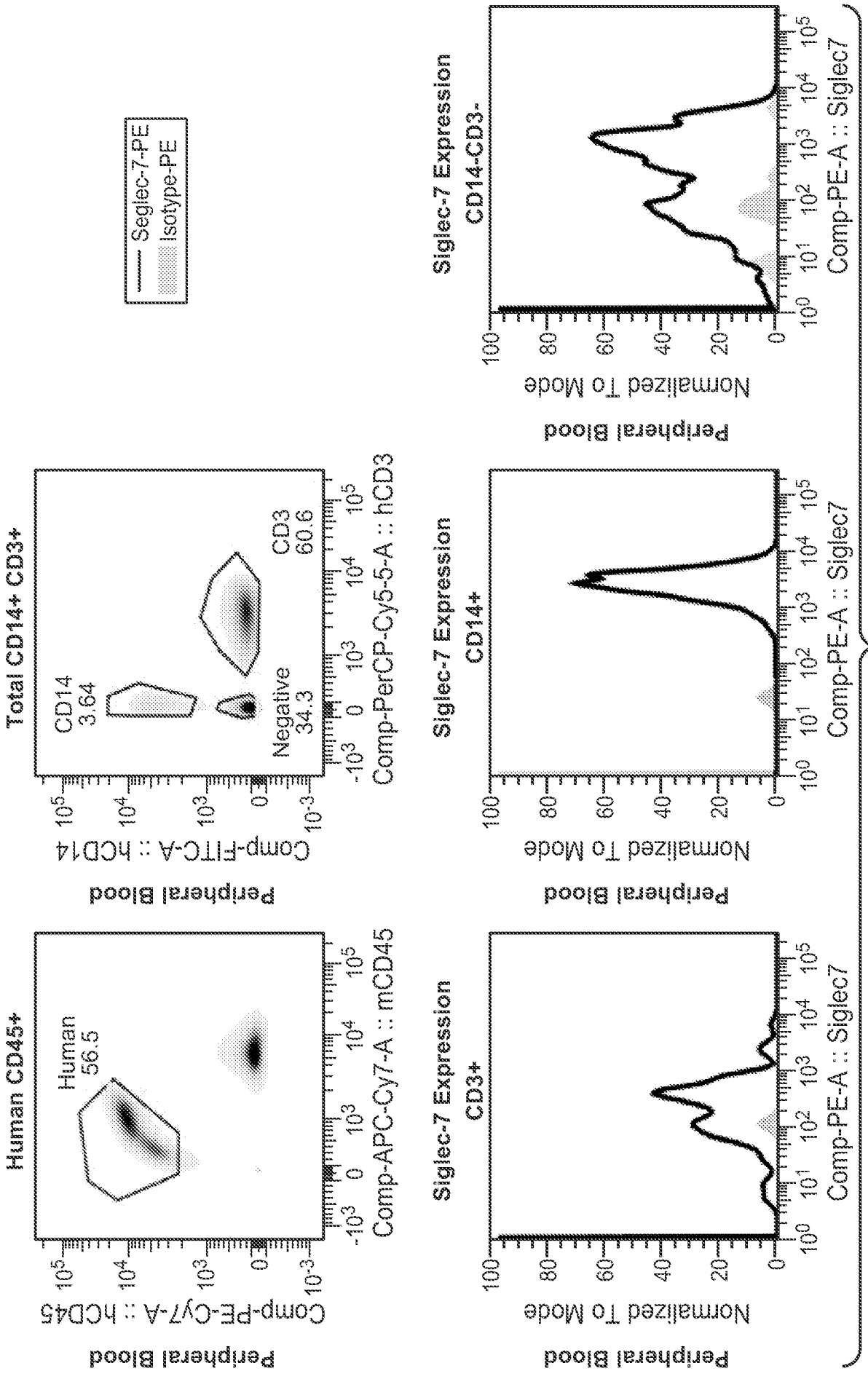

Seglec-7-PE
Isotype-PE
Human CD45+
Human
56.5
Peripheral Blood
Comp-PE-Cy7-A :: hCD45
Comp-APC-Cy7-A :: mCD45
Total CD14+ CD3+
CD14
3.64
Negative
34.3
CD3
60.6
Peripheral Blood
Comp-FITC-A :: hCD14
Comp-PerCP-Cy5-5-A :: hCD3
Siglec-7 Expression
CD3+
Peripheral Blood
Normalized To Mode
Comp-PE-A :: Siglec7
Siglec-7 Expression
CD14+
Peripheral Blood
Normalized To Mode
Comp-PE-A :: Siglec7
Siglec-7 Expression
CD14-CD3-
Peripheral Blood
Normalized To Mode
Comp-PE-A :: Siglec7

FIG. 15

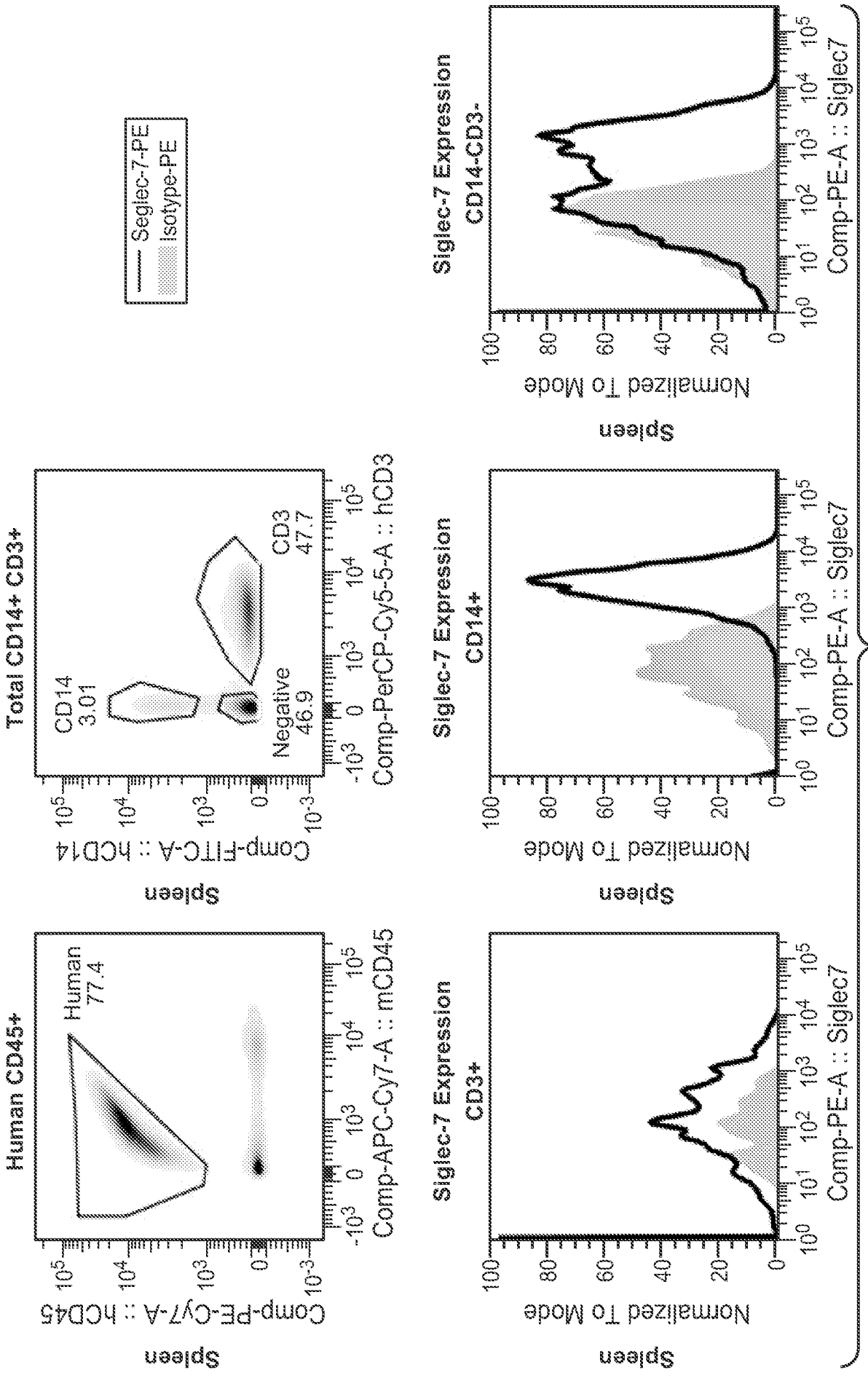

Human CD45+
Human
77.4
Comp-PE-Cy7-A :: hCD45
Comp-APC-Cy7-A :: mCD45
Spleen
Total CD14+ CD3+
CD14
3.01
Negative
46.9
CD3
47.7
Comp-FITC-A :: hCD14
Comp-PerCP-Cy5-5-A :: hCD3
Spleen
Seglec-7-PE
Isotype-PE
Siglec-7 Expression
CD3+
Siglec-7 Expression
CD14+
Siglec-7 Expression
CD14-CD3-
Normalized To Mode
Comp-PE-A :: Siglec7
Spleen

FIG. 15 (Cont.)

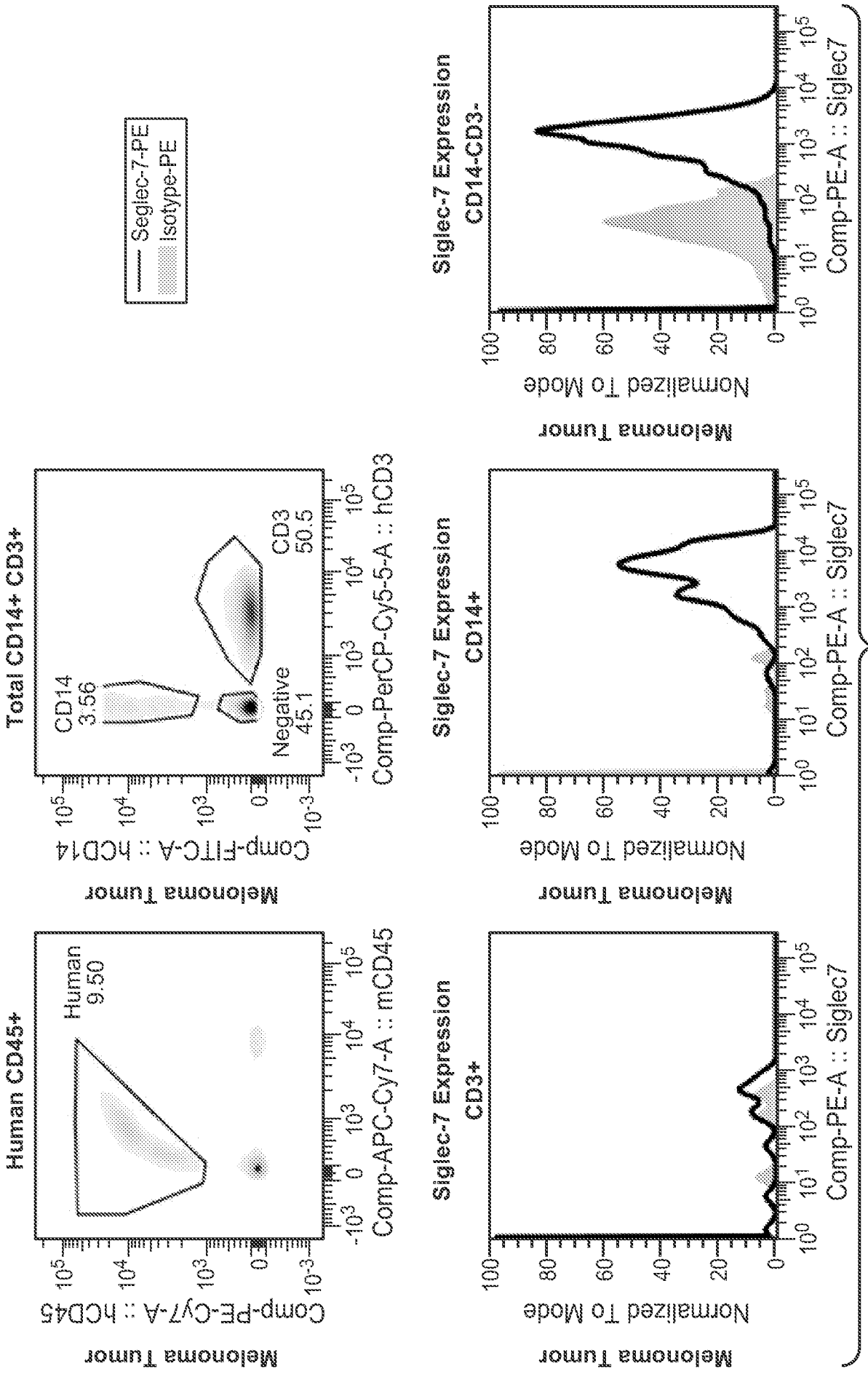

Seglec-7-PE
Isotype-PE
Human CD45+
Human
9.50
Melonoma Tumor
Comp-PE-Cy7-A :: hCD45
Comp-APC-Cy7-A :: mCD45
Total CD14+ CD3+
CD14
3.56
Negative
45.1
CD3
50.5
Melonoma Tumor
Comp-FITC-A :: hCD14
Comp-PerCP-Cy5-5-A :: hCD3
Siglec-7 Expression
CD3+
Melonoma Tumor
Normalized To Mode
Comp-PE-A :: Siglec7
Siglec-7 Expression
CD14+
Melonoma Tumor
Normalized To Mode
Comp-PE-A :: Siglec7
Siglec-7 Expression
CD14-CD3-
Melonoma Tumor
Normalized To Mode
Comp-PE-A :: Siglec7

FIG. 15 (Cont.)

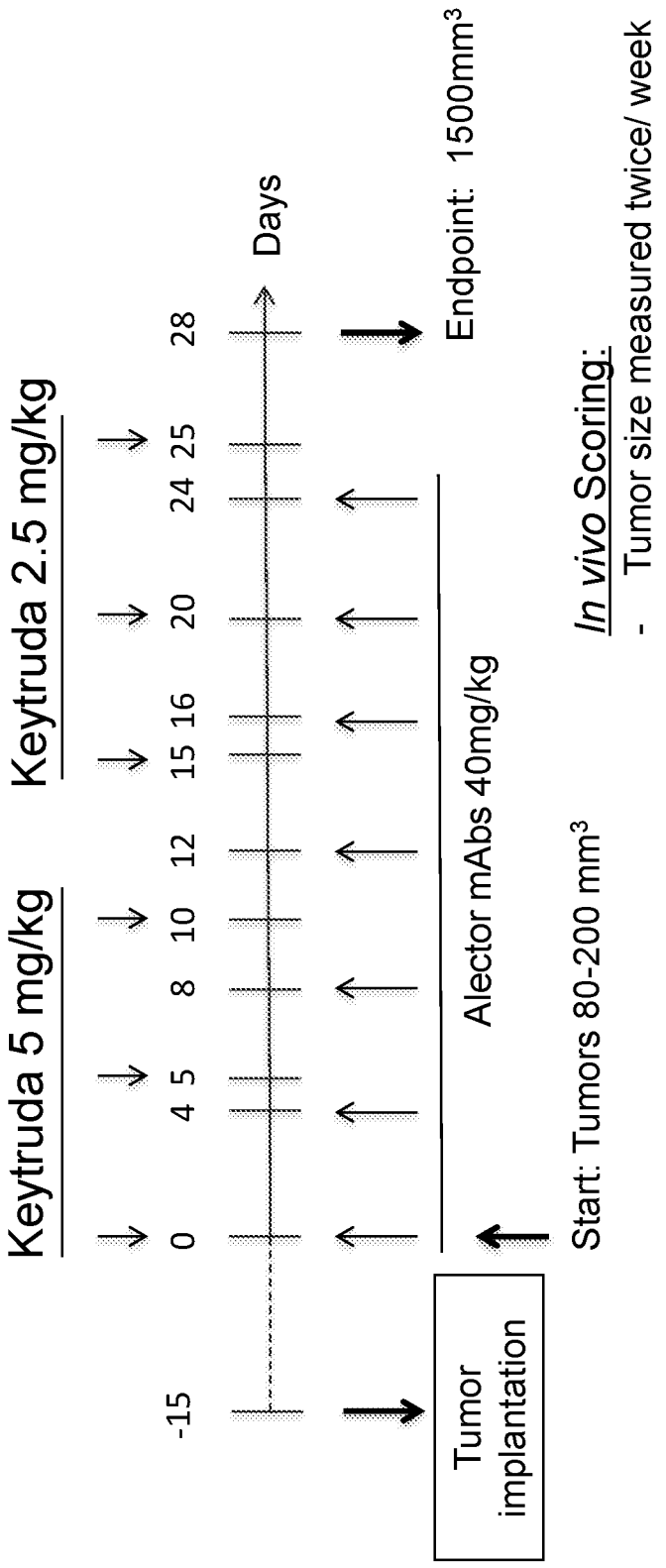

Keytruda 5 mg/kg
Keytruda 2.5 mg/kg
-15
0
4 5
8
10
12
15 16
20
24 25
28
Days
Endpoint: 1500mm3
Alector mAbs 40mg/kg
Tumor implantation
Start: Tumors 80-200 mm3
In vivo Scoring:
- Tumor size measured twice/ week

FIG. 16A

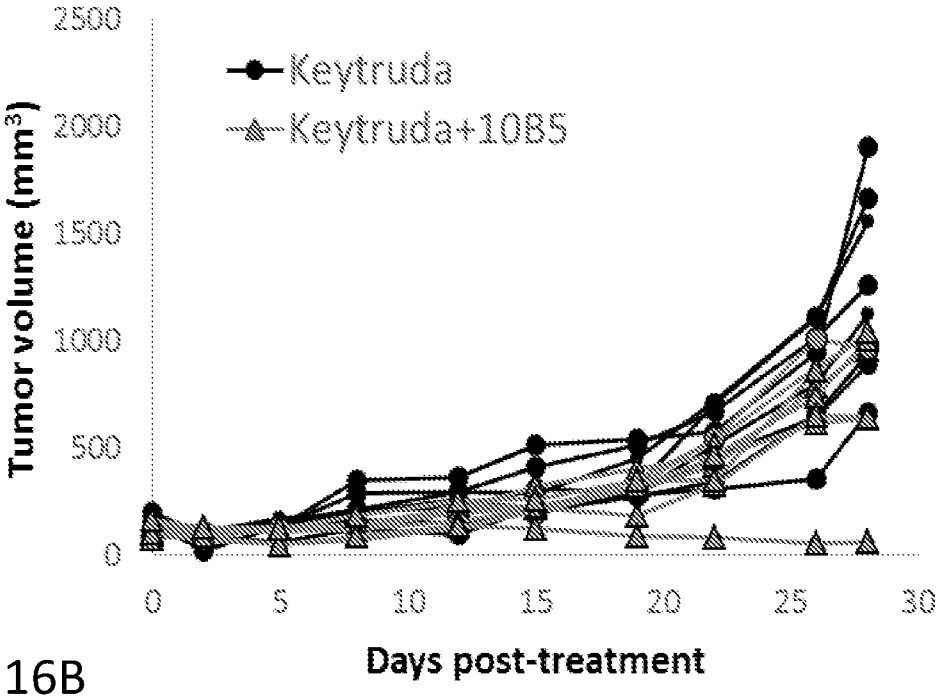


FIG. 16B

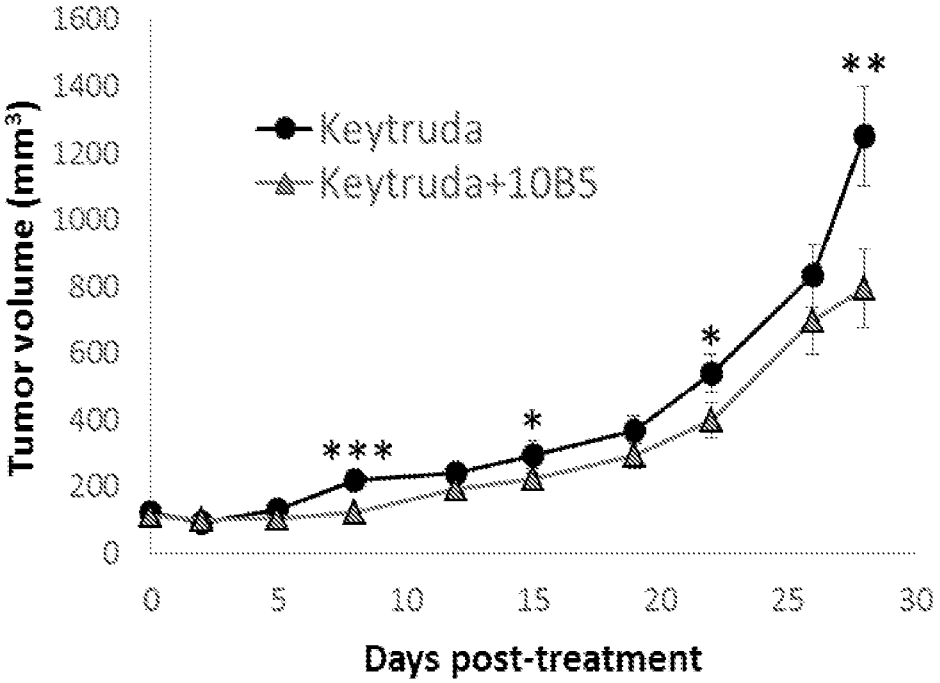


FIG. 16C

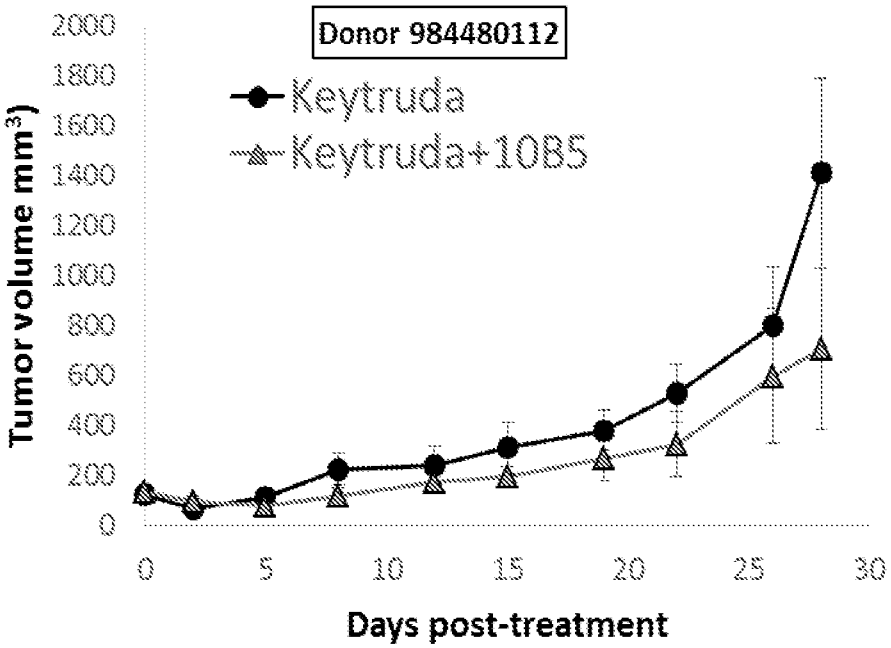


FIG. 16D

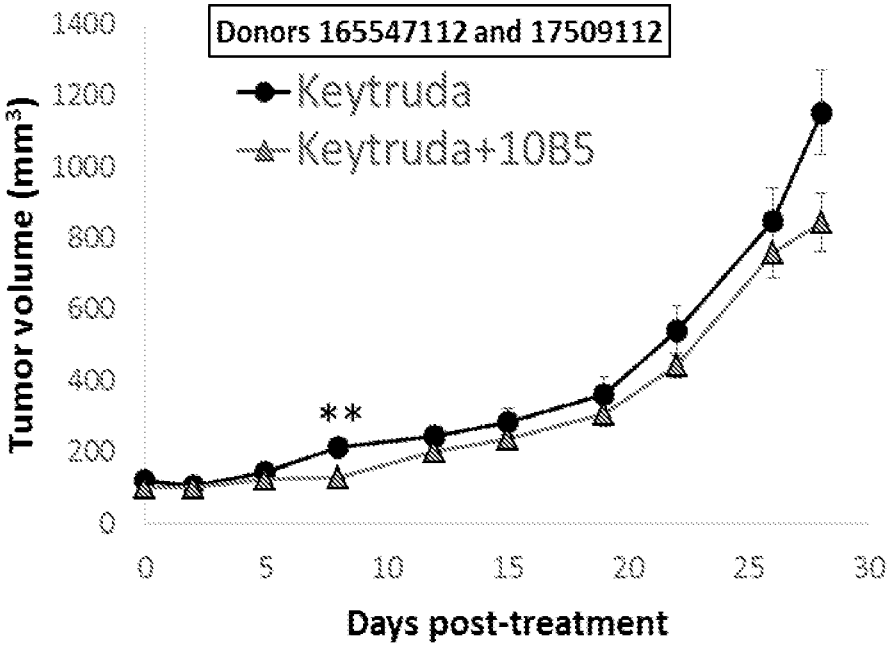


FIG. 16E

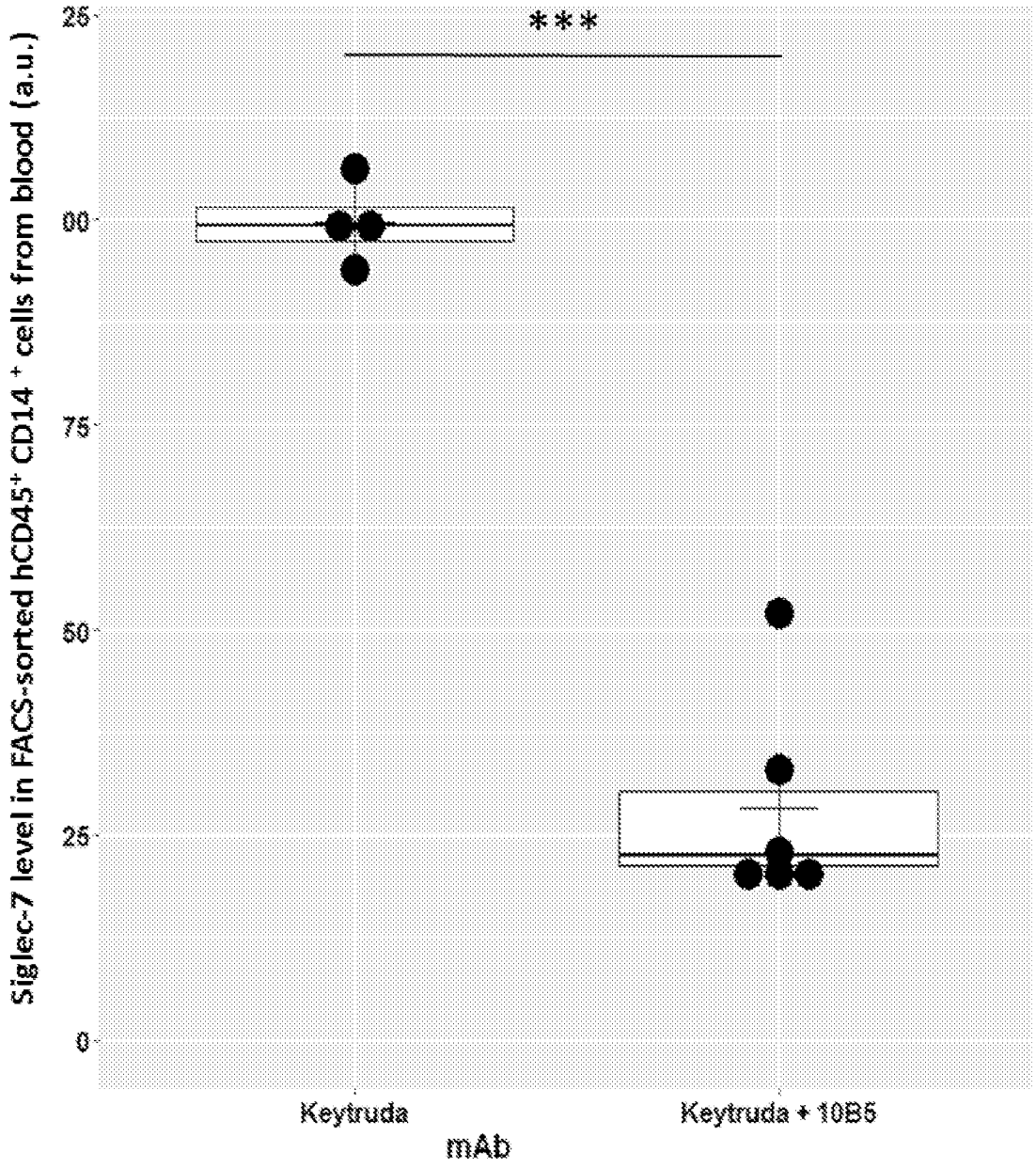

***
Siglec-7 level in FACS-sorted hCD45+ CD14 + cells from blood (a.u.)
25
00
75
50
25
0
Keytruda
Keytruda + 10B5
mAb

FIG. 16F

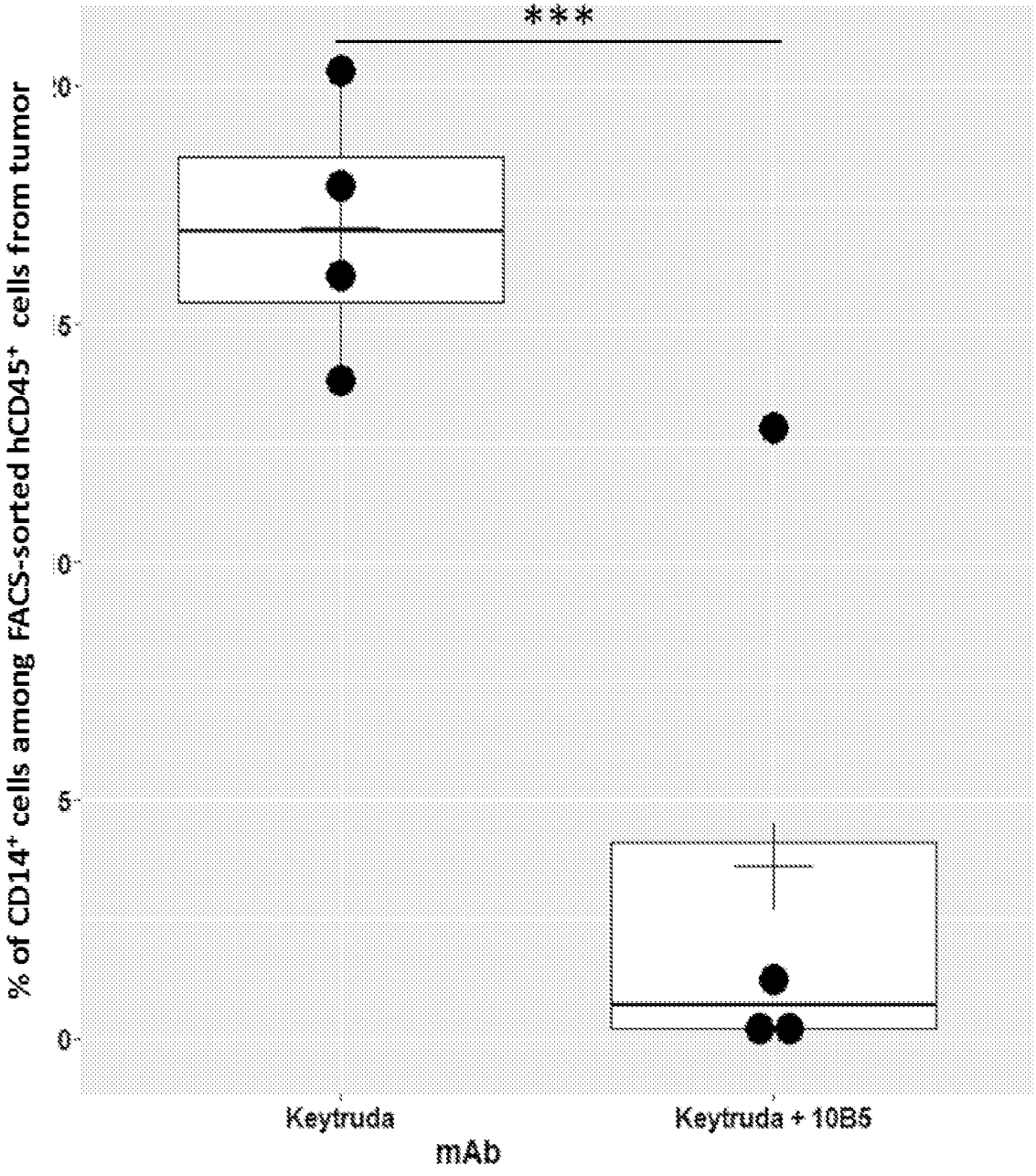

***
% of CD14+ cells among FACS-sorted hCD45+ cells from tumor
10
5
0
5
0
Keytruda
Keytruda + 10B5
mAb

FIG. 16G

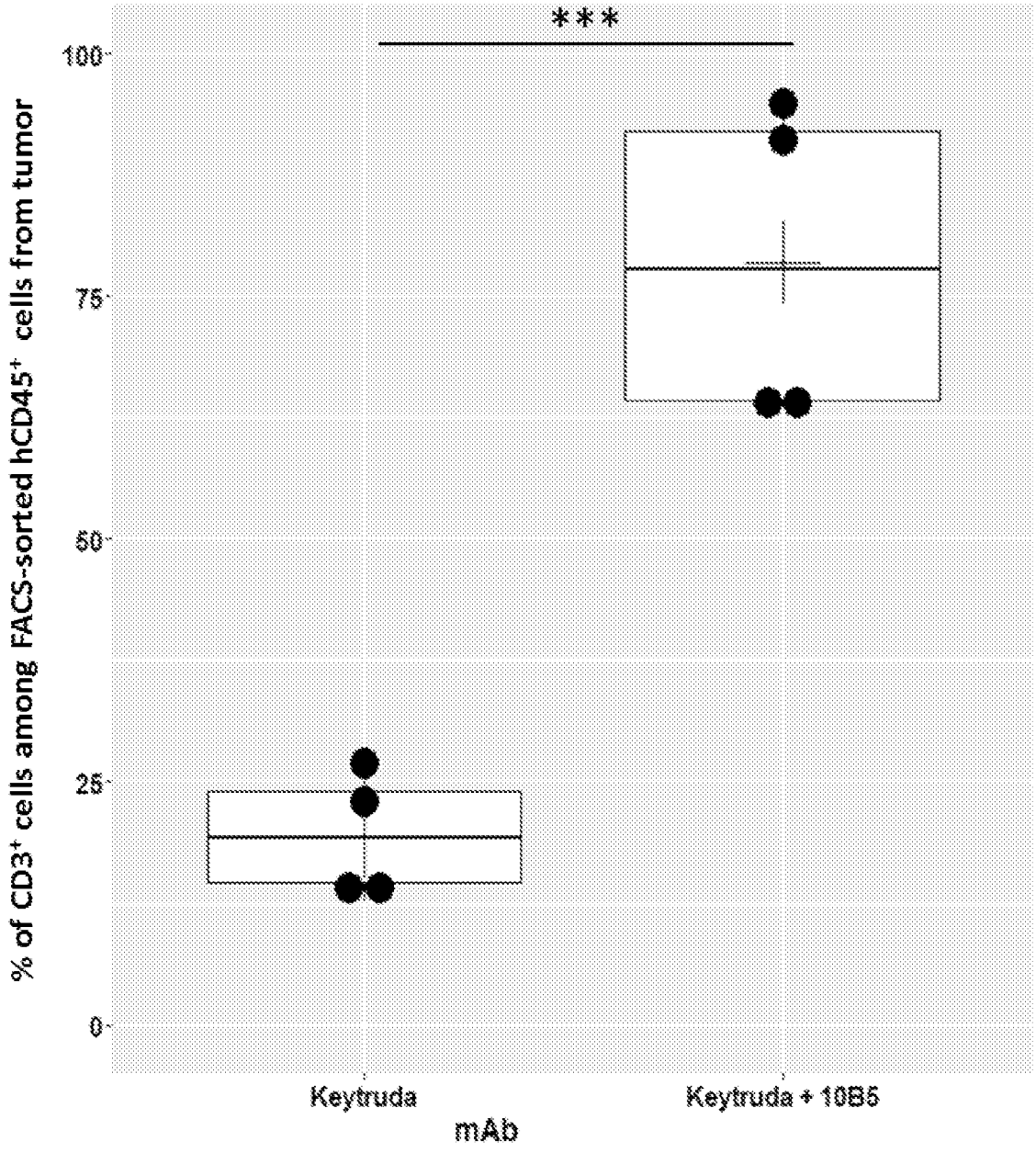

***
100
75
50
25
0
% of CD3+ cells among FACS-sorted hCD45+ cells from tumor
Keytruda
Keytruda + 10B5
mAb

FIG. 16H

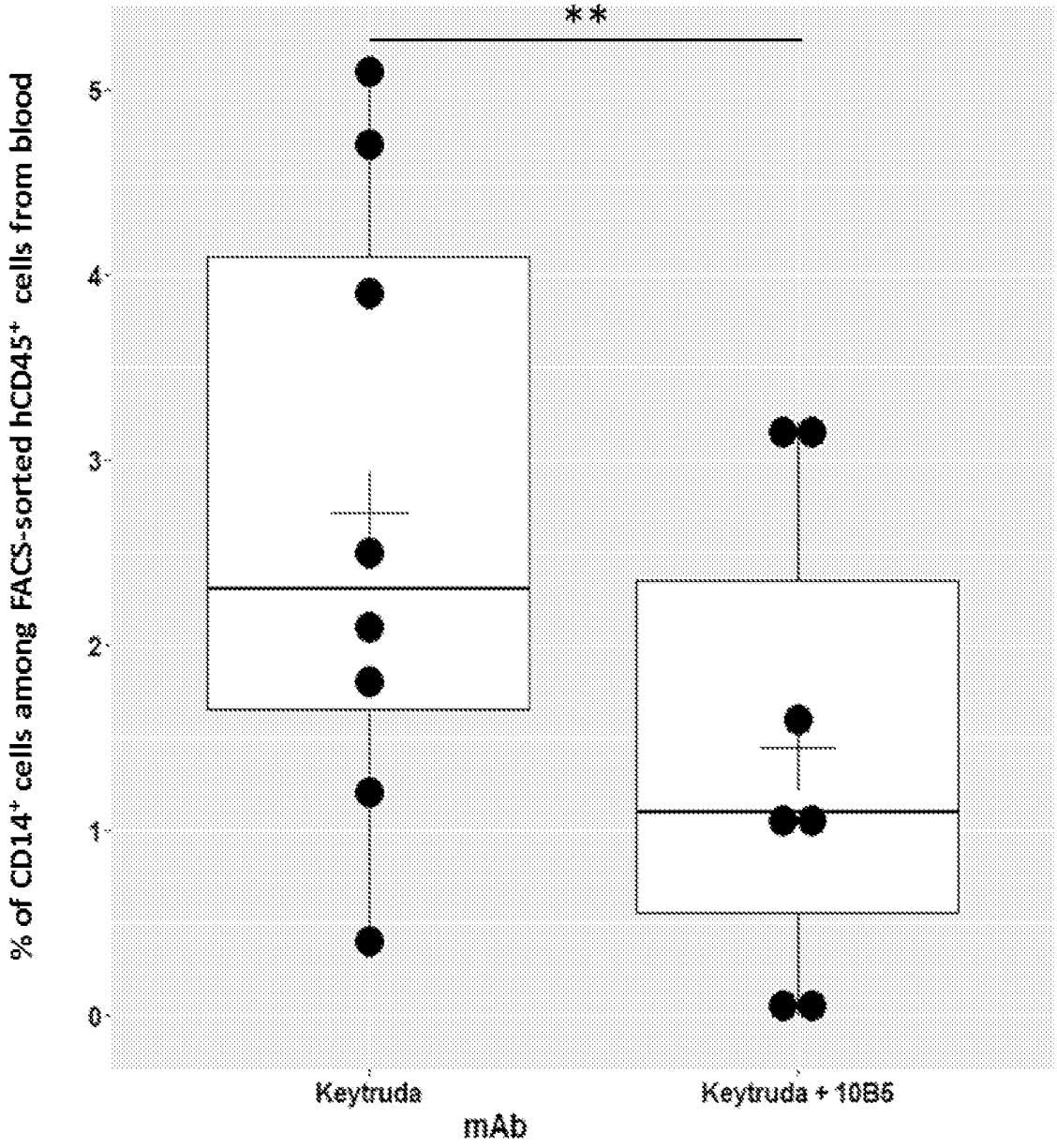

**
% of CD14+ cells among FACS-sorted hCD45+ cells from blood
0
1
2
3
4
5
Keytruda
Keytruda + 10B5
mAb

FIG. 16I

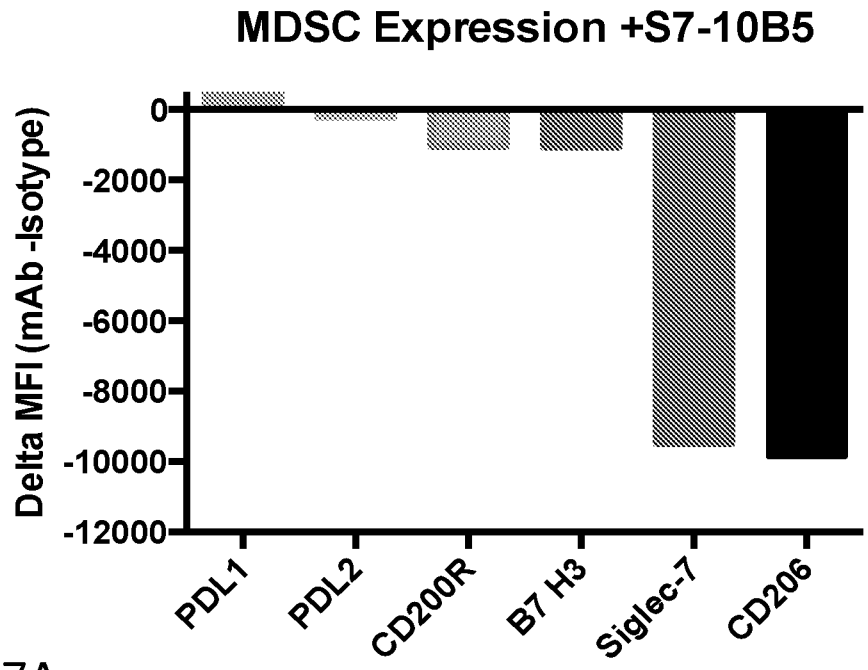


FIG. 17A

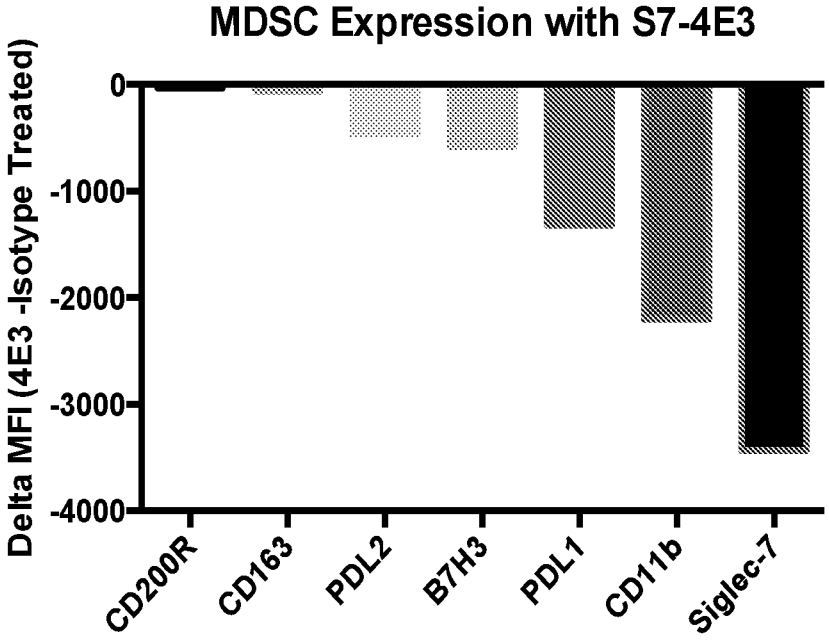


FIG. 17B

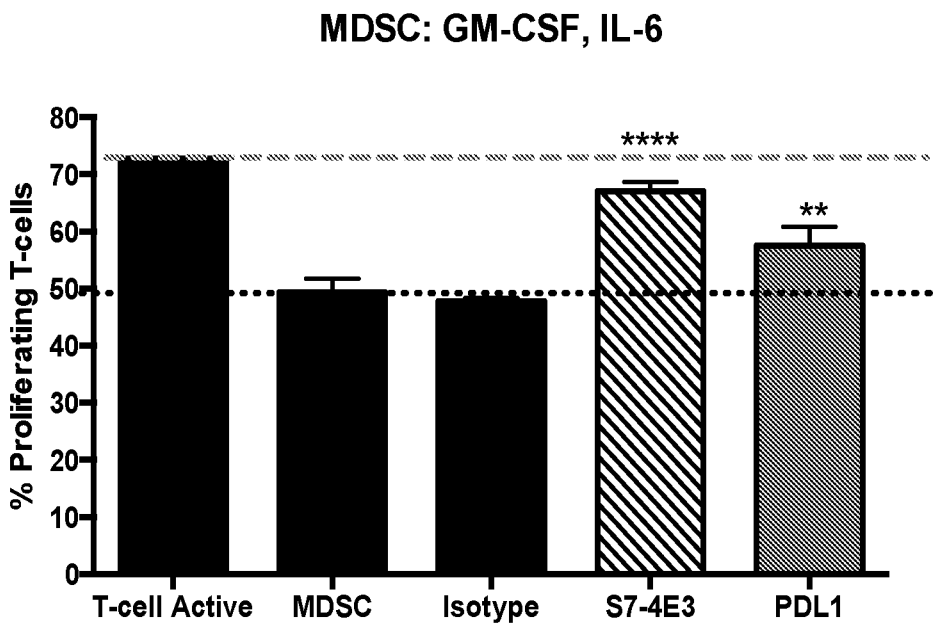


FIG. 17C

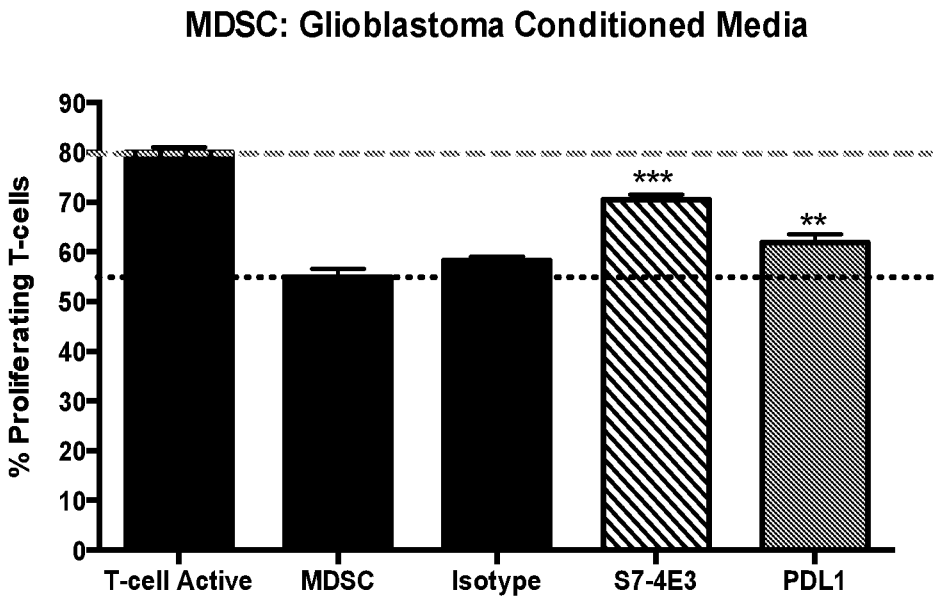


FIG. 17D

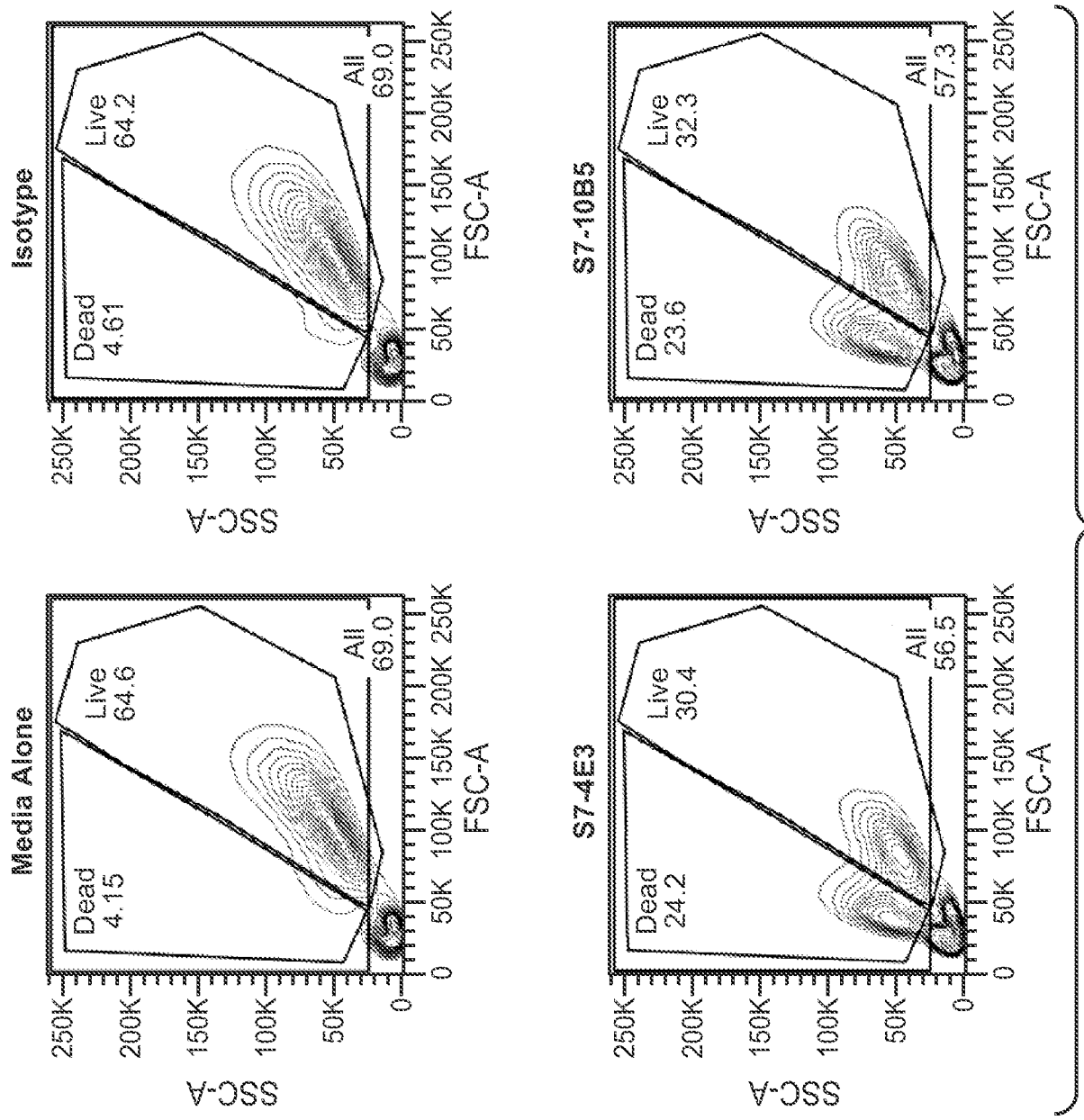

Media Alone
Dead
4.15
Live
64.6
All
69.0
Isotype
Dead
4.61
Live
64.2
All
69.0
S7-4E3
Dead
24.2
Live
30.4
All
56.5
S7-10B5
Dead
23.6
Live
32.3
All
57.3
SSC-A
FSC-A
0
50K
100K
150K
200K
250K

FIG. 18

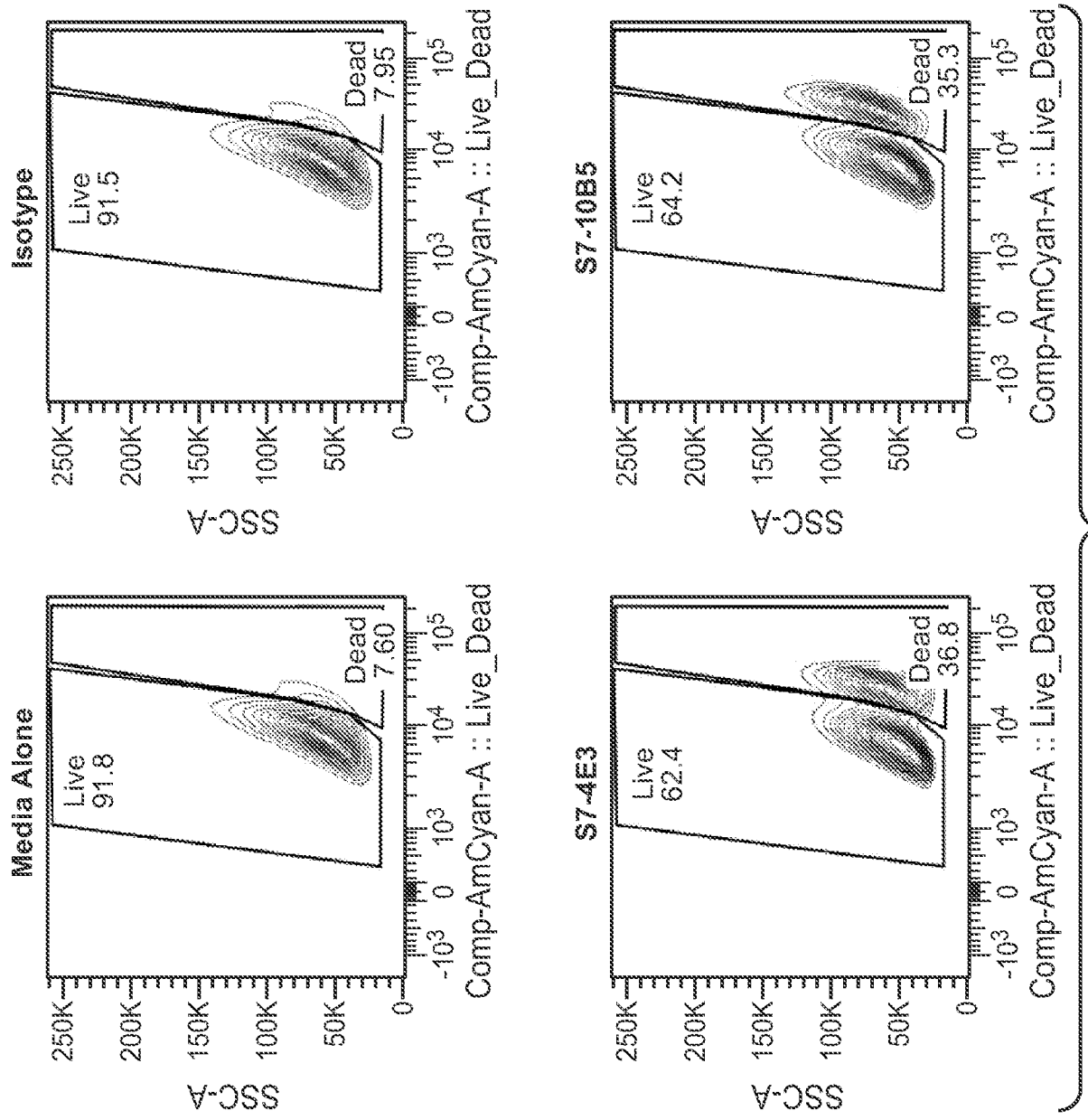

Media Alone
Live
91.8
Dead
7.60
Isotype
Live
91.5
Dead
7.95
S7-4E3
Live
62.4
Dead
36.8
S7-10B5
Live
64.2
Dead
35.3
SSC-A
250K
200K
150K
100K
50K
0
-10^3 0 10^3 10^4 10^5
Comp-AmCyan-A :: Live_Dead

FIG. 18 (Cont.)

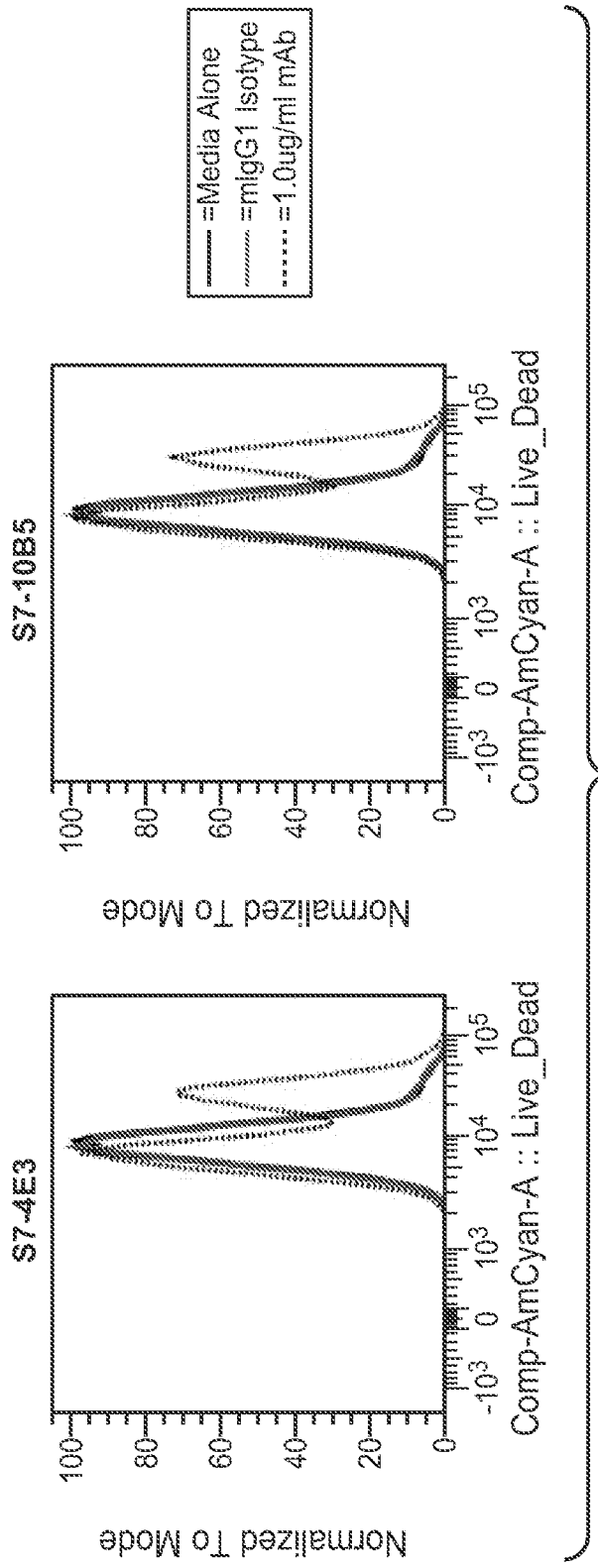

S7-4E3
S7-10B5
Normalized To Mode
Comp-AmCyan-A :: Live_Dead
=Media Alone
=mIgG1 Isotype
=1.0ug/ml mAb

FIG. 18 (Cont.)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/049032

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61P25/00 A61P35/00 A61K39/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/44808 A2 (UNIV GENOVA BIOFISICA [IT]; BIASSONI ROBERTO [IT]; MORETTA ALESSANDRO) 21 June 2001 (2001-06-21) page 19	1,3-80
X	S. J. ORR ET AL: "SOCS3 Targets Siglec 7 for Proteasomal Degradation and Blocks Siglec 7-mediated Responses", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 282, no. 6, 14 August 2006 (2006-08-14), pages 3418-3422, XP55312126, US ISSN: 0021-9258, DOI: 10.1074/jbc.C600216200 page 3419 - page 3420	1,3-80

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 January 2017	18/01/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wagner, René

6

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/90193 A1 (SMITHKLINE BEECHAM CORP [US]; SMITHKLINE BEECHAM PLC [GB]; ABRAHAMSON) 29 November 2001 (2001-11-29) page 54	1-117
X	STEFANIA VARCHETTA ET AL: "Sialic acid-binding Ig-like lectin-7 interacts with HIV-1 gp120 and facilitates infection of CD4pos T cells and macrophages", RETROVIROLOGY, BIOMED CENTRAL LTD., LONDON, GB, vol. 10, no. 1, 13 December 2013 (2013-12-13), page 154, XP021171427, ISSN: 1742-4690, DOI: 10.1186/1742-4690-10-154 page 2, left-hand column, last paragraph	1,3-117
A	STEFANIA VARCHETTA ET AL: "Engagement of Siglec-7 Receptor Induces a Pro-Inflammatory Response Selectively in Monocytes", PLOS ONE, vol. 7, no. 9, 28 September 2012 (2012-09-28), page e45821, XP55227713, DOI: 10.1371/journal.pone.0045821 page 10, left-hand column, paragraph 2	2
A	VITALE CHIARA ET AL: "Engagement of p75 / AIRM1 or CD33 inhibits the proliferation of normal or leukemic myeloid cells", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 96, no. 26, 21 December 1999 (1999-12-21), pages 15091-15096, XP002171141, ISSN: 0027-8424, DOI: 10.1073/PNAS.96.26.15091 the whole document	1,3-117
A	KELM S ET AL: "THE SIALOADHESINS - A FAMILY OF SIALIC ACID-DEPENDENT CELLULAR RECOGNITION MOLECULES WITHIN THE IMMUNOGLOBULIN SUPERFAMILY", GLYCOCONJUGATE JOURNAL, CHAPMAN & HALL, BOSTON, vol. 13, no. 6, 1 January 1996 (1996-01-01), pages 913-926, XP002066896, ISSN: 0282-0080, DOI: 10.1007/BF01053186 the whole document	1,3-117

-/--

6

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	N. KAWASAKI ET AL: "Targeted Delivery of Mycobacterial Antigens to Human Dendritic Cells via Siglec-7 Induces Robust T Cell Activation", THE JOURNAL OF IMMUNOLOGY, vol. 193, no. 4, 7 July 2014 (2014-07-07), pages 1560-1566, XP55311976, US ISSN: 0022-1767, DOI: 10.4049/jimmunol.1303278 the whole document -----	1,3-117

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/049032

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/049032

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

2-4(completely); 1, 5-117(partially)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3, 4(completely); 1, 5-117(partially)

   Claims as far and only as far as they are directed to the group of specific antibodies which both decrease the cell surface Siglec-7 content and which inhibit Siglec-7 ligand binding. This group is formed by the antibodies referred to as : 1A12, 1E8, 2G4, 3E11, 4A1, 4E3 and 7F12.

   ---

2. claims: 29-117(partially)

   Claims as far and only as far as they are directed to the antibody 2G1, which does not decrease cell surface Siglec-7 cellular levels and inhibits Siglec-7 ligand binding.

   ---

3. claims: 2(completely); 1, 5-117(partially)

   Claims as far and only as far as the are directed to the specific antibodies of the group of antibodies which decrease cell surface Siglec-7 expression without inhibiting Siglec-7 ligand binding. The group is formed by the antibodies referred to as : 4D7, 7A3, 7E11, 10B5 and 10G8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/049032

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0144808 A2	21-06-2001	AT 426812 T	15-04-2009
		AU 3009301 A	25-06-2001
		DK 1238282 T3	27-07-2009
		EP 1238282 A2	11-09-2002
		IT FI990254 A1	18-06-2001
		JP 4890715 B2	07-03-2012
		JP 2003517482 A	27-05-2003
		US 2003077285 A1	24-04-2003
		WO 0144808 A2	21-06-2001
WO 0190193 A1	29-11-2001	AU 7493901 A	03-12-2001
		EP 1290031 A1	12-03-2003
		WO 0190193 A1	29-11-2001

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 108137702 A
(43)申请公布日 2018.06.08

(21)申请号 201680059071.6

(22)申请日 2016.08.26

(30)优先权数据
62/211,656 2015.08.28 US
62/265,742 2015.12.10 US

(85)PCT国际申请进入国家阶段日
2018.04.09

(86)PCT国际申请的申请数据
PCT/US2016/049032 2016.08.26

(87)PCT国际申请的公布数据
WO2017/040301 EN 2017.03.09

(71)申请人 艾利妥
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(74)专利代理机构 北京坤瑞律师事务所 11494
代理人 封新琴

(51)Int.Cl.
C07K 16/28(2006.01)
A61P 25/00(2006.01)
A61P 35/00(2006.01)
A61K 39/00(2006.01)

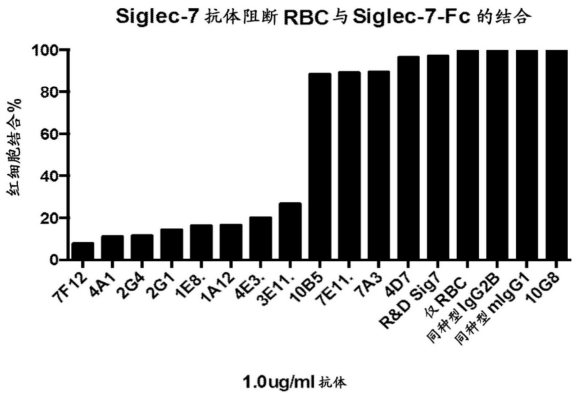
权利要求书21页 说明书213页
序列表246页 附图61页

(54)发明名称

抗SIGLEC-7抗体及其使用方法

(57)摘要

本公开总体上涉及组合物,所述组合物包含特异性地结合Siglec-7蛋白,例如人Siglec-7或哺乳动物Siglec-7内的一个或多个表位的抗体,例如单克隆抗体、嵌合抗体、人源化抗体、抗体片段等;以及此类组合物用于预防有需要的个体、降低有需要的个体的风险或治疗有需要的个体的用途。



CN 108137702 A

1.一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体降低Siglec-7的细胞水平。

2.如权利要求1所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体降低Siglec-7的细胞水平而不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。

3.如权利要求1所述的抗Siglec-7抗体，其中所述抗体进一步抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。

4.一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体降低Siglec-7的细胞水平并抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。

5.如权利要求1-4中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体降低Siglec-7的细胞表面水平、降低Siglec-7的细胞内水平、降低Siglec-7的总水平或其任何组合。

6.如权利要求1-5中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体诱导Siglec-7降解、Siglec-7裂解、Siglec-7内化、Siglec-7脱落、Siglec-7表达下调或其任何组合。

7.如权利要求1-6中任一项所述的抗Siglec-7抗体，其中所述抗体降低体内Siglec-7的细胞水平。

8.如权利要求1-7中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体抑制Siglec-7的细胞表面簇集。

9.如权利要求1-8中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体抑制一种或多种Siglec-7活性。

10.如权利要求9所述的抗Siglec-7抗体，其中所述一种或多种Siglec-7活性选自由以下各项组成的组：

(a)Siglec-7与一种或多种Siglec-7配体的结合，任选地其中所述一种或多种Siglec-7配体选自由以下各项组成的组：含唾液酸的糖蛋白、含唾液酸的糖脂以及其任何组合；

(b)降低一种或多种细胞的增殖，所述一种或多种细胞选自由以下各项组成的组：树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；

(c)抑制一种或多种细胞的迁移，所述一种或多种细胞选自由以下各项组成的组：树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；

(d)抑制一种或多种细胞的一种或多种功能，所述一种或多种细胞选自由以下各项组成的组：树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1NK细胞、M2巨

噬细胞、M2嗜中性粒细胞、M2NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；

(e)抑制一种或多种类型的清除，所述清除选自由以下各项组成的组：凋亡神经元清除、神经组织碎片清除、功能障碍性突触清除、非神经组织碎片清除、细菌清除、其它异物清除、致病蛋白清除、致病肽清除以及肿瘤细胞清除；任选地，其中所述致病蛋白选自由以下各项组成的组：淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽，并且所述肿瘤细胞来自选自由以下各项组成的组的癌症：膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌；

(f)通过以下中的一种或多种抑制肿瘤细胞杀伤：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；

(g)抑制以下中的一种或多种的抗肿瘤细胞增殖活性：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；

(h)调节一种或多种炎性受体的表达，任选地其中所述一种或多种炎性受体包含CD86并且所述一种或多种炎性受体在以下中的一种或多种上表达：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突状细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；

(i)促进或挽救以下中的一种或多种的功能性：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；

(j)增加以下中的一种或多种浸润到肿瘤中：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；

(k)增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量；

(l)增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性；

(m)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化；

(n)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润；

(o)增加肿瘤体积;

(p)增加肿瘤生长速率;以及

(q)降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效,任选地其中所述一种或多种免疫疗法是靶向选自由以下各项组成的组的一种或多种靶蛋白的免疫疗法:PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、TREM1、TREM2、CSF-1受体以及其任何组合。

11.如权利要求1-8中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体展示一种或多种选自由以下各项组成的组的活性:

(a)增加肿瘤浸润$CD3^+$T细胞的数量;

(b)抑制Siglec-7与一种或多种Siglec-7配体的结合;

(c)降低外周免疫细胞中Siglec-7的细胞水平;

(d)减少非致瘤性$CD14^+$骨髓细胞的数量,任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞,或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于血液中;

(e)减少非致瘤性$CD14^+$骨髓细胞的数量,任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞,或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于所述肿瘤中;

(f)降低一种或多种细胞中的PD-L1水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);

(g)降低一种或多种细胞中的PD-L2水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);

(h)降低一种或多种细胞中的CD11b水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);

(i)降低一种或多种细胞中的B7-H3水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);

(j)降低一种或多种细胞中的CD200R水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);

(k)降低一种或多种细胞中的CD163水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);

(l)降低一种或多种细胞中的CD206水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);

(m)降低实体肿瘤的肿瘤生长速率;

(n)减小肿瘤体积;

(o)提高一种或多种PD-1抑制剂的功效;

(p)提高一种或多种检查点抑制剂疗法和/或免疫调节疗法的功效,任选地其中所述一种或多种检查点抑制剂疗法和/或免疫调节疗法靶向以下中的一种或多种:CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3、LAG3或其任何组合;

(q)抑制非致瘤性骨髓源性抑制细胞的(MDSC)分化、存活和/或一种或多种功能;

(r)诱导一种或多种骨髓源性抑制细胞(MDSC)的细胞死亡;以及

(s)在非致瘤性骨髓源性抑制细胞(MDSC)存在下增加T细胞的增殖。

12.如权利要求2-11中任一项所述的抗Siglec-7抗体，其中所述一种或多种Siglec-7配体选自由以下各项组成的组：在红细胞上表达的Siglec-7配体、在细菌细胞上表达的Siglec-7配体、在凋亡细胞上表达的Siglec-7配体、在神经细胞上表达的Siglec-7配体、在神经胶质细胞上表达的Siglec-7配体、在小神经胶质细胞上表达的Siglec-7配体、在星形胶质细胞上表达的Siglec-7配体、在肿瘤细胞上表达的Siglec-7配体、在病毒上表达的Siglec-7配体、在树突细胞上表达的Siglec-7配体、与β淀粉样蛋白斑块结合的Siglec-7配体、与Tau缠结结合的Siglec-7配体、致病蛋白上的Siglec-7配体、致病肽上的Siglec-7配体、在巨噬细胞上表达的Siglec-7配体、在嗜中性粒细胞上表达的Siglec-7配体、在单核细胞上表达的Siglec-7配体、在天然杀伤细胞上表达的Siglec-7配体、在T细胞上表达的Siglec-7配体、在T辅助细胞上表达的Siglec-7配体、在细胞毒性T细胞上表达的Siglec-7配体、在B细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制树突细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制巨噬细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制嗜中性粒细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制NK细胞上表达的Siglec-7配体、在骨髓源性抑制细胞上表达的Siglec-7配体、在调控性T细胞上表达的Siglec-7配体、分泌的粘蛋白、唾液酸、含唾液酸的糖脂、含唾液酸的糖蛋白、含α-2,8-二唾液酸的糖脂、含支链α-2,6-连接的唾液酸的糖蛋白、含末端α-2,6-连接的唾液酸的糖脂、含末端α-2,3-连接的唾液酸的糖蛋白以及双唾液酸神经节苷脂。

13.如权利要求1-12中任一项所述的抗Siglec-7抗体，其中在选自选自由以下各项组成的组的原代细胞上或在细胞系上测量Siglec-7的细胞水平：树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞、嗜中性粒细胞以及NK细胞，并且其中使用体外细胞测定来测量Siglec-7的细胞水平。

14.如权利要求1-13中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体不降低TREM2表达。

15.如权利要求1-14中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体结合不连续的Siglec-7表位。

16.如权利要求15所述的抗Siglec-7抗体，其中所述不连续的Siglec-7表位包含两种或更多种肽、三种或更多种肽、四种或更多种肽、五种或更多种肽、六种或更多种肽、七种或更多种肽、八种或更多种肽、九种或更多种肽或10种或更多种肽。

17.如权利要求16所述的抗Siglec-7抗体，其中所述肽的每一条包含SEQ ID NO:1的氨基酸序列的5个或更多个、6个或更多个、7个或更多个、8个或更多个、9个或更多个、10个或更多个、11个或更多个、12个或更多个、13个或更多个、14个或更多个、15个或更多个、16个或更多个、17个或更多个、18个或更多个、19个或更多个或20个或更多个氨基酸残基；或对应于SEQ ID NO:1的氨基酸序列的哺乳动物Siglec-7蛋白上的5个或更多个、6个或更多个、7个或更多个、8个或更多个、9个或更多个、10个或更多个、11个或更多个、12个或更多个、13个或更多个、14个或更多个、15个或更多个、16个或更多个、17个或更多个、18个或更多个、19个或更多个或20个或更多个氨基酸残基。

18.如权利要求1-14中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体结合至Siglec-7的构象表位。

19.如权利要求1-14中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体结合

至SEQ ID NO:1的氨基酸残基39-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353内的一个或多个氨基酸;或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基39-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353的氨基酸残基内的一个或多个氨基酸。

20.如权利要求1-14中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体结合至选自由以下各项组成的组的氨基酸残基内的一个或多个氨基酸:

i.SEQ ID NO:1的氨基酸残基60-69,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69的氨基酸残基;

ii.SEQ ID NO:1的氨基酸残基60-69和84-95,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69和84-95的氨基酸残基;

iii.SEQ ID NO:1的氨基酸残基60-69和117-127,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69和117-127的氨基酸残基;

iv.SEQ ID NO:1的氨基酸残基68-78,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基68-78的氨基酸残基;

V.SEQ ID NO:1的氨基酸残基84-95,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基84-95的氨基酸残基;

vi.SEQ ID NO:1的氨基酸残基111-122,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基111-122的氨基酸残基;

vii.SEQ ID NO:1的氨基酸残基111-122和282-291,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基111-122和282-291的氨基酸残基;

V11i.SEQ ID NO:1的氨基酸残基113-123,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基113-123的氨基酸残基;

ix.SEQ ID NO:1的氨基酸残基113-125,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基113-125的氨基酸残基;

x.SEQ ID NO:1的氨基酸残基117-127,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基117-127的氨基酸残基;以及

xi.SEQ ID NO:1的氨基酸残基282-291,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基282-291的氨基酸残基。

21.如权利要求1-14中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体结合至一个或多个选自由以下各项组成的组的氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、I72、W74、N81、T103、K104、T107以及R124,或哺乳动物Siglec-7蛋白上对应于选自由以下各项组成的组的氨基酸残基的一个或多个氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、I72、W74、N81、T103、K104、T107以及R124。

22.如权利要求1-21中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体与一种或多种选自由以下各项组成的组的抗体竞争结合至Siglec-7:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合。

23.如权利要求1-22中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域和重链可变结构域,其中所述轻链可变结构域、所述重链可变结构域或两

者包含至少一个、两个、三个、四个、五个或六个HVR，所述HVR选自单克隆抗体的HVR-L1、HVR-L2、HVR-L3、HVR-H1、HVR-H2以及HVR-H3，所述单克隆抗体选自由以下各项组成的组：1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。

24.如权利要求23所述的抗Siglec-7抗体，其中：

(a)所述HVR-L1包含选自由SEQ ID NO:7-19和476组成的组的氨基酸序列；

(b)所述HVR-L2包含选自由SEQ ID NO:20-32和477组成的组的氨基酸序列；

(c)所述HVR-L3包含选自由SEQ ID NO:33-45和478组成的组的氨基酸序列；

(d)所述HVR-H1包含选自由SEQ ID NO:46-58和479组成的组的氨基酸序列；

(e)所述HVR-H2包含选自由SEQ ID NO:59-71和480-482组成的组的氨基酸序列；或

(f)所述HVR-H3包含选自由SEQ ID NO:72-84和483组成的组的氨基酸序列。

25.如权利要求23或24所述的抗Siglec-7抗体，其中：

(a)所述HVR-L1包含SEQ ID NO:7的氨基酸序列，所述HVR-L2包含SEQ ID NO:20的氨基酸序列，所述HVR-L3包含SEQ ID NO:33的氨基酸序列，所述HVR-H1包含SEQ ID NO:46的氨基酸序列，所述HVR-H2包含SEQ ID NO:59的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:72的氨基酸序列；

(b)所述HVR-L1包含SEQ ID NO:8的氨基酸序列，所述HVR-L2包含SEQ ID NO:21的氨基酸序列，所述HVR-L3包含SEQ ID NO:34的氨基酸序列，所述HVR-H1包含SEQ ID NO:47的氨基酸序列，所述HVR-H2包含SEQ ID NO:60的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:73的氨基酸序列；

(c)所述HVR-L1包含SEQ ID NO:10的氨基酸序列，所述HVR-L2包含SEQ ID NO:23的氨基酸序列，所述HVR-L3包含SEQ ID NO:36的氨基酸序列，所述HVR-H1包含SEQ ID NO:49的氨基酸序列，所述HVR-H2包含SEQ ID NO:62的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:75的氨基酸序列；

(d)所述HVR-L1包含SEQ ID NO:11的氨基酸序列，所述HVR-L2包含SEQ ID NO:24的氨基酸序列，所述HVR-L3包含SEQ ID NO:37的氨基酸序列，所述HVR-H1包含SEQ ID NO:50的氨基酸序列，所述HVR-H2包含SEQ ID NO:63的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:76的氨基酸序列；

(e)所述HVR-L1包含SEQ ID NO:12的氨基酸序列，所述HVR-L2包含SEQ ID NO:25的氨基酸序列，所述HVR-L3包含SEQ ID NO:38的氨基酸序列，所述HVR-H1包含SEQ ID NO:51的氨基酸序列，所述HVR-H2包含SEQ ID NO:64的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:77的氨基酸序列；

(f)所述HVR-L1包含SEQ ID NO:13的氨基酸序列，所述HVR-L2包含SEQ ID NO:26的氨基酸序列，所述HVR-L3包含SEQ ID NO:39的氨基酸序列，所述HVR-H1包含SEQ ID NO:52的氨基酸序列，所述HVR-H2包含SEQ ID NO:65的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:78的氨基酸序列；

(g)所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:66的氨基酸序列，并且所述HVR-H3包含SEQ ID

NO:79的氨基酸序列；

(h)所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:480的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列；

(i)所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:481的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列；

(j)所述HVR-L1包含SEQ ID NO:15的氨基酸序列，所述HVR-L2包含SEQ ID NO:28的氨基酸序列，所述HVR-L3包含SEQ ID NO:41的氨基酸序列，所述HVR-H1包含SEQ ID NO:54的氨基酸序列，所述HVR-H2包含SEQ ID NO:67的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:80的氨基酸序列；

(k)所述HVR-L1包含SEQ ID NO:16的氨基酸序列，所述HVR-L2包含SEQ ID NO:29的氨基酸序列，所述HVR-L3包含SEQ ID NO:42的氨基酸序列，所述HVR-H1包含SEQ ID NO:55的氨基酸序列，所述HVR-H2包含SEQ ID NO:68的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:81的氨基酸序列；

(l)所述HVR-L1包含SEQ ID NO:17的氨基酸序列，所述HVR-L2包含SEQ ID NO:30的氨基酸序列，所述HVR-L3包含SEQ ID NO:43的氨基酸序列，所述HVR-H1包含SEQ ID NO:56的氨基酸序列，所述HVR-H2包含SEQ ID NO:69的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:82的氨基酸序列；

(m)所述HVR-L1包含SEQ ID NO:18的氨基酸序列，所述HVR-L2包含SEQ ID NO:31的氨基酸序列，所述HVR-L3包含SEQ ID NO:44的氨基酸序列，所述HVR-H1包含SEQ ID NO:57的氨基酸序列，所述HVR-H2包含SEQ ID NO:70的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列；

(n)所述HVR-L1包含SEQ ID NO:476的氨基酸序列，所述HVR-L2包含SEQ ID NO:477的氨基酸序列，所述HVR-L3包含SEQ ID NO:478的氨基酸序列，所述HVR-H1包含SEQ ID NO:57的氨基酸序列，所述HVR-H2包含SEQ ID NO:70的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列；

(o)所述HVR-L1包含SEQ ID NO:18的氨基酸序列，所述HVR-L2包含SEQ ID NO:31的氨基酸序列，所述HVR-L3包含SEQ ID NO:44的氨基酸序列，所述HVR-H1包含SEQ ID NO:479的氨基酸序列，所述HVR-H2包含SEQ ID NO:482的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:483的氨基酸序列；或

(p)所述HVR-L1包含SEQ ID NO:19的氨基酸序列，所述HVR-L2包含SEQ ID NO:32的氨基酸序列，所述HVR-L3包含SEQ ID NO:45的氨基酸序列，所述HVR-H1包含SEQ ID NO:58的氨基酸序列，所述HVR-H2包含SEQ ID NO:71的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:84的氨基酸序列。

26.如权利要求1-22中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域和重链可变结构域，其中所述轻链可变结构域包含：

(a)HVR-L1,其包含选自由SEQ ID NO:7-19和476组成的组的氨基酸序列,或与选自由SEQ ID NO:7-19和476组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;

(b)HVR-L2,其包含选自由SEQ ID NO:20-32和477组成的组的氨基酸序列,或与选自由SEQ ID NO:20-32和477组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;以及

(c)HVR-L3,其包含选自由SEQ ID NO:33-45和478组成的组的氨基酸序列,或与选自由SEQ ID NO:33-45和478组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;以及

其中所述重链可变结构域包含:

(a)HVR-H1,其包含选自由SEQ ID NO:46-58和479组成的组的氨基酸序列,或与选自由SEQ ID NO:46-58和479组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;

(b)HVR-H2,其包含选自由SEQ ID NO:59-71和480-482组成的组的氨基酸序列,或与选自由SEQ ID NO:59-71和480-482组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;以及

(c)HVR-H3,其包含选自由SEQ ID NO:72-84和483组成的组的氨基酸序列,或与选自由SEQ ID NO:72-84和483组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列。

27.如权利要求1-26中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含选自由SEQ ID NO:189-318、449-461和484-489组成的组的氨基酸序列;和/或重链可变结构域,所述重链可变结构域包含选自由SEQ ID NO:319-448、462-474和490-496组成的组的氨基酸序列。

28.如权利要求1-26中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体包含单克隆抗体的轻链可变结构域,所述单克隆抗体选自由以下各项组成的组:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8;和/或单克隆抗体的重链可变结构域,所述单克隆抗体选自由以下各项组成的组:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。

29.一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体结合至SEQ ID NO:1的氨基酸残基39-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353内的一个或多个氨基酸;或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基39-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353的氨基酸残基内的一个或多个氨基酸。

30.如权利要求29所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体结合至选自由以下各项组成的组的氨基酸残基内的一个或多个氨基酸:

i.SEQ ID NO:1的氨基酸残基60-69,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69的氨基酸残基;

ii.SEQ ID NO:1的氨基酸残基60-69和84-95,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69和84-95的氨基酸残基;

iii.SEQ ID NO:1的氨基酸残基60-69和117-127,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69和117-127的氨基酸残基;

iv.SEQ ID NO:1的氨基酸残基68-78,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基68-78的氨基酸残基;

v.SEQ ID NO:1的氨基酸残基84-95,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基84-95的氨基酸残基;

vi.SEQ ID NO:1的氨基酸残基111-122,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基111-122的氨基酸残基;

vii.SEQ ID NO:1的氨基酸残基111-122和SEQ ID NO:1的282-291,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基111-122和SEQ ID NO:1的282-291的氨基酸残基;

Viii.SEQ ID NO:1的氨基酸残基113-123,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基113-123的氨基酸残基;

ix.SEQ ID NO:1的氨基酸残基113-125,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基113-125的氨基酸残基;

x.SEQ ID NO:1的氨基酸残基117-127,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基117-127的氨基酸残基;以及

xi.SEQ ID NO:1的氨基酸残基282-291,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基282-291的氨基酸残基。

31.一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体结合至一个或多个选自由以下各项组成的组的氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、I72、W74、N81、T103、K104、T107以及R124,或哺乳动物Siglec-7蛋白上对应于选自由以下各项组成的组的氨基酸残基的一个或多个氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、I72、W74、N81、T103、K104、T107以及R124。

32.一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域和重链可变结构域,其中所述轻链可变结构域、所述重链可变结构域或两者包含至少一个、两个、三个、四个、五个或六个HVR,所述HVR选自单克隆抗体的HVR-L1、HVR-L2、HVR-L3、HVR-H1、HVR-H2以及HVR-H3,所述单克隆抗体选自由以下各项组成的组:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。

33.如权利要求32所述的抗Siglec-7抗体,其中:

(a)所述HVR-L1包含选自由SEQ ID NO:7-19和476组成的组的氨基酸序列;

(b)所述HVR-L2包含选自由SEQ ID NO:20-32和477组成的组的氨基酸序列;

(c)所述HVR-L3包含选自由SEQ ID NO:33-45和478组成的组的氨基酸序列;

(d)所述HVR-H1包含选自由SEQ ID NO:46-58和479组成的组的氨基酸序列;

(e)所述HVR-H2包含选自由SEQ ID NO:59-71和480-482组成的组的氨基酸序列;或

(f)所述HVR-H3包含选自由SEQ ID NO:72-84和483组成的组的氨基酸序列。

34.如权利要求32或33所述的抗Siglec-7抗体,其中:

(a)所述HVR-L1包含SEQ ID NO:7的氨基酸序列,所述HVR-L2包含SEQ ID NO:20的氨基酸序列,所述HVR-L3包含SEQ ID NO:33的氨基酸序列,所述HVR-H1包含SEQ ID NO:46的氨基酸序列,所述HVR-H2包含SEQ ID NO:59的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:72的氨基酸序列;

(b)所述HVR-L1包含SEQ ID NO:8的氨基酸序列,所述HVR-L2包含SEQ ID NO:21的氨基酸序列,所述HVR-L3包含SEQ ID NO:34的氨基酸序列,所述HVR-H1包含SEQ ID NO:47的氨

基酸序列,所述HVR-H2包含SEQ ID NO:60的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:73的氨基酸序列;

(c)所述HVR-L1包含SEQ ID NO:9的氨基酸序列,所述HVR-L2包含SEQ ID NO:22的氨基酸序列,所述HVR-L3包含SEQ ID NO:35的氨基酸序列,所述HVR-H1包含SEQ ID NO:48的氨基酸序列,所述HVR-H2包含SEQ ID NO:61的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列;

(d)所述HVR-L1包含SEQ ID NO:10的氨基酸序列,所述HVR-L2包含SEQ ID NO:23的氨基酸序列,所述HVR-L3包含SEQ ID NO:36的氨基酸序列,所述HVR-H1包含SEQ ID NO:49的氨基酸序列,所述HVR-H2包含SEQ ID NO:62的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:75的氨基酸序列;

(e)所述HVR-L1包含SEQ ID NO:11的氨基酸序列,所述HVR-L2包含SEQ ID NO:24的氨基酸序列,所述HVR-L3包含SEQ ID NO:37的氨基酸序列,所述HVR-H1包含SEQ ID NO:50的氨基酸序列,所述HVR-H2包含SEQ ID NO:63的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:76的氨基酸序列;

(f)所述HVR-L1包含SEQ ID NO:12的氨基酸序列,所述HVR-L2包含SEQ ID NO:25的氨基酸序列,所述HVR-L3包含SEQ ID NO:38的氨基酸序列,所述HVR-H1包含SEQ ID NO:51的氨基酸序列,所述HVR-H2包含SEQ ID NO:64的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:77的氨基酸序列;

(g)所述HVR-L1包含SEQ ID NO:13的氨基酸序列,所述HVR-L2包含SEQ ID NO:26的氨基酸序列,所述HVR-L3包含SEQ ID NO:39的氨基酸序列,所述HVR-H1包含SEQ ID NO:52的氨基酸序列,所述HVR-H2包含SEQ ID NO:65的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:78的氨基酸序列;

(h)所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:66的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列;

(i)所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:480的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列;

(j)所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:481的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列;

(k)所述HVR-L1包含SEQ ID NO:15的氨基酸序列,所述HVR-L2包含SEQ ID NO:28的氨基酸序列,所述HVR-L3包含SEQ ID NO:41的氨基酸序列,所述HVR-H1包含SEQ ID NO:54的氨基酸序列,所述HVR-H2包含SEQ ID NO:67的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:80的氨基酸序列;

(l)所述HVR-L1包含SEQ ID NO:16的氨基酸序列,所述HVR-L2包含SEQ ID NO:29的氨

基酸序列，所述HVR-L3包含SEQ ID NO:42的氨基酸序列，所述HVR-H1包含SEQ ID NO:55的氨基酸序列，所述HVR-H2包含SEQ ID NO:68的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:81的氨基酸序列；

(m)所述HVR-L1包含SEQ ID NO:17的氨基酸序列，所述HVR-L2包含SEQ ID NO:30的氨基酸序列，所述HVR-L3包含SEQ ID NO:43的氨基酸序列，所述HVR-H1包含SEQ ID NO:56的氨基酸序列，所述HVR-H2包含SEQ ID NO:69的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:82的氨基酸序列；

(n)所述HVR-L1包含SEQ ID NO:18的氨基酸序列，所述HVR-L2包含SEQ ID NO:31的氨基酸序列，所述HVR-L3包含SEQ ID NO:44的氨基酸序列，所述HVR-H1包含SEQ ID NO:57的氨基酸序列，所述HVR-H2包含SEQ ID NO:70的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列；

(o)所述HVR-L1包含SEQ ID NO:476的氨基酸序列，所述HVR-L2包含SEQ ID NO:477的氨基酸序列，所述HVR-L3包含SEQ ID NO:478的氨基酸序列，所述HVR-H1包含SEQ ID NO:57的氨基酸序列，所述HVR-H2包含SEQ ID NO:70的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列；

(p)所述HVR-L1包含SEQ ID NO:18的氨基酸序列，所述HVR-L2包含SEQ ID NO:31的氨基酸序列，所述HVR-L3包含SEQID NO:44的氨基酸序列，所述HVR-H1包含SEQ ID NO:479的氨基酸序列，所述HVR-H2包含SEQ ID NO:482的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:483的氨基酸序列；或

(q)所述HVR-L1包含SEQ ID NO:19的氨基酸序列，所述HVR-L2包含SEQ ID NO:32的氨基酸序列，所述HVR-L3包含SEQ ID NO:45的氨基酸序列，所述HVR-H1包含SEQ ID NO:58的氨基酸序列，所述HVR-H2包含SEQ ID NO:71的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:84的氨基酸序列。

35.如权利要求32所述的抗Siglec-7抗体，其中所述轻链可变结构域包含：

(a)HVR-L1，其包含选自由SEQ ID NO:7-19和476组成的组的氨基酸序列，或与选自由SEQ ID NO:7-19和476组成的组的氨基酸序列具有至少约90％同源性的氨基酸序列；

(b)HVR-L2，其包含选自由SEQ ID NO:20-32和477组成的组的氨基酸序列，或与选自由SEQ ID NO:20-32和477组成的组的氨基酸序列具有至少约90％同源性的氨基酸序列；以及

(c)HVR-L3，其包含选自由SEQ ID NO:33-45和478组成的组的氨基酸序列，或与选自由SEQ ID NO:33-45和478组成的组的氨基酸序列具有至少约90％同源性的氨基酸序列；以及

其中所述重链可变结构域包含：

(a)HVR-H1，其包含选自由SEQ ID NO:46-58和479组成的组的氨基酸序列，或与选自由SEQ ID NO:46-58和479组成的组的氨基酸序列具有至少约90％同源性的氨基酸序列；

(b)HVR-H2，其包含选自由SEQ ID NO:59-71和480-482组成的组的氨基酸序列，或与选自由SEQ ID NO:59-71和480-482组成的组的氨基酸序列具有至少约90％同源性的氨基酸序列；以及

(c)HVR-H3，其包含选自由SEQ ID NO:72-84和483组成的组的氨基酸序列，或与选自由SEQ ID NO:72-84和483组成的组的氨基酸序列具有至少约90％同源性的氨基酸序列。

36.一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构

域,所述轻链可变结构域包含选自由SEQ ID NO:189-318、449-461和484-489组成的组的氨基酸序列;和/或重链可变结构域,所述重链可变结构域包含选自由SEQ ID NO:319-448、462-474和490-496组成的组的氨基酸序列。

37.一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含单克隆抗体的轻链可变结构域,所述单克隆抗体选自由以下各项组成的组:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8;和/或单克隆抗体的重链可变结构域,所述单克隆抗体选自由以下各项组成的组:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。

38.一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体与一种或多种选自由以下各项组成的组的抗体竞争结合至Siglec-7:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合。

39.一种分离的单克隆抗Siglec-7抗体,所述抗Siglec-7抗体与选自由以下各项组成的组的单克隆抗体结合基本相同的Siglec-7表位:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。

40.一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域和重链可变结构域,其中所述轻链可变结构域包含:

(a)HVR-L1,其包含选自由SEQ ID NO:7-19和476组成的组的氨基酸序列,或与选自由SEQ ID NO:7-19和476组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;

(b)HVR-L2,其包含选自由SEQ ID NO:20-32和477组成的组的氨基酸序列,或与选自由SEQ ID NO:20-32和477组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;以及

(c)HVR-L3,其包含选自由SEQ ID NO:33-45和478组成的组的氨基酸序列,或与选自由SEQ ID NO:33-45和478组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;和/或

其中所述重链可变结构域包含:

(a)HVR-H1,其包含选自由SEQ ID NO:46-58和479组成的组的氨基酸序列,或与选自由SEQ ID NO:46-58和479组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;

(b)HVR-H2,其包含选自由SEQ ID NO:59-71和480-482组成的组的氨基酸序列,或与选自由SEQ ID NO:59-71和480-482组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列;以及

(c)HVR-H3,其包含选自由SEQ ID NO:72-84和483组成的组的氨基酸序列,或与选自由SEQ ID NO:72-84和483组成的组的氨基酸序列具有至少约90%同源性的氨基酸序列。

41.如权利要求1-40中任一项所述的抗Siglec-7抗体,其中所述抗体具有IgG类、IgM类或IgA类。

42.如权利要求41所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体具有IgG1、IgG2、IgG3或IgG4同种型。

43.如权利要求42所述的抗Siglec-7抗体,其中所述抗体结合抑制剂Fc受体。

44.如权利要求43所述的抗Siglec-7抗体,其中所述抑制性Fc受体是抑制性Fc-γ受体IIB(FcγIIB)。

45.如权利要求44所述的抗Siglec-7抗体,其中:

(a)所述抗Siglec-7抗体具有人或小鼠IgG1同种型,并且包含在Fc区中在选自由以下各项组成的组的残基位置处的一种或多种氨基酸取代: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以及其任何组合,其中所述残基的编号根据EU编号,或包含在所述Fc区中在对应于甘氨酸236的位置处的氨基酸缺失;

(b)所述抗Siglec-7抗体具有IgG1同种型并且包含IgG2同种型重链恒定结构域1(CH1)和铰链区,任选地其中所述IgG2同种型CH1和铰链区包含ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVERKCCVECPPCP(SEQ ID NO:475)的氨基酸序列,并且任选地其中所述抗体Fc区包含S267E氨基酸取代、L328F氨基酸取代或两者,和/或N297A或N297Q氨基酸取代,其中所述残基的编号根据EU编号;

(c)所述抗Siglec-7抗体具有IgG2同种型并且包含在所述Fc区中在选自由以下各项组成的组的残基位置处的一种或多种氨基酸取代:P238S、V234A、G237A、H268A、H268Q、V309L、A330S、P331S、C214S、C232S、C233S、S267E、L328F、M252Y、S254T、T256E、H268E、N297A、N297Q、A330L以及其任何组合,其中所述残基的编号根据EU编号;

(d)所述抗Siglec-7抗体具有人或小鼠IgG4同种型并且包含在所述Fc区中在选自由以下各项组成的组的残基位置处的一种或多种氨基酸取代:L235A、G237A、S228P、L236E、S267E、E318A、L328F、M252Y、S254T、T256E、E233P、F234V、L234A/F234A、S228P、S241P、L248E、T394D、N297A、N297Q、L235E以及其任何组合,其中所述残基的编号根据EU编号;或

(e)所述抗Siglec-7抗体具有杂合IgG2/4同种型,并且任选地其中所述抗体包含氨基酸序列,所述氨基酸序列包含人IgG2的氨基酸118至260和人IgG4的氨基酸261至447,其中所述残基的编号根据EU或Kabat编号。

46.如权利要求42所述的抗Siglec-7抗体,其中:

(a)所述抗Siglec-7抗体具有人或小鼠IgG1同种型,并且包含在所述Fc区中在选自由以下各项组成的组的残基位置处的一种或多种氨基酸取代:N297A、N297Q、D270A、D265A、L234A、L235A、C226S、C229S、P238S、E233P、L234V、P238A、A327Q、A327G、P329A、K322A、L234F、L235E、P331S、T394D、A330L、M252Y、S254T、T256E以及其任何组合,其中所述残基的编号根据EU编号;

(b)所述抗Siglec-7抗体具有IgG2同种型并且包含在所述Fc区中在选自由以下各项组成的组的残基位置处的一种或多种氨基酸取代:P238S、V234A、G237A、H268A、H268Q、H268E、V309L、N297A、N297Q、A330S、P331S、C232S、C233S、M252Y、S254T、T256E以及其任何组合,其中所述残基的编号根据EU编号;或

(c)所述抗Siglec-7抗体具有IgG4同种型并且包含在所述Fc区中在选自由以下各项组成的组的残基位置处的一种或多种氨基酸取代:E233P、F234V、L234A/F234A、L235A、G237A、E318A、S228P、L236E、S241P、L248E、T394D、M252Y、S254T、T256E、N297A、N297Q以及其任何组合,其中所述残基的编号根据EU编号。

47.如权利要求46所述的抗Siglec-7抗体,其中:

(a)所述Fc区还包含在选自由A330L、L234F、L235E、P331S以及其任何组合组成的组的

位置处的一种或多种另外的氨基酸取代,其中所述残基的编号根据EU编号;

(b)所述Fc区还包含在选自由M252Y、S254T、T256E以及其任何组合组成的组的位置处的一种或多种另外的氨基酸取代,其中所述残基的编号根据EU编号;或

(c)所述Fc区还包含根据EU编号的S228P氨基酸取代。

48.如权利要求1-40中任一项所述的抗Siglec-7抗体,其中所述抗体具有IgG4同种型。

49.如权利要求48所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体包含在残基位置228处的S228P氨基酸取代、在残基位置234处的F234A氨基酸取代以及在残基位置235处的L235A氨基酸取代,其中所述残基位置的编号根据EU编号。

50.如权利要求1-49中任一项所述的抗Siglec-7抗体,其中所述Siglec-7蛋白是哺乳动物蛋白或人蛋白。

51.如权利要求1-50中任一项所述的抗Siglec-7抗体,其中所述Siglec-7蛋白是野生型蛋白。

52.如权利要求1-50中任一项所述的抗Siglec-7抗体,其中所述Siglec-7蛋白是天然存在的变体。

53.如权利要求1-52中任一项所述的抗Siglec-7抗体,其中所述Siglec-7蛋白在选自由以下各项组成的组的一种或多种细胞上表达:人树突细胞、人巨噬细胞、人嗜中性粒细胞、人NK细胞、人单核细胞、人破骨细胞、人T细胞、人T辅助细胞、人细胞毒性T细胞、人粒细胞以及人小神经胶质细胞。

54.如权利要求1-53中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体特异性地结合至哺乳动物Siglec-7蛋白、人Siglec-7蛋白或两者。

55.如权利要求1-54中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体以pH依赖性方式结合Siglec-7。

56.如权利要求55所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体在5.5至8.0范围内的pH下结合Siglec-7。

57.如权利要求55所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体在小于5.0的pH下从Siglec-7解离。

58.如权利要求1-57中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体是结合至包含人Siglec-7或哺乳动物Siglec-7蛋白上的氨基酸残基的表位的抗体片段。

59.如权利要求1-57中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体是与选自由以下各项组成的组的一种或多种人蛋白质结合的抗体片段:人Siglec-7、人Siglec-7的天然存在的变体和人Siglec-7的疾病变体。

60.如权利要求58或权利要求59所述的抗Siglec-7抗体,其中所述抗体片段与第二抗体片段交联,所述第二抗体片段结合至选自由以下各项组成的组的一种或多种人蛋白质:人Siglec-7、人Siglec-7的天然存在的变体和人Siglec-7的疾病变体。

61.如权利要求58-60中任一项所述的抗Siglec-7抗体,其中所述片段是Fab、Fab′、Fab′-SH、F(ab′)2、Fv或scFv片段。

62.如权利要求1-61中任一项所述的抗Siglec-7抗体,其中所述Siglec-7抗体是鼠抗体。

63.如权利要求1-62中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体是人

源化抗体、双特异性抗体、单克隆抗体、多价抗体、缀合抗体或嵌合抗体。

64.如权利要求1-63中任一项所述的抗Siglec-7抗体，其中所述Siglec-7抗体是识别第一抗原和第二抗原的双特异性抗体。

65.如权利要求64所述的抗Siglec-7抗体，其中所述第一抗原是Siglec-7，并且所述第二抗原是：

(a)促进跨血脑屏障的转运的抗原；

(b)选自由以下各项组成的组的促进跨血脑屏障的转运的抗原：转铁蛋白受体(TR)、胰岛素受体(HIR)、胰岛素样生长因子受体(IGFR)、低密度脂蛋白受体相关蛋白1和2(LPR-1和2)、白喉毒素受体、CRM197、美洲驼单结构域抗体、TMEM 30(A)、蛋白质转导结构域、TAT、Syn-B、穿膜肽、聚精氨酸肽、血管肽以及ANG1005；

(c)选自由致病肽或蛋白或致病核酸组成的组的致病因子，其中所述致病核酸是反义GGCCCC(G2C4)重复序列-扩增RNA，所述致病蛋白选自由以下各项组成的组：淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽；以及

(d)在免疫细胞上表达的配体和/或蛋白质，其中所述配体和/或蛋白质选自由以下各项组成的组：PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG以及磷脂酰丝氨酸；以及

(e)在一种或多种肿瘤细胞上表达的蛋白质、脂质、多糖或糖脂。

66.如权利要求1-65中任一项所述的抗Siglec-7抗体，其中所述Siglec-7抗体是缀合抗体。

67.如权利要求66所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体缀合至可检测标记、毒素或治疗剂。

68.如权利要求67所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体缀合至选自由以下各项组成的组的毒素：蓖麻毒素、蓖麻毒素A链、多柔比星、道诺霉素、类美登素、紫杉醇、溴化乙锭、丝裂霉素、依托泊苷、替尼泊苷、长春新碱、长春花碱、秋水仙碱、二羟基炭疽菌素二酮、放线菌素、白喉毒素、假单胞菌外毒素(PE)A、PE40、相思豆毒素、相思豆毒素A链、蒴莲根毒素A链、α-八叠球菌素、白树毒素、丝林霉素、局限曲菌素、酚霉素、伊诺霉素、麻疯树逆境蛋白、巴豆毒素、加利车霉素、肥皂草抑制剂、糖皮质激素、奥瑞斯他汀、金霉素、钇、铋、康普瑞汀、倍癌霉素、多拉司他汀、cc1065以及顺铂。

69.如权利要求1-68中任一项所述的抗Siglec-7抗体，其中所述抗Siglec-7抗体与一种或多种特异性地结合致病因子的抗体组合使用，所述致病因子选自由以下各项组成的组：致病肽、致病蛋白、淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体

蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽,以及其任何组合;或与结合选自由以下各项组成的组的免疫调节蛋白的一种或多种抗体组合使用:PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、TREM1、TREM2、CD33、Siglec-5、Siglec-9、Siglec-11、磷脂酰丝氨酸、致病核酸、反义GGCCCC(G2C4)重复序列-扩增RNA以及其任何组合。

70.如前述权利要求中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体对于人Siglec-7和哺乳动物Siglec-7具有在约10nM至约10pM或小于10pM范围内的解离常数(K_D),其中所述K_D在大约25℃的温度下测定。

71.如前述权利要求中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体对于人Siglec-7具有在约9.5nM至约17pM或小于17pM范围内的解离常数(K_D),其中所述K_D在大约25℃的温度下测定。

72.如前述权利要求中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体以在2nM至100pM范围内的EC_{50}结合至人树突细胞,其中所述EC_{50}在大约4℃的温度下测定。

73.如前述权利要求中任一项所述的抗Siglec-7抗体,其中所述抗Siglec-7抗体以在500pM至18pM范围内的EC_{50}降低Siglec-7的细胞水平,其中所述EC_{50}在大约37℃的温度下测定。

74.一种分离的核酸,其包含编码如前述权利要求中任一项所述的抗Siglec-7抗体的核酸序列。

75.一种载体,其包含如权利要求74所述的核酸。

76.一种分离的宿主细胞,其包含如权利要求75所述的载体。

77.一种产生抗Siglec-7抗体的方法,其包括培养如权利要求76所述的宿主细胞以使得产生所述抗Siglec-7抗体。

78.如权利要求77所述的方法,其还包括回收由所述宿主细胞产生的所述抗Siglec-7抗体。

79.一种分离的抗Siglec-7抗体,其通过如权利要求77或权利要求78所述的方法产生。

80.一种药物组合物,其包含如权利要求1-73中任一项所述的抗Siglec-7抗体以及药学上可接受的载体。

81.一种预防疾病、病症或损伤,降低所述疾病、病症或损伤的风险或治疗所述疾病、病症或损伤的方法,所述疾病、病症或损伤选自由以下各项组成的组:痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、Tau蛋白病、感染以及癌症,所述方法包括向有需要的个体施用治疗有效量的降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7

配体之间的相互作用或两者的药剂。

82.如权利要求81所述的方法，其中所述疾病、病症或损伤是癌症，并且其中所述药剂抑制一种或多种选自由以下各项组成的组的Siglec-7活性：

(a)促进以下中的一种或多种的增殖、成熟、迁移、分化和/或功能性：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关抑制嗜中性粒细胞、肿瘤相关抑制NK细胞以及调控性T细胞；

(b)增强以下中的一种或多种浸润到肿瘤中：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关抑制嗜中性粒细胞、肿瘤相关抑制NK细胞以及调控性T细胞；

(c)增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量；

(d)增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性；

(e)增加肿瘤或外周血液中肿瘤促进细胞因子的表达，任选地其中所述肿瘤促进细胞因子是TGF-β或IL-10；

(f)增加肿瘤促进FoxP3+调控性T淋巴细胞的肿瘤浸润；

(g)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化；

(h)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润；

(i)减少具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润；

(j)降低NK细胞的肿瘤杀伤潜力；

(k)减少具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润；

(l)增加肿瘤体积；

(m)增加肿瘤生长速率；

(n)增加转移；

(o)增加肿瘤复发率；

(p)降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效，任选地其中所述一种或多种免疫疗法是靶向一种或多种靶蛋白的免疫疗法，所述一种或多种靶蛋白选自由以下各项组成的组：PD1/PDL1、CTLA4、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5以及其任何组合；

(q)抑制PLCγ/PKC/钙动员；以及

(r)抑制PI3K/Akt、Ras/MAPK信号传导。

83.如权利要求82所述的方法，其中所述癌症表达Siglec-7或一种或多种Siglec-7配体。

84.如权利要求81-83中任一项所述的方法，其中所述癌症选自由以下各项组成的组：膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)以及多发性骨髓瘤。

85.如权利要求81-84中任一项所述的方法，其中所述药剂展示一种或多种选自由以下

各项组成的组的活性：

(a)增加肿瘤浸润$CD3^+$T细胞的数量；

(b)抑制Siglec-7与一种或多种Siglec-7配体的结合；

(c)降低外周免疫细胞中Siglec-7的细胞水平

(d)减少非致瘤性$CD14^+$骨髓细胞的数量，任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞，或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于血液中；

(e)减少非致瘤性$CD14^+$骨髓细胞的数量，任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞，或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于所述肿瘤中；

(f)降低一种或多种细胞中的PD-L1水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；

(g)降低一种或多种细胞中的PD-L2水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；

(h)降低一种或多种细胞中的CD11b水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；

(i)降低一种或多种细胞中的B7-H3水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；

(j)降低一种或多种细胞中的CD200R水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；

(k)降低一种或多种细胞中的CD163水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；

(1)降低一种或多种细胞中的CD206水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；

(m)降低实体肿瘤的肿瘤生长速率；

(n)减小肿瘤体积；

(o)提高一种或多种PD-1抑制剂的功效；

(p)提高一种或多种检查点抑制剂疗法和/或免疫调节疗法的功效，任选地其中所述一种或多种检查点抑制剂疗法和/或免疫调节疗法靶向以下中的一种或多种：CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3、LAG3或其任何组合；

(q)抑制非致瘤性骨髓源性抑制细胞的(MDSC)分化、存活和/或一种或多种功能；

(r)诱导一种或多种骨髓源性抑制细胞(MDSC)的细胞死亡；

(s)在非致瘤性骨髓源性抑制细胞(MDSC)存在下增加T细胞的增殖。

86.一种诱导或促进有需要的个体中一种或多种免疫细胞的存活、成熟、功能性、迁移或增殖的方法，所述方法包括向所述个体施用治疗有效量的降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者的药剂。

87.如权利要求86所述的方法，其中所述一种或多种免疫细胞选自由以下各项组成的组：树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、小神经胶质细胞、T细胞、T辅助细胞、细胞毒性T细胞以及其任何组合。

88.如权利要求81-87中任一项所述的方法，其中所述药剂选自由以下各项组成的组：抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、反义分子、

siRNA、小分子抑制剂、蛋白质以及肽。

89.如权利要求81-87中任一项所述的方法，其中所述药剂是分离的抗Siglec-7抗体。

90.如权利要求89所述的方法，其中所述抗Siglec-7抗体是如权利要求1-73中任一项所述的抗Siglec-7抗体。

91.一种降低有需要的个体中调控性T细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、急性骨髓性白血病(AML)细胞、慢性淋巴细胞性白血病(CLL)细胞或慢性骨髓性白血病(CML)细胞的活性、功能性或存活的方法，所述方法包括向所述个体施用治疗有效量的与Siglec-7结合或相互作用的试剂。

92.如权利要求91所述的方法，其中所述药剂是分离的抗Siglec-7抗体或抗Siglec-7抗体缀合物。

93.如权利要求92所述的方法，其中所述抗Siglec-7抗体是如权利要求1-73中任一项所述的抗Siglec-7抗体。

94.一种降低有需要的个体中一种或多种细胞上的Siglec-7的细胞水平的方法，所述方法包括向所述个体施用治疗有效量的分离的抗Siglec-7抗体。

95.如权利要求94所述的方法，其中所述抗Siglec-7抗体降低体内Siglec-7的细胞水平。

96.如权利要求94或权利要求95所述的方法，其中所述抗Siglec-7抗体以在500pM至18pM范围内的EC_{50}降低Siglec-7的细胞水平，其中所述EC_{50}在大约37℃的温度下测定。

97.如权利要求94-96中任一项所述的方法，其中所述抗Siglec-7抗体对于人Siglec-7具有在约10nM至10pM或小于10pM范围内的解离常数(K_D)，其中所述K_D在大约25℃的温度下测定。

98.如权利要求94-97中任一项所述的方法，其中所述抗Siglec-7抗体以在2nM至100pM范围内的EC_{50}结合至人树突细胞，其中所述EC_{50}在大约4℃的温度下测定。

99.如权利要求94-98中任一项所述的方法，其中所述抗Siglec-7抗体是如权利要求1-73中任一项所述的抗Siglec-7抗体。

100.如权利要求81-99中任一项所述的方法，其还包括向所述个体施用至少一种特异性地结合至抑制性检查点分子的抗体，和/或一种或多种标准或研究性抗癌疗法。

101.如权利要求100所述的方法，其中所述至少一种特异性地结合至抑制性检查点分子的抗体与所述抗Siglec-7抗体组合施用。

102.如权利要求100或权利要求101所述的方法，其中所述至少一种特异性地结合至抑制性检查点分子的抗体选自由以下各项组成的组：抗PD-L1抗体、抗CTLA4抗体、抗PD-L2抗体、抗PD-1抗体、抗B7-H3抗体、抗B7-H4抗体和抗HVEM抗体、抗B-和T-淋巴细胞衰减子(BTLA)抗体、抗杀伤抑制性受体(KIR)抗体、抗GAL9抗体、抗TIM3抗体、抗A2AR抗体、抗LAG-3抗体、抗磷脂酰丝氨酸抗体、抗CD27抗体、抗TNFa抗体、抗CD33抗体、抗Siglec-5抗体、抗Siglec-9抗体、抗Siglec-11抗体、拮抗性抗TREM1抗体、拮抗性抗TREM2抗体以及其任何组合。

103.如权利要求100所述的方法，其中所述一种或多种标准或研究性抗癌疗法选自由以下各项组成的组：放射疗法、细胞毒性化学疗法、靶向疗法、伊马替尼疗法、曲妥珠单抗疗

法、依那西普疗法、过继细胞转移(ACT)疗法、嵌合抗原受体T细胞转移(CAR-T)疗法、疫苗疗法以及细胞因子疗法。

104.如权利要求81-103中任一项所述的方法,其还包括向所述个体施用至少一种特异性地结合至抑制性细胞因子的抗体。

105.如权利要求104所述的方法,其中所述至少一种特异性地结合至抑制性细胞因子的抗体与所述抗Siglec-7抗体组合施用。

106.如权利要求104或权利要求105所述的方法,其中所述至少一种特异性地结合至抑制性细胞因子的抗体选自由以下各项组成的组:抗CCL2抗体、抗CSF-1抗体、抗IL-2抗体以及其任何组合。

107.如权利要求81-106中任一项所述的方法,其还包括向所述个体施用至少一种特异性地结合至刺激性检查点蛋白的激动性抗体。

108.如权利要求107所述的方法,其中所述至少一种特异性地结合至刺激性检查点蛋白的激动性抗体与所述抗Siglec-7抗体组合施用。

109.如权利要求107或权利要求108所述的方法,其中所述至少一种特异性地结合至刺激性检查点蛋白的激动性抗体选自由以下各项组成的组:激动剂抗CD40抗体、激动剂抗OX40抗体、激动剂抗ICOS抗体、激动剂抗CD28抗体、激动性抗TREM1抗体、激动性抗TREM2抗体、激动剂抗CD137/4-1BB抗体、激动剂抗CD27抗体、激动剂抗糖皮质激素诱导的TNFR相关蛋白GITR抗体以及其任何组合。

110.如权利要求81-109中任一项所述的方法,其还包括向所述个体施用至少一种刺激性细胞因子。

111.如权利要求110所述的方法,其中所述至少一种刺激性细胞因子与所述抗Siglec-7抗体组合施用。

112.如权利要求110或权利要求111所述的方法,其中所述至少一种刺激性细胞因子选自由以下各项组成的组:IFN-a4、IFN-b、IL-1β、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-23、CXCL10、IL-33、MCP-1、MIP-1-β以及其任何组合。

113.一种评估有需要的个体对与Siglec-7结合或相互作用的药剂的应答性的方法,所述方法包括:

a.测量在向所述个体施用与Siglec-7结合或相互作用的药剂之前从所述个体获得的血液样品中非致瘤性骨髓细胞上$CD45^+$和$CD14^+$的表达水平;

b.向所述个体施用治疗有效量的所述药剂;以及

c.测量在施用所述药剂后从所述个体获得的血液样品中非致瘤性骨髓细胞上$CD45^+$和$CD14^+$的表达水平,

其中在施用所述抗Siglec-7抗体后,非致瘤性骨髓细胞上$CD45^+CD14^+$的水平降低表明所述个体对所述药剂有应答。

114.如权利要求113所述的方法,其还包括施用一种或多种另外的治疗有效量的所述药剂。

115.如权利要求112或权利要求113所述的方法,其中所述药剂选自由以下各项组成的组:抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、反义分子、

siRNA、小分子抑制剂、蛋白质以及肽。

116.如权利要求112或权利要求113所述的方法，其中所述药剂是分离的抗Siglec-7抗体或抗Siglec-7抗体缀合物。

117.如权利要求112或权利要求113所述的方法，其中所述抗Siglec-7抗体是如权利要求1-73中任一项所述的抗Siglec-7抗体。

抗SIGLEC-7抗体及其使用方法

[0001] 相关申请的交叉引用

[0002] 本申请要求2015年8月28日提交的美国临时申请号62/211,656和2015年12月10日提交的美国临时申请号62/265,742的权益,所述申请各自特此以引用的方式整体并入。

[0003] 呈ASCII文本文件形式的序列表的提交

[0004] 呈ASCII文本文件形式的以下提交的内容以引用的方式整体并入本文:序列表的计算机可读形式(CRF)(文件名称:735022000840SEQLISTING.TXT,记录日期:2016年8月26日,大小:405KB)。

发明领域

[0005] 本公开涉及抗Siglec-7抗体以及此类抗体的治疗用途。

[0006] 发明背景

[0007] 结合唾液酸的Ig样凝集素-7(Siglec-7)是在免疫和造血细胞上表达的1型免疫球蛋白样跨膜蛋白,所述免疫和造血细胞包括未成熟的和成熟的骨髓细胞如单核细胞、巨噬细胞、树突细胞、嗜中性粒细胞、肥大细胞和小神经胶质细胞,以及淋巴细胞如天然杀伤细胞和T细胞亚群(Crocker等人(2007)Nat Rev Immunol.7:255-266;Angata和Varki(2000)Glycobiology 10:4:431-438;Nicoll等人(1999)JBC 274:48:34089-34095;Falco等人(1999)J.Exp.Med.190:793-802)。Siglec-7是结合糖蛋白和糖脂的唾液酸残基的凝集素的Siglec家族的成员。Siglec蛋白的一种潜在结合靶标是神经节苷脂;即由与唾液酸化聚糖连接的神经酰胺组成的糖脂。大多数神经节苷脂共有共同的乳-神经酰胺核心和一个或多个唾液酸残基。Siglec配体的多样性通过在不同键联中添加其它中性糖和唾液酸以及唾液酸本身的修饰而产生。

[0008] 已经在人类中鉴定了14种Siglec蛋白并且在小鼠中鉴定了9种Siglec蛋白,所述Siglec蛋白由包括氨基末端V-组结构域的2-17个细胞外Ig结构域组成,所述V-组结构域含有唾液酸结合位点。唾液酸结合区位于V-组Ig-样结构域上,所述结构域含有在所有Siglec中高度保守的两个芳族残基和一个精氨酸的基序(Crocker等人(2007)Nat Rev Immunol.7:255-266;McMillan和Crocker(2008)Carbohydr Res.343:2050-2056;Von Gunten和Bochner(2008)Ann NY Acad Sci.1143:61-82;May等人(1998)Mol Cell.1:719-728;Crocker等人(1999)Biochem J.341:355-361;以及Crocker和Varki(2001)Trends Immunol.2:337-342)。与唾液酸化配体的结合位点已经通过有或无结合的配体的晶体结构作图(Alphey等人,(2003)J.Biol.Chem.278:5:3372-3377;Attrill等人,(2006)J.Biol.Chem.281 32774-32783;以及Varki等人,Glycobiology,16第1R-27R页)。由于细胞膜富含唾液酸,因此Siglec的配体结合可以顺式和反式形式发生,两者均影响它们的功能性质。每种Siglec对于结合在哺乳动物细胞的表面上发现的不同类型的唾液酸化聚糖均具有不同的偏好(Crocker等人(2007)Nat Rev Immunol.7:255-266;以及Crocker等人(2007)Nat Rev Immunol.7:255-266)。包括Siglec-7在内的大多数Siglec蛋白在其胞质尾区中含有一条或多条基于免疫受体酪氨酸的抑制性基序(ITIM)序列,所述序列通过募集酪氨酸磷

酸酶SHP1和SHP2而使所述Siglec蛋白能够充当免疫功能的抑制性受体和负调节子(Crocker等人(2007)Nat Rev Immunol.7:255-266;McMillan和Crocker(2008)Carbohydr Res.343:2050-2056;以及Von Gunten和Bochner(2008)Ann NY Acad Sci.1143:61-82)。某些Siglec在其细胞质尾中含有基于免疫受体酪氨酸的活化基序(ITAM)序列,所述序列通过预测的脾酪氨酸激酶(Syk)募集而使所述Siglec能够充当免疫功能的活化受体和正调节子(Macauley SM.等人,(2014)Nature Reviews Immunology 14,653-666)。Siglec蛋白家族与多种人疾病相关,所述疾病包括自身免疫性、对感染的易感性、多种类型的癌症(包括淋巴瘤、白血病和急性骨髓性白血病)、全身性红斑狼疮、类风湿性关节炎、神经退行性病症、哮喘、过敏症、败血症、慢性阻塞性肺疾病、移植物抗宿主疾病、嗜酸性粒细胞增多症和骨质疏松症(Macauley SM.等人,(2014)Nature Reviews Immunology 14,653-666)。

[0009] Siglec-7在1999年克隆(Falco等人(1999)J.Exp.Med.190:793-802;Nicoll等人(1999)JBC 274:48:34089-34095;Angata和Varki(2000)Glycobiology 10:4:431-438),并且在人外周血中的粒细胞、单核细胞、静息和活化的天然杀伤细胞以及静息$CD8^+$ T细胞亚群上检测到选择性表达(Nicoll等人(1999)JBC 274:48:34089-34095;Falco等人(1999)J.Exp.Med.190:793-802)。

[0010] Siglec-7含有细胞外N-末端Ig样(免疫球蛋白样)V-型结构域、两个Ig样C2-组结构域以及一个共有ITIM基序和不一致膜远端ITIM样基序(在其细胞质结构域中)。由于在唾液酸酶处理后结合的丧失,Siglec-7显示以唾液酸依赖性方式结合红细胞。所述结合被认为是由α2-3或α2-6唾液酸键联介导的(Nicoll等人(1999)JBC 274:48:34089-34095;Angata和Varki(2000)Glycobiology 10:4:431-438)。进一步的研究揭示,Siglec-7以10nM的亲和力更有效地结合α2-8二唾液酸残基,并且与末端α2-3或α2-6唾液酸相比,对分支的α2-6唾液酸残基展现更高的亲和力(Yamaji(2002)J.Biol.Chem.277:86324-6332)。体内Siglec-7配体在b系列神经节苷脂如GD2、GD3和GT1b上表达,其可在中枢神经系统细胞、黑色素瘤细胞和T细胞亚群中发现(Urmacher等人(1989)Am.J.Dermatopathol.11:577-581;Kniep等人(1993)Blood 82:1776-1786)。Siglec-7的N-末端V-组Ig-样结构域的高分辨率晶体结构表明Siglec家族成员的配体结合特异性存在于可变C-C′环中(Alphey等人(2003)J.Biol.Chem 278:5 3372-3377)。

[0011] Siglec-7通过酪氨酸激酶(可能是c-Src或Lck)进行Tyr-437和Tyr-460的磷酸化(Avril等人,(2004)J.Imm.173:6841-6849)。主要在其近端Tyr-437上、但也在其ITIM结构域的远端Tyr-460上进行磷酸化后,Siglec-7结合SHP-2/PTPN11和SHP-1/PTPN6(Avril等人,(2004)J.Imm.173:6841-6849)。磷酸酶活性与以下各项相关:细胞内钙动员减少和对多种蛋白质的酪氨酸磷酸化减少(Ulyanova,T.等人,(1999)Eur Jlmmunol 29,3440-3449;Paul,S.P.等人,(2000).blood 96,483-490)以及与信号转导和免疫应答的阻断,部分是通过相邻活化受体上的信号传导分子的去磷酸化,包括含有ITAM基序的那些、模式识别受体、Toll样受体和损伤相关分子模式(DAMP)受体。

[0012] 一些但并非所有的Siglec配体诱导受体下调(Macauley SM.等人,(2014)Nature Reviews Immunology 14,653-666)。已经对酪氨酸激酶受体(Monsonego-Oran等人,(2002)Febs letters 528,83-89;和Fasen等人,(2008)Cell&Molecular Biology 9.251-266)以及类固醇受体(Callige等人,(2005)Mol.Cell.Biol.25.4349-4358;和Pollenz等人,

(2006)Chemico-Biological Interactions.164.49-59)报道了配体诱导的受体降解。细胞因子信号传导3(SOCS3)的抑制子已显示在Siglec-7交联存在下与SHP-1/2竞争并在ITIM磷酸化后结合Siglec-7(Orr等人(2007)J.Biol.Chem.282:3418-3422)。SOCS3结合导致Siglec-7的ECS E3连接酶靶向以进行蛋白酶体降解(Willams和Palmer(2012)Biochem.Soc.Trans.40:215-218;Orr等人(2007)J.Biol.Chem.282:3418-3422)。

[0013] 还已经显示Siglec-7信号传导的活化与促炎性细胞因子IL-6、IL-1α、MIP-1β、IL-8和TNFα的产生增加以及粘附分子ICAM-1和CD49e选择性地在人单核细胞中的上调相关(Varchetta等人(2012)PLOS One 7:9:e45821)。Siglec-7的这些活性似乎是通过ERK的磷酸化介导的(Varchetta等人(2012)PLOS One 7:9:e45821)。已经提出含有ITIM的Siglec受体与活化受体之间的缔合可由结合并桥接这些受体的细胞外配体介导(Macauley SM.等人,(2014)Nature Reviews Immunology 14,653-666)。

[0014] 多项研究表明Siglec-7在天然杀伤细胞的功能、T细胞受体信号传导的调控和DC中信号传导的衰减中的抑制作用(Crocker等人,(2012)Ann.N Y Acad.Sci.1253,102-111;Pillai等人,(2012)Annu.Rev.Immunol.30,357-392;von Gunten和Bochner(2008)Ann.N Y Acad.Sci.1143,61-82;Ikehara等人(2004)J.Biol.Chem.279:4143117-43125;Nicoll等人(2003)Eur.J.Imm.33:6:1642-1648;Hudak等人(2013)Nat.Chem.Biol.;Bax等人(2007)J.Imm 179:12:8216-8224;Lock等人(2004)Immunobiology 209:1-2:199-207)。对天然杀伤细胞的功能研究已经证明表达Siglec-7结合唾液酸配体的肿瘤细胞抑制NK细胞活化和肿瘤细胞杀伤。许多人肿瘤稳健地上调唾液酸配体,这使得能够免疫逃避和癌症进展(Jandus等人(2014)J.Clinic.Invest.124:4:1810-1820)。此外,Hudak等人进行了糖被膜工程化并且显示保护用合成唾液酸苷(sialoside)含糖聚合物包被的细胞免于NK细胞毒性。已提出,肿瘤上的唾液酸上调促进强烈抑制天然杀伤细胞免疫监视的“超自我”状态(Macauley和Paulson(2014)Nat.Chem.Biol.10:1:7-8)。

[0015] 不存在Siglec-7的明显小鼠同系物;然而,小鼠Siglec-E是53%相似的,因此是最接近相关的Siglec。在小鼠中,Siglec-E的遗传失活不会导致明显的发育、组织学或行为异常;并且Siglec-E缺陷型小鼠正常繁殖,从而表明Siglec-E不是必需基因并且其功能可能限于先天免疫(McMillan等人(2013)Blood 121:11:2084-2094)。在用气溶胶LPS激发Siglec-E缺陷型小鼠后,展示肺中嗜中性粒细胞募集增加,这可通过阻断β2-整联蛋白CD11b而逆转。Siglec-E缺陷型嗜中性粒细胞显示以CD11b依赖性方式增加Syk和p38 MAPK的磷酸化。此数据表明Siglec-E在急性肺部炎症模型中遏制嗜中性粒细胞募集(McMillan等人(2013)Blood 121:11:2084-2094)。

[0016] 在肿瘤学中,由于交联Siglec-7抑制细胞增殖,所以Siglec-7已被认为是慢性和急性骨髓性白血病的治疗靶标(Vitale等人(1999)PNAS 96:15091-15096;Vitale等人(2001)PNAS 98:10:5764-5769)。还已显示Siglec-7活性抑制细胞因子诱导的细胞增殖(Orr等人(2007)J.Biol.Chem.282:3418-3422)。

[0017] 针对Siglec-7的抗体已经描述于例如WO2011038301;Jandus等人(2014)J.Clinical Invest.124:4:1810-1820;Varchetta等人(2012)PLOS One 7:9:e45821等人(2012).Falco等人(1999)J.Exp.Med.190:793-802;Nicoll等人(1999)JBC 274:48:34089-34095;Nicoll等人(2003)Eur.J.Imm.33:1642-1648中。然而,这些抗体不显示治疗性抗体

所需的功能特征。

[0018] 因此，需要特异性地结合Siglec-7并降低细胞表面上的Siglec-7表达、减少Siglec-7与一种或多种Siglec-7配体之间的相互作用和/或降低一种或多种Siglec-7活性的治疗性抗体以便治疗与不希望的Siglec-7活性相关的一种或多种疾病、病症和病况。

[0019] 本文所引用的所有参考文献(包括专利、专利申请和公布)均特此以引用的方式整体并入。

[0020] 发明概述

[0021] 本公开总体上涉及Siglec-7药剂，诸如抗Siglec-7抗体，以及使用此类Siglec-7药剂的方法。本文提供的方法可用于预防患有以下疾病的个体、降低所述个体的风险或治疗所述个体：痴呆、额颞叶痴呆、阿尔茨海默氏病(Alzheimer's disease)、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病(Creutzfeldt-Jakob disease)、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病(Huntington's disease)、Tau蛋白病(taupathy disease)、那须哈科拉病(Nasu-Hakola disease)、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病(Crohn's disease)、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病(Behcet′s disease)、帕金森氏病(Parkinson′s disease)、路易体痴呆(dementia with Lewy bodies)、多系统萎缩症、夏伊-德拉戈综合征(Shy-Drager syndrome)、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病(Paget′s disease of bone)、实体癌和血癌、膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤(non-Hodgkin′s lymphoma)、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7和/或Siglec-7配体的肿瘤、甲状腺癌、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染(Cruzi infection)、铜绿假单胞菌(Pseudomonas aeruginosa)感染、杜氏利什曼(Leishmania donovani)原虫感染、B族链球菌(group B Streptococcus)感染、空肠弯曲杆菌(Campylobacter jejuni)感染、脑膜炎奈瑟氏菌(Neisseria meningiditis)感染、I型HIV以及流感嗜血杆菌(Haemophilus influenza)。本文提供的方法还可用于诱导或促进有需要的个体中一种或多种免疫细胞的存活、成熟、功能性、迁移或增殖。本文提供的方法进一步用于降低以下各项的活性、功能性或存活：调控性T细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、嗜中性粒细胞、天然杀伤(NK)细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、嗜中性粒细胞、NK细胞、急性骨髓性白血病(AML)细胞、慢性淋巴细胞性白血病(CLL)细胞或慢性骨髓性白血病(CML)细胞。

[0022] 本公开的某些方面至少部分地基于鉴定能够降低人原代免疫细胞和表达Siglec-7的细胞系上Siglec-7的细胞表面水平和/或能够抑制Siglec-7配体与Siglec-7的结合的抗Siglec-7抗体(参见例如实施例3-5)。

[0023] 因此，本公开的某些方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体降低Siglec-7的细胞水平。在一些实施方案中，所述抗Siglec-7抗体降低Siglec-7的细胞水平而不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。在一些实施方案中，所述抗体进一步抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。

[0024] 本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体降低Siglec-7的细胞水平并抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。

[0025] 在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体降低Siglec-7的细胞表面水平、降低Siglec-7的细胞内水平、降低Siglec-7的总水平或其任何组合。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体诱导Siglec-7降解、Siglec-7裂解、Siglec-7内化、Siglec-7脱落、Siglec-7表达的下调或其任何组合。在可与前述实施方案中的任一项组合的一些实施方案中，抗体降低体内Siglec-7的细胞水平。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体抑制Siglec-7的细胞表面簇集。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体抑制一种或多种Siglec-7活性。在可与前述实施方案中的任一项组合的一些实施方案中，所述一种或多种Siglec-7活性选自：(a)Siglec-7与一种或多种Siglec-7配体的结合，任选地其中所述一种或多种Siglec-7配体选自含唾液酸的糖蛋白、含唾液酸的糖脂以及其任何组合；(b)Siglec-7与SHP1或SHP2的结合；(c)由一种或多种SRC家族酪氨酸激酶诱导的Tyr-437、Tyr-460或两者的磷酸化，任选地，其中所述一种或多种SRC家族酪氨酸激酶选自Syk、LCK、FYM和ZAP-70；(d)调节一种或多种促炎性细胞因子的表达，任选地其中所述一种或多种促炎性细胞因子选自IFN-a4、IFN-β、IL-1β、IL-1α、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-33、MCP-1以及MIP-1-β；(e)调节一种或多种细胞中的一种或多种促炎性细胞因子的表达，所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞；(f)调节一种或多种抗炎细胞因子的表达，任选地其中所述一种或多种抗炎细胞因子选自IL-4、IL-10、IL-13、IL-35、IL-16、TGF-β、IL-1Ra、G-CSF和TNF，以及TNF、IFN-β1a、IFN-β1b或IL-6的可溶性受体；(g)调节一种或多种细胞中的一种或多种抗炎细胞因子的表达，所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞；(h)调节一种或多种选自由以下各项组成的组的蛋白质的表达：C1qa、C1qB、C1qC、C1s、C1R、C4、C2、C3、ITGB2、HMOX1、LAT2、CASP1、CSTA、VSIG4、MS4A4A、C3AR1、GPX1、TyroBP、ALOX5AP、ITGAM、SLC7A7、CD4、ITGAX、以及PYCARD；(i)抑制细胞外信号调控激酶(ERK)磷酸化；(j)降低一种或多种细胞蛋白上的酪氨酸磷酸化，任选地，其中所述一种或多种细胞蛋白包含ZAP-70并且所述酪氨酸磷酸化发生在ZAP-70的Tyr-319上；(k)调节C-C趋化因子受体7(CCR7)的表达；(l)抑制针对表达CCL19的细胞和表达CCL21的细胞的小神经胶质细胞趋化性；(m)减少由一种或多种细胞诱导的T细胞增殖，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞、

M2小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞以及M2 NK细胞；(n)抑制破骨细胞产生，降低破骨细胞生成速率或两者；(o)降低一种或多种细胞的存活，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；(p)降低一种或多种细胞的增殖，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；(q)抑制一种或多种细胞的迁移，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；(r)抑制一种或多种细胞的一种或多种功能，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；(s)抑制一种或多种细胞的成熟，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；(t)抑制一种或多种类型的清除，所述清除选自凋亡神经元清除、神经组织碎片清除、功能障碍性突触清除、非神经组织碎片清除、细菌清除、其它异物清除、致病蛋白清除、致病肽清除以及肿瘤细胞清除；任选地，其中所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重

复序列肽，并且所述肿瘤细胞来自癌症，所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌；(u)抑制以下中的一种或多种的吞噬：凋亡神经元、神经组织碎片、功能障碍性突触、非神经组织碎片、细菌、其它异物、致病蛋白、致病肽、致病核酸或肿瘤细胞；任选地其中所述致病核酸是反义GGCCCC(G2C4)重复序列-扩增RNA，所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽，并且所述肿瘤细胞来自癌症，所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤或甲状腺癌；(v)与肿瘤细胞上的Siglec-7配体结合；(w)与细胞上的Siglec-7配体结合，所述细胞选自嗜中性粒细胞、树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞以及NK细胞；(x)通过以下中的一种或多种抑制肿瘤细胞杀伤：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；(y)抑制以下中的一种或多种的抗肿瘤细胞增殖活性：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；(z)抑制以下中的一种或多种的抗肿瘤细胞转移活性：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；(aa)抑制一种或多种含ITAM基序的受体，任选地其中所述一种或多种含ITAM基序的受体选自TREM1、TREM2、Sirpβ、FcgR、DAP10以及DAP12；(bb)通过一种或多种模式识别受体(PRR)抑制信号传导，任选地其中所述一种或多种PRR选自鉴定病原体相关分子模式(PAMP)的受体、鉴定损伤相关分子模式(DAMP)的受体以及其任何组合；(cc)抑制包含基序$D/E_{x0-2}YxxL/I_{X6-8}YxxL/I$(SEQ ID NO:537)的一种或多种受体；(dd)通过一种或多种Toll样受体抑制信号传导；(ee)抑制JAK-STAT信号传导途径；(ff)抑制活化的B细胞的核因子κ-轻链增强子(NFκB)；(gg)含有ITAM基序的受体的去磷酸化；(hh)调节一种或多种炎性受体的表达，任选地其中所述一种或多种炎性受体包含CD86并且所述一种或多种炎性受体在以下中的一种或多种上表达：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突状细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；(ii)增加一种或多种Siglec-7依赖性基因的表达；(jj)破坏的Siglec-7依赖性基因表达的正常化；(kk)降低一种或多种ITAM依赖性基因的表达，任选地其中所述一种或多种ITAM依赖性基因通过活化T细胞(NFAT)转录因子的核因子活化；(ll)促进以下中的一种或多种的分化：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相

关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；(mm)促进或挽救以下中的一种或多种的功能性：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；(nn)增加以下中的一种或多种浸润到肿瘤中：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；(oo)增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量；(pp)增强骨髓源性抑制细胞的肿瘤促进活性；(qq)增加肿瘤或外周血液中肿瘤促进细胞因子的表达，任选地其中所述肿瘤促进细胞因子是TGF-β或IL-10；(rr)增加肿瘤促进FoxP3+调控性T淋巴细胞的肿瘤浸润；(ss)增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性；(tt)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化；(uu)减少具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润；(vv)降低NK细胞的肿瘤杀伤潜力；(ww)减少具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润；(xx)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润；(yy)增加肿瘤体积；(zz)增加肿瘤生长速率；(aaa)增加转移；(bbb)增加肿瘤复发率；(ccc)降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效，任选地其中所述一种或多种免疫疗法是靶向一种或多种靶蛋白的免疫疗法，所述一种或多种靶蛋白选自PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、TREM1、TREM2、CSF-1受体以及其任何组合；(ddd)抑制PLCγ/PKC/钙动员；以及(eee)抑制PI3K/Akt、Ras/MAPK信号传导。在可与前述实施方案中的任一项组合的一些实施方案中，所述一种或多种Siglec-7活性选自：(a)Siglec-7与一种或多种Siglec-7配体的结合，任选地其中所述一种或多种Siglec-7配体选自由以下各项组成的组：含唾液酸的糖蛋白、含唾液酸的糖脂以及其任何组合；(b)降低一种或多种细胞的增殖，所述一种或多种细胞选自由以下各项组成的组：树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；(c)抑制一种或多种细胞的迁移，所述一种或多种细胞选自由以下各项组成的组：树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；(d)抑制一种或多种细胞的一种或多种功能，所述一种或多种细胞选自由以下各项组成的组：树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；(e)抑制一种或多种类型的清除，所述清除选自由以下各项组成的组：凋亡神经元清除、神经组织碎片清除、功能障碍性突触

清除、非神经组织碎片清除、细菌清除、其它异物清除、致病蛋白清除、致病肽清除以及肿瘤细胞清除；任选地，其中所述致病蛋白选自由以下各项组成的组：淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽，并且所述肿瘤细胞来自癌症，所述癌症选自由以下各项组成的组：膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌；(f)通过以下中的一种或多种抑制肿瘤细胞杀伤：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；(g)抑制以下中的一种或多种的抗肿瘤细胞增殖活性：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；(h)调节一种或多种炎性受体的表达，任选地其中所述一种或多种炎性受体包含CD86并且所述一种或多种炎性受体在以下中的一种或多种上表达：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突状细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；(i)促进或挽救以下中的一种或多种的功能性：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；(j)增加以下中的一种或多种浸润到肿瘤中：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；(k)增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量；(l)增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性；(m)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化；(n)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润；(o)增加肿瘤体积；(p)增加肿瘤生长速率；以及(q)降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效，任选地其中所述一种或多种免疫疗法是靶向一种或多种靶蛋白的免疫疗法，所述一种或多种靶蛋白选自由以下各项组成的组：PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、TREM1、TREM2、CSF-1受体以及其任何组合。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体展示一种或多种选自由以下各项组成的组的活性：(a)增加肿瘤浸润$CD3^+$ T细胞的数量；(b)抑制Siglec-7与一种或多种Siglec-7配体的结合；(c)降低外周免疫细胞中Siglec-7的细胞水平；(d)减少非致瘤性$CD14^+$骨髓细胞的数量，任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞，或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于血液中；(e)减少非致瘤性$CD14^+$骨髓细胞的数量，任选地其

中所述非致瘤性CD14$^+$骨髓细胞是肿瘤浸润细胞，或任选地其中所述非致瘤性CD14$^+$骨髓细胞存在于肿瘤中；(f)降低一种或多种细胞中的PD-L1水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(g)降低一种或多种细胞中的PD-L2水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(h)降低一种或多种细胞中的CD11b水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(i)降低一种或多种细胞中的B7-H3水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(j)降低一种或多种细胞中的CD200R水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(k)降低一种或多种细胞中的CD163水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(l)降低一种或多种细胞中的CD206水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(m)降低实体肿瘤的肿瘤生长速率；(n)减小肿瘤体积；(o)提高一种或多种PD-1抑制剂的功效；(p)提高一种或多种检查点抑制剂疗法和/或免疫调节疗法的功效，任选地其中所述一种或多种检查点抑制剂疗法和/或免疫调节疗法靶向以下中的一种或多种：CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3、LAG3或其任何组合；(q)抑制非致瘤性骨髓源性抑制细胞的(MDSC)分化、存活和/或一种或多种功能；(r)诱导一种或多种骨髓源性抑制细胞(MDSC)的细胞死亡；以及(s)在非致瘤性骨髓源性抑制细胞(MDSC)存在下增加T细胞的增殖。在可与前述实施方案中的任一项组合的一些实施方案中，所述一种或多种Siglec-7配体选自在红细胞上表达的Siglec-7配体、在细菌细胞上表达的Siglec-7配体、在凋亡细胞上表达的Siglec-7配体、在神经细胞上表达的Siglec-7配体、在神经胶质细胞上表达的Siglec-7配体、在小神经胶质细胞上表达的Siglec-7配体、在星形胶质细胞上表达的Siglec-7配体、在肿瘤细胞上表达的Siglec-7配体、在病毒上表达的Siglec-7配体、在树突细胞上表达的Siglec-7配体、与β淀粉样蛋白斑块结合的Siglec-7配体、与Tau缠结结合的Siglec-7配体、致病蛋白上的Siglec-7配体、致病肽上的Siglec-7配体、在巨噬细胞上表达的Siglec-7配体、在嗜中性粒细胞上表达的Siglec-7配体、在单核细胞上表达的Siglec-7配体、在天然杀伤细胞上表达的Siglec-7配体、在T细胞上表达的Siglec-7配体、在T辅助细胞上表达的Siglec-7配体、在细胞毒性T细胞上表达的Siglec-7配体、在B细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制树突细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制巨噬细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制嗜中性粒细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制NK细胞上表达的Siglec-7配体、在骨髓源性抑制细胞上表达的Siglec-7配体、在调控性T细胞上表达的Siglec-7配体、分泌的粘蛋白、唾液酸、含唾液酸的糖脂、含唾液酸的糖蛋白、含α-2,8-二唾液酸的糖脂、含支链α-2,6-连接的唾液酸的糖蛋白、含末端α-2,6-连接的唾液酸的糖脂、含末端α-2,3-连接的唾液酸的糖蛋白以及双唾液酸神经节苷脂。在可与前述实施方案中的任一项组合的一些实施方案中，在选自树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞、嗜中性粒细胞和NK细胞的原代细胞上或在细胞系上测量Siglec-7的细胞水平，并且其中使用体外细胞测定来测量Siglec-7的细胞水平。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体不降低TREM2表达。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体不降低TREM2的细胞表面水平、不降低TREM2的细胞内水平、不降低TREM2的总水平或其任何组合。在可与前述实施方案中的任一项组合的一些实施方案中，所

述抗Siglec-7抗体不降低体内TREM2的细胞水平。在可与前述实施方案中的任一项组合的一些实施方案中，在选自树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞、嗜中性粒细胞和NK细胞的原代细胞上或在细胞系上测量TREM2的细胞水平，并且其中使用体外细胞测定来测量TREM2的细胞水平。

[0026] 在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合不连续的Siglec-7表位。在可与前述实施方案中的任一项组合的一些实施方案中，所述不连续的Siglec-7表位包含两种或更多种肽、三种或更多种肽、四种或更多种肽、五种或更多种肽、六种或更多种肽、七种或更多种肽、八种或更多种肽、九种或更多种肽或10种或更多种肽。在可与前述实施方案中的任一项组合的一些实施方案中，所述肽各自包含SEQ ID NO:1的氨基酸序列的5个或更多个、6个或更多个、7个或更多个、8个或更多个、9个或更多个、10个或更多个、11个或更多个、12个或更多个、13个或更多个、14个或更多个、15个或更多个、16个或更多个、17个或更多个、18个或更多个、19个或更多个或20个或更多个氨基酸残基；或对应于SEQ ID NO:1的氨基酸序列的哺乳动物Siglec-7蛋白上的5个或更多个、6个或更多个、7个或更多个、8个或更多个、9个或更多个、10个或更多个、11个或更多个、12个或更多个、13个或更多个、14个或更多个、15个或更多个、16个或更多个、17个或更多个、18个或更多个、19个或更多个或20个或更多个氨基酸残基。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至Siglec-7的构象表位。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至SEQ ID NO:1的氨基酸残基39-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353内的一个或多个氨基酸；或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基39-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至选自由以下各项组成的组的氨基酸残基内的一个或多个氨基酸：i.SEQ ID NO:1的氨基酸残基60-69，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69的氨基酸残基；ii.SEQ ID NO:1的氨基酸残基60-69和84-95，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69和84-95的氨基酸残基；iii.SEQ ID NO:1的氨基酸残基60-69和117-127，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69和117-127的氨基酸残基；iv.SEQ ID NO:1的氨基酸残基68-78，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基68-78的氨基酸残基；v.SEQ ID NO:1的氨基酸残基84-95，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基84-95的氨基酸残基；vi.SEQ ID NO:1的氨基酸残基111-122，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基111-122的氨基酸残基；vii.SEQ ID NO:1的氨基酸残基111-122和282-291，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基111-122和282-291的氨基酸残基；viii.SEQ ID NO:1的氨基酸残基113-123，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基113-123的氨基酸残基；ix.SEQ ID NO:1的氨基酸残基113-125，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基113-125的氨基酸残基；x.SEQ ID NO:1的氨基酸残基117-127，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基117-127的氨基酸残基；以及xi.SEQ ID NO:1的氨基酸残基282-291，或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的

氨基酸残基282-291的氨基酸残基。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和84-95的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和117-127的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基68-78内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基68-78的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基84-95的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122和282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122和282-291的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-123内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-123的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-125内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-125的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基117-127的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基282-29的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体结合至一个或多个选自由以下各项组成的组的氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、I72、W74、N81、T103、K104、T107以及R124，或哺乳动物Siglec-7蛋白上对应于选自由以下各项组成的组的氨基酸残基的一个或多个氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、172、W74、N81、T103、K104、T107以及R124。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体与选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何

组合的一种或多种抗体竞争结合至Siglec-7。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体包含轻链可变结构域和重链可变结构域，其中所述轻链可变结构域、所述重链可变结构域或两者包含至少一个、两个、三个、四个、五个或六个HVR，所述HVR选自单克隆抗体的HVR-L1、HVR-L2、HVR-L3、HVR-H1、HVR-H2以及HVR-H3，所述单克隆抗体选自：1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。在可与前述实施方案中的任一项组合的一些实施方案中：(a)所述HVR-L1包含选自SEQ ID NO:7-19和476的氨基酸序列；(b)所述HVR-L2包含选自SEQ ID NO:20-32和477的氨基酸序列；(c)所述HVR-L3包含选自SEQ ID NO:33-45和478的氨基酸序列；(d)所述HVR-H1包含选自SEQ ID NO:46-58和479的氨基酸序列；(e)所述HVR-H2包含选自SEQ ID NO:59-71和480-482的氨基酸序列；或(f)所述HVR-H3包含选自SEQ ID NO:72-84和483的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中：(a)所述HVR-L1包含SEQ ID NO:7的氨基酸序列，所述HVR-L2包含SEQ ID NO:20的氨基酸序列，所述HVR-L3包含SEQ ID NO:33的氨基酸序列，所述HVR-H1包含SEQ ID NO:46的氨基酸序列，所述HVR-H2包含SEQ ID NO:59的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:72的氨基酸序列；(b)所述HVR-L1包含SEQ ID NO:8的氨基酸序列，所述HVR-L2包含SEQ ID NO:21的氨基酸序列，所述HVR-L3包含SEQ ID NO:34的氨基酸序列，所述HVR-H1包含SEQ ID NO:47的氨基酸序列，所述HVR-H2包含SEQ ID NO:60的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:73的氨基酸序列；(c)所述HVR-L1包含SEQ ID NO:10的氨基酸序列，所述HVR-L2包含SEQ ID NO:23的氨基酸序列，所述HVR-L3包含SEQ ID NO:36的氨基酸序列，所述HVR-H1包含SEQ ID NO:49的氨基酸序列，所述HVR-H2包含SEQ ID NO:62的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:75的氨基酸序列；(d)所述HVR-L1包含SEQ ID NO:11的氨基酸序列，所述HVR-L2包含SEQ ID NO:24的氨基酸序列，所述HVR-L3包含SEQ ID NO:37的氨基酸序列，所述HVR-H1包含SEQ ID NO:50的氨基酸序列，所述HVR-H2包含SEQ ID NO:63的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:76的氨基酸序列；(e)所述HVR-L1包含SEQ ID NO:12的氨基酸序列，所述HVR-L2包含SEQ ID NO:25的氨基酸序列，所述HVR-L3包含SEQ ID NO:38的氨基酸序列，所述HVR-H1包含SEQ ID NO:51的氨基酸序列，所述HVR-H2包含SEQ ID NO:64的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:77的氨基酸序列；(f)所述HVR-L1包含SEQ ID NO:13的氨基酸序列，所述HVR-L2包含SEQ ID NO:26的氨基酸序列，所述HVR-L3包含SEQ ID NO:39的氨基酸序列，所述HVR-H1包含SEQ ID NO:52的氨基酸序列，所述HVR-H2包含SEQ ID NO:65的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:78的氨基酸序列；(g)所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:66的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列；(h)所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:480的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列；(i)所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:481的氨基酸序列，并且所述HVR-H3包含

SEQ ID NO:79的氨基酸序列;(j)所述HVR-L1包含SEQ ID NO:15的氨基酸序列,所述HVR-L2的氨基酸序列SEQ ID NO:28的氨基酸序列,所述HVR-L3包含SEQ ID NO:41的氨基酸序列,所述HVR-H1包含SEQ ID NO:54的氨基酸序列,所述HVR-H2包含SEQ ID NO:67的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:80的氨基酸序列;(k)所述HVR-L1包含SEQ ID NO:16的氨基酸序列,所述HVR-L2包含SEQ ID NO:29的氨基酸序列,所述HVR-L3包含SEQ ID NO:42的氨基酸序列,所述HVR-H1包含SEQ ID NO:55的氨基酸序列,所述HVR-H2包含SEQ ID NO:68的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:81的氨基酸序列;(l)所述HVR-L1包含SEQ ID NO:17的氨基酸序列,所述HVR-L2包含SEQ ID NO:30的氨基酸序列,所述HVR-L3包含SEQ ID NO:43的氨基酸序列,所述HVR-H1包含SEQ ID NO:56的氨基酸序列,所述HVR-H2包含SEQ ID NO:69的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:82的氨基酸序列;(m)所述HVR-L1包含SEQ ID NO:18的氨基酸序列,所述HVR-L2包含SEQ ID NO:31的氨基酸序列,所述HVR-L3包含SEQ ID NO:44的氨基酸序列,所述HVR-H1包含SEQ ID NO:57的氨基酸序列,所述HVR-H2包含SEQ ID NO:70的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列;(n)所述HVR-L1包含SEQ ID NO:476的氨基酸序列,所述HVR-L2包含SEQ ID NO:477的氨基酸序列,所述HVR-L3包含SEQ ID NO:478的氨基酸序列,所述HVR-H1包含SEQ ID NO:57的氨基酸序列,所述HVR-H2包含SEQ ID NO:70的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列;(o)所述HVR-L1包含SEQ ID NO:18的氨基酸序列,所述HVR-L2包含SEQ ID NO:31的氨基酸序列,所述HVR-L3包含SEQ ID NO:44的氨基酸序列,所述HVR-H1包含SEQ ID NO:479的氨基酸序列,所述HVR-H2包含SEQ ID NO:482的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:483的氨基酸序列;或(p)所述HVR-L1包含SEQ ID NO:19的氨基酸序列,所述HVR-L2包含SEQ ID NO:32的氨基酸序列,所述HVR-L3包含SEQ ID NO:45的氨基酸序列,所述HVR-H1包含SEQ ID NO:58的氨基酸序列,所述HVR-H2包含SEQ ID NO:71的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:84的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:7的氨基酸序列,所述HVR-L2包含SEQ ID NO:20的氨基酸序列,所述HVR-L3包含SEQ ID NO:33的氨基酸序列,所述HVR-H1包含SEQ ID NO:46的氨基酸序列,所述HVR-H2包含SEQ ID NO:59的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:72的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:8的氨基酸序列,所述HVR-L2包含SEQ ID NO:21的氨基酸序列,所述HVR-L3包含SEQ ID NO:34的氨基酸序列,所述HVR-H1包含SEQ ID NO:47的氨基酸序列,所述HVR-H2包含SEQ ID NO:60的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:73的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:10的氨基酸序列,所述HVR-L2包含SEQ ID NO:23的氨基酸序列,所述HVR-L3包含SEQ ID NO:36的氨基酸序列,所述HVR-H1包含SEQ ID NO:49的氨基酸序列,所述HVR-H2包含SEQ ID NO:62的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:75的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:11的氨基酸序列,所述HVR-L2包含SEQ ID NO:24的氨基酸序列,所述HVR-L3包含SEQ ID NO:37的氨基酸序列,所述HVR-H1包含SEQ ID NO:50的氨基酸序列,所述HVR-H2包含SEQ ID NO:63的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:76的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:12的氨基酸序列,所述HVR-

L2包含SEQ ID NO:25的氨基酸序列,所述HVR-L3包含SEQ ID NO:38的氨基酸序列,所述HVR-H1包含SEQ ID NO:51的氨基酸序列,所述HVR-H2包含SEQ ID NO:64的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:77的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:13的氨基酸序列,所述HVR-L2包含SEQ ID NO:26的氨基酸序列,所述HVR-L3包含SEQ ID NO:39的氨基酸序列,所述HVR-H1包含SEQ ID NO:52的氨基酸序列,所述HVR-H2包含SEQ ID NO:65的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:78的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:66的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:480的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:481的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:15的氨基酸序列,所述HVR-L2包含SEQ ID NO:28的氨基酸序列,所述HVR-L3包含SEQ ID NO:41的氨基酸序列,所述HVR-H1包含SEQ ID NO:54的氨基酸序列,所述HVR-H2包含SEQ ID NO:67的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:80的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:16的氨基酸序列,所述HVR-L2包含SEQ ID NO:29的氨基酸序列,所述HVR-L3包含SEQ ID NO:42的氨基酸序列,所述HVR-H1包含SEQ ID NO:55的氨基酸序列,所述HVR-H2包含SEQ ID NO:68的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:81的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:17的氨基酸序列,所述HVR-L2包含SEQ ID NO:30的氨基酸序列,所述HVR-L3包含SEQ ID NO:43的氨基酸序列,所述HVR-H1包含SEQ ID NO:56的氨基酸序列,所述HVR-H2包含SEQ ID NO:69的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:82的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:18的氨基酸序列,所述HVR-L2包含SEQ ID NO:31的氨基酸序列,所述HVR-L3包含SEQ ID NO:44的氨基酸序列,所述HVR-H1包含SEQ ID NO:57的氨基酸序列,所述HVR-H2包含SEQ ID NO:70的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:476的氨基酸序列,所述HVR-L2包含SEQ ID NO:477的氨基酸序列,所述HVR-L3包含SEQ ID NO:478的氨基酸序列,所述HVR-H1包含SEQ ID NO:57的氨基酸序列,所述HVR-H2包含SEQ ID NO:70的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:18的氨基酸序列,所述HVR-L2包含SEQ ID NO:31的氨基酸序列,所述HVR-L3包含SEQ ID NO:44的氨基酸序列,所述HVR-H1包含SEQ ID NO:479的

氨基酸序列,所述HVR-H2包含SEQ ID NO:482的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:483的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:19的氨基酸序列,所述HVR-L2包含SEQ ID NO:32的氨基酸序列,所述HVR-L3包含SEQ ID NO:45的氨基酸序列,所述HVR-H1包含SEQ ID NO:58的氨基酸序列,所述HVR-H2包含SEQ ID NO:71的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:84的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体包含轻链可变结构域和重链可变结构域,其中所述轻链可变结构域包含:(a)HVR-L1,其包含选自SEQ ID NO:7-19和476的氨基酸序列,或与选自SEQ ID NO:7-19和476的氨基酸序列具有至少约90%同源性的氨基酸序列;(b)HVR-L2,其包含选自SEQ ID NO:20-32和477的氨基酸序列,或与选自SEQ ID NO:20-32和477的氨基酸序列具有至少约90%同源性的氨基酸序列;以及(c)HVR-L3,其包含选自SEQ ID NO:33-45和478的氨基酸序列,或与选自SEQ ID NO:33-45和478的氨基酸序列具有至少约90%同源性的氨基酸序列;并且其中所述重链可变结构域包含:(a)HVR-H1,其包含选自SEQ ID NO:46-58和479的氨基酸序列,或与选自SEQ ID NO:46-58和479的氨基酸序列具有至少约90%同源性的氨基酸序列;(b)HVR-H2,其包含选自SEQ ID NO:59-71和480-482的氨基酸序列或与选自SEQ ID NO:59-71和480-482的氨基酸序列具有至少约90%同源性的氨基酸序列;以及(c)HVR-H3,其包含选自SEQ ID NO:72-84和483的氨基酸序列,或与选自SEQ ID NO:72-84和483的氨基酸序列具有至少约90%同源性的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含选自SEQ ID NO:189-318、449-461和484-489的氨基酸序列;和/或重链可变结构域,所述重链可变结构域包含选自SEQ ID NO:319-448、462-474和490-496的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体包含单克隆抗体的轻链可变结构域,所述单克隆抗体选自:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8;和/或单克隆抗体的重链可变结构域,所述单克隆抗体选自:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。

[0027] 本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体结合至SEQ ID NO:1的氨基酸残基39-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353内的一个或多个氨基酸;或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基39-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至选自由以下各项组成的组的氨基酸残基内的一个或多个氨基酸:i.SEQ ID NO:1的氨基酸残基60-69,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69的氨基酸残基;ii.SEQ ID NO:1的氨基酸残基60-69和84-95,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69和84-95的氨基酸残基;iii.SEQ ID NO:1的氨基酸残基60-69和117-127,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基60-69和117-127的氨基酸残基;iv.SEQ ID NO:1的氨基酸残基68-78,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基68-78的氨基酸残基;v.SEQ ID NO:1

的氨基酸残基84-95,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基84-95的氨基酸残基;vi.SEQ ID NO:1的氨基酸残基111-122,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基111-122的氨基酸残基;vii.SEQ ID NO:1的氨基酸残基111-122和282-291,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基111-122和282-291的氨基酸残基;viii.SEQ ID NO:1的氨基酸残基113-123,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基113-123的氨基酸残基;ix.SEQ ID NO:1的氨基酸残基113-125,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基113-125的氨基酸残基;x.SEQ ID NO:1的氨基酸残基117-127,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基117-127的氨基酸残基;以及xi.SEQ ID NO:1的氨基酸残基282-291,或哺乳动物Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基282-291的氨基酸残基。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和84-95的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和117-127的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基68-78内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基68-78的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基84-95的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122和282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122和282-291的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-123内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-123的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-125内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-125的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基117-127的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任

一项组合的一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基282-29的氨基酸残基内的一个或多个氨基酸。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体结合至一个或多个选自由以下各项组成的组的氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、I72、W74、N81、T103、K104、T107以及R124，或哺乳动物Siglec-7蛋白上对应于选自由以下各项组成的组的氨基酸残基的一个或多个氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、I72、W74、N81、T103、K104、T107以及R124。

[0028] 本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域和重链可变结构域，其中所述轻链可变结构域、所述重链可变结构域或两者包含至少一个、两个、三个、四个、五个或六个HVR，所述HVR选自单克隆抗体的HVR-L1、HVR-L2、HVR-L3、HVR-H1、HVR-H2以及HVR-H3，所述单克隆抗体选自:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。

[0029] 在可与前述实施方案中的任一项组合的一些实施方案中:(a)所述HVR-L1包含选自SEQ ID NO:7-19和476的氨基酸序列;(b)所述HVR-L2包含选自SEQ ID NO:20-32和477的氨基酸序列;(c)所述HVR-L3包含选自SEQ ID NO:33-45和478的氨基酸序列;(d)所述HVR-H1包含选自SEQ ID NO:46-58和479的氨基酸序列;(e)所述HVR-H2包含选自SEQ ID NO:59-71和480-482的氨基酸序列;或(f)所述HVR-H3包含选自SEQ ID NO:72-84和483的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中:(a)所述HVR-L1包含SEQ ID NO:7的氨基酸序列，所述HVR-L2包含SEQ ID NO:20的氨基酸序列，所述HVR-L3包含SEQ ID NO:33的氨基酸序列，所述HVR-H1包含SEQ ID NO:46的氨基酸序列，所述HVR-H2包含SEQ ID NO:59的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:72的氨基酸序列;(b)所述HVR-L1包含SEQ ID NO:8的氨基酸序列，所述HVR-L2包含SEQ ID NO:21的氨基酸序列，所述HVR-L3包含SEQ ID NO:34的氨基酸序列，所述HVR-H1包含SEQ ID NO:47的氨基酸序列，所述HVR-H2包含SEQ ID NO:60的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:73的氨基酸序列;(c)所述HVR-L1包含SEQ ID NO:9的氨基酸序列，所述HVR-L2包含SEQ ID NO:22的氨基酸序列，所述HVR-L3包含SEQ ID NO:35的氨基酸序列，所述HVR-H1包含SEQ ID NO:48的氨基酸序列，所述HVR-H2包含SEQ ID NO:61的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列;(d)所述HVR-L1包含SEQ ID NO:10的氨基酸序列，所述HVR-L2包含SEQ ID NO:23的氨基酸序列，所述HVR-L3包含SEQ ID NO:36的氨基酸序列，所述HVR-H1包含SEQ ID NO:49的氨基酸序列，所述HVR-H2包含SEQ ID NO:62的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:75的氨基酸序列;(e)所述HVR-L1包含SEQ ID NO:11的氨基酸序列，所述HVR-L2包含SEQ ID NO:24的氨基酸序列，所述HVR-L3包含SEQ ID NO:37的氨基酸序列，所述HVR-H1包含SEQ ID NO:50的氨基酸序列，所述HVR-H2包含SEQ ID NO:63的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:76的氨基酸序列;(f)所述HVR-L1包含SEQ ID NO:12的氨基酸序列，所述HVR-L2包含SEQ ID NO:25的氨基酸序列，所述HVR-L3包含SEQ ID NO:38的氨基酸序列，所述HVR-H1包含SEQ ID NO:51的氨基酸序列，所述HVR-H2包含SEQ ID NO:64的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:77的氨基酸序列;(g)所述HVR-L1包含SEQ ID NO:13的氨基酸序列，所述HVR-L2包含SEQ ID NO:26的氨基酸序列，所述HVR-L3包含SEQ ID NO:39的氨

基酸序列，所述HVR-H1包含SEQ ID NO:52的氨基酸序列，所述HVR-H2包含SEQ ID NO:65的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:78的氨基酸序列；(h)所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:66的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列；(i)所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:480的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列；(j)所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:481的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列；(k)所述HVR-L1包含SEQ ID NO:15的氨基酸序列，所述HVR-L2包含SEQ ID NO:28的氨基酸序列，所述HVR-L3包含SEQ ID NO:41的氨基酸序列，所述HVR-H1包含SEQ ID NO:54的氨基酸序列，所述HVR-H2包含SEQ ID NO:67的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:80的氨基酸序列；(l)所述HVR-L1包含SEQ ID NO:16的氨基酸序列，所述HVR-L2包含SEQ ID NO:29的氨基酸序列，所述HVR-L3包含SEQ ID NO:42的氨基酸序列，所述HVR-H1包含SEQ ID NO:55的氨基酸序列，所述HVR-H2包含SEQ ID NO:68的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:81的氨基酸序列；(m)所述HVR-L1包含SEQ ID NO:17的氨基酸序列，所述HVR-L2包含SEQ ID NO:30的氨基酸序列，所述HVR-L3包含SEQ ID NO:43的氨基酸序列，所述HVR-H1包含SEQ ID NO:56的氨基酸序列，所述HVR-H2包含SEQ ID NO:69的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:82的氨基酸序列；(n)所述HVR-L1包含SEQ ID NO:18的氨基酸序列，所述HVR-L2包含SEQ ID NO:31的氨基酸序列，所述HVR-L3包含SEQ ID NO:44的氨基酸序列，所述HVR-H1包含SEQ ID NO:57的氨基酸序列，所述HVR-H2包含SEQ ID NO:70的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列；(o)所述HVR-L1包含SEQ ID NO:476的氨基酸序列，所述HVR-L2包含SEQ ID NO:477的氨基酸序列，所述HVR-L3包含SEQ ID NO:478的氨基酸序列，所述HVR-H1包含SEQ ID NO:57的氨基酸序列，所述HVR-H2包含SEQ ID NO:70的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列；(p)所述HVR-L1包含SEQ ID NO:18的氨基酸序列，所述HVR-L2包含SEQ ID NO:31的氨基酸序列，所述HVR-L3包含SEQ ID NO:44的氨基酸序列，所述HVR-H1包含SEQ ID NO:479的氨基酸序列，所述HVR-H2包含SEQ ID NO:482的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:483的氨基酸序列；或(q)所述HVR-L1包含SEQ ID NO:19的氨基酸序列，所述HVR-L2包含SEQ ID NO:32的氨基酸序列，所述HVR-L3包含SEQ ID NO:45的氨基酸序列，所述HVR-H1包含SEQ ID NO:58的氨基酸序列，所述HVR-H2包含SEQ ID NO:71的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:84的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中，所述HVR-L1包含SEQ ID NO:7的氨基酸序列，所述HVR-L2包含SEQ ID NO:20的氨基酸序列，所述HVR-L3包含SEQ ID NO:33的氨基酸序列，所述HVR-H1包含SEQ ID NO:46的氨基酸序列，所述HVR-H2包含SEQ ID NO:59的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:72的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中，所述HVR-L1包含SEQ ID NO:8的氨基酸序列，所述HVR-L2包含SEQ ID NO:21的氨基酸序列，所述HVR-L3包含SEQ

ID NO:34的氨基酸序列,所述HVR-H1包含SEQ ID NO:47的氨基酸序列,所述HVR-H2包含SEQ ID NO:60的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:73的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:9的氨基酸序列,所述HVR-L2包含SEQ ID NO:22的氨基酸序列,所述HVR-L3包含SEQ ID NO:35的氨基酸序列,所述HVR-H1包含SEQ ID NO:48的氨基酸序列,所述HVR-H2包含SEQ ID NO:61的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:10的氨基酸序列,所述HVR-L2包含SEQ ID NO:23的氨基酸序列,所述HVR-L3包含SEQ ID NO:36的氨基酸序列,所述HVR-H1包含SEQ ID NO:49的氨基酸序列,所述HVR-H2包含SEQ ID NO:62的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:75的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:11的氨基酸序列,所述HVR-L2包含SEQ ID NO:24的氨基酸序列,所述HVR-L3包含SEQ ID NO:37的氨基酸序列,所述HVR-H1包含SEQ ID NO:50的氨基酸序列,所述HVR-H2包含SEQ ID NO:63的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:76的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:12的氨基酸序列,所述HVR-L2包含SEQ ID NO:25的氨基酸序列,所述HVR-L3包含SEQ ID NO:38的氨基酸序列,所述HVR-H1包含SEQ ID NO:51的氨基酸序列,所述HVR-H2包含SEQ ID NO:64的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:77的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:13的氨基酸序列,所述HVR-L2包含SEQ ID NO:26的氨基酸序列,所述HVR-L3包含SEQ ID NO:39的氨基酸序列,所述HVR-H1包含SEQ ID NO:52的氨基酸序列,所述HVR-H2包含SEQ ID NO:65的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:78的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:66的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:480的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:481的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:15的氨基酸序列,所述HVR-L2包含SEQ ID NO:28的氨基酸序列,所述HVR-L3包含SEQ ID NO:41的氨基酸序列,所述HVR-H1包含SEQ ID NO:54的氨基酸序列,所述HVR-H2包含SEQ ID NO:67的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:80的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中,所述HVR-L1包含SEQ ID NO:16的氨基酸序列,所述HVR-L2包含SEQ ID NO:29的氨基酸序列,所述HVR-L3包含SEQ ID NO:42的氨基酸序列,所述HVR-H1包含SEQ ID NO:55的氨基酸序列,所述HVR-H2包含SEQ ID NO:68的氨基酸序列,并且所述HVR-H3包

含SEQ ID NO:81的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中，所述HVR-L1包含SEQ ID NO:17的氨基酸序列，所述HVR-L2包含SEQ ID NO:30的氨基酸序列，所述HVR-L3包含SEQ ID NO:43的氨基酸序列，所述HVR-H1包含SEQ ID NO:56的氨基酸序列，所述HVR-H2包含SEQ ID NO:69的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:82的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中，所述HVR-L1包含SEQ ID NO:18的氨基酸序列，所述HVR-L2包含SEQ ID NO:31的氨基酸序列，所述HVR-L3包含SEQ ID NO:44的氨基酸序列，所述HVR-H1包含SEQ ID NO:57的氨基酸序列，所述HVR-H2包含SEQ ID NO:70的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中，所述HVR-L1包含SEQ ID NO:476的氨基酸序列，所述HVR-L2包含SEQ ID NO:477的氨基酸序列，所述HVR-L3包含SEQ ID NO:478的氨基酸序列，所述HVR-H1包含SEQ ID NO:57的氨基酸序列，所述HVR-H2包含SEQ ID NO:70的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中，所述HVR-L1包含SEQ ID NO:18的氨基酸序列，所述HVR-L2包含SEQ ID NO:31的氨基酸序列，所述HVR-L3包含SEQ ID NO:44的氨基酸序列，所述HVR-H1包含SEQ ID NO:479的氨基酸序列，所述HVR-H2包含SEQ ID NO:482的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:483的氨基酸序列。在可与前述实施方案中的任一项组合的一些实施方案中，所述HVR-L1包含SEQ ID NO:19的氨基酸序列，所述HVR-L2包含SEQ ID NO:32的氨基酸序列，所述HVR-L3包含SEQ ID NO:45的氨基酸序列，所述HVR-H1包含SEQ ID NO:58的氨基酸序列，所述HVR-H2包含SEQ ID NO:71的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:84的氨基酸序列。在一些实施方案中，所述轻链可变结构域包含：(a)HVR-L1，其包含选自SEQ ID NO:7-19和476的氨基酸序列，或与选自SEQ ID NO:7-19和476的氨基酸序列具有至少约90％同源性的氨基酸序列；(b)HVR-L2，其包含选自SEQ ID NO:20-32和477的氨基酸序列，或与选自SEQ ID NO:20-32和477的氨基酸序列具有至少约90％同源性的氨基酸序列；以及(c)HVR-L3，其包含选自SEQ ID NO:33-45和478的氨基酸序列，或与选自SEQ ID NO:33-45和478的氨基酸序列具有至少约90％同源性的氨基酸序列；并且其中所述重链可变结构域包含：(a)HVR-H1，其包含选自SEQ ID NO:46-58和479的氨基酸序列，或与选自SEQ ID NO:46-58和479的氨基酸序列具有至少约90％同源性的氨基酸序列；(b)HVR-H2，其包含选自SEQ ID NO:59-71和480-482的氨基酸序列，或与选自SEQ ID NO:59-71和480-482的氨基酸序列具有至少约90％同源性的氨基酸序列；以及(c)HVR-H3，其包含选自SEQ ID NO:72-84和483的氨基酸序列，或与选自SEQ ID NO:72-84和483的氨基酸序列具有至少约90％同源性的氨基酸序列。

[0030] 本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域，所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3；以及重链可变结构域，所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3，其中所述HVR-L1包含SEQ ID NO:7的氨基酸序列，所述HVR-L2包含SEQ ID NO:20的氨基酸序列，所述HVR-L3包含SEQ ID NO:33的氨基酸序列，所述HVR-H1包含SEQ ID NO:46的氨基酸序列，所述HVR-H2包含SEQ ID NO:59的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:72的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域，所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3；以及重链可变结构域，所述重链可变结

构域包含HVR-H1、HVR-H2和HVR-H3，其中所述HVR-L1包含SEQ ID NO:8的氨基酸序列，所述HVR-L2包含SEQ ID NO:21的氨基酸序列，所述HVR-L3包含SEQ ID NO:34的氨基酸序列，所述HVR-H1包含SEQ ID NO:47的氨基酸序列，所述HVR-H2包含SEQ ID NO:60的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:73的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域，所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3；以及重链可变结构域，所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3，其中所述HVR-L1包含SEQ ID NO:9的氨基酸序列，所述HVR-L2包含SEQ ID NO:22的氨基酸序列，所述HVR-L3包含SEQ ID NO:35的氨基酸序列，所述HVR-H1包含SEQ ID NO:48的氨基酸序列，所述HVR-H2包含SEQ ID NO:61的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域，所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3；以及重链可变结构域，所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3，其中所述HVR-L1包含SEQ ID NO:10的氨基酸序列，所述HVR-L2包含SEQ ID NO:23的氨基酸序列，所述HVR-L3包含SEQ ID NO:36的氨基酸序列，所述HVR-H1包含SEQ ID NO:49的氨基酸序列，所述HVR-H2包含SEQ ID NO:62的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:75的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域，所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3；以及重链可变结构域，所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3，其中所述HVR-L1包含SEQ ID NO:11的氨基酸序列，所述HVR-L2包含SEQ ID NO:24的氨基酸序列，所述HVR-L3包含SEQ ID NO:37的氨基酸序列，所述HVR-H1包含SEQ ID NO:50的氨基酸序列，所述HVR-H2包含SEQ ID NO:63的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:76的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域，所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3；以及重链可变结构域，所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3，其中所述HVR-L1包含SEQ ID NO:12的氨基酸序列，所述HVR-L2包含SEQ ID NO:25的氨基酸序列，所述HVR-L3包含SEQ ID NO:38的氨基酸序列，所述HVR-H1包含SEQ ID NO:51的氨基酸序列，所述HVR-H2包含SEQ ID NO:64的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:77的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域，所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3；以及重链可变结构域，所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3，其中所述HVR-L1包含SEQ ID NO:13的氨基酸序列，所述HVR-L2包含SEQ ID NO:26的氨基酸序列，所述HVR-L3包含SEQ ID NO:39的氨基酸序列，所述HVR-H1包含SEQ ID NO:52的氨基酸序列，所述HVR-H2包含SEQ ID NO:65的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:78的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体，其中所述抗Siglec-7抗体包含轻链可变结构域，所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3；以及重链可变结构域，所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3，其中所述HVR-L1包含SEQ ID NO:14的氨基酸序列，所述HVR-L2包含SEQ ID NO:27的氨基酸序列，所述HVR-L3包含SEQ ID NO:40的氨基酸序列，所述HVR-H1包含SEQ ID NO:53的氨基酸序列，所述HVR-H2包含SEQ ID NO:66的氨基酸序列，并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗

体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3;以及重链可变结构域,所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3,其中所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:480的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3;以及重链可变结构域,所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3,其中所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:481的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3;以及重链可变结构域,所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3,其中所述HVR-L1包含SEQ ID NO:15的氨基酸序列,所述HVR-L2包含SEQ ID NO:28的氨基酸序列,所述HVR-L3包含SEQ ID NO:41的氨基酸序列,所述HVR-H1包含SEQ ID NO:54的氨基酸序列,所述HVR-H2包含SEQ ID NO:67的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:80的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3;以及重链可变结构域,所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3,其中所述HVR-L1包含SEQ ID NO:16的氨基酸序列,所述HVR-L2包含SEQ ID NO:29的氨基酸序列,所述HVR-L3包含SEQ ID NO:42的氨基酸序列,所述HVR-H1包含SEQ ID NO:55的氨基酸序列,所述HVR-H2包含SEQ ID NO:68的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:81的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3;以及重链可变结构域,所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3,其中所述HVR-L1包含SEQ ID NO:17的氨基酸序列,所述HVR-L2包含SEQ ID NO:30的氨基酸序列,所述HVR-L3包含SEQ ID NO:43的氨基酸序列,所述HVR-H1包含SEQ ID NO:56的氨基酸序列,所述HVR-H2包含SEQ ID NO:69的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:82的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3;以及重链可变结构域,所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3,其中所述HVR-L1包含SEQ ID NO:18的氨基酸序列,所述HVR-L2包含SEQ ID NO:31的氨基酸序列,所述HVR-L3包含SEQ ID NO:44的氨基酸序列,所述HVR-H1包含SEQ ID NO:57的氨基酸序列,所述HVR-H2包含SEQ ID NO:70的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3;以及重链可变结构域,所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3,其中所述HVR-L1包含SEQ ID NO:476的氨基酸序列,所述HVR-L2包含SEQ ID NO:477的氨基酸序列,所述HVR-L3包含SEQ ID NO:478的氨基酸序列,所述HVR-H1包含SEQ ID NO:57的氨基酸序列,所述

HVR-H2包含SEQ ID NO:70的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3;以及重链可变结构域,所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3,其中所述HVR-L1包含SEQ ID NO:18的氨基酸序列,所述HVR-L2包含SEQ ID NO:31的氨基酸序列,所述HVR-L3包含SEQ ID NO:44的氨基酸序列,所述HVR-H1包含SEQ ID NO:479的氨基酸序列,所述HVR-H2包含SEQ ID NO:482的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:483的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含HVR-L1、HVR-L2和HVR-L3;以及重链可变结构域,所述重链可变结构域包含HVR-H1、HVR-H2和HVR-H3,其中所述HVR-L1包含SEQ ID NO:19的氨基酸序列,所述HVR-L2包含SEQ ID NO:32的氨基酸序列,所述HVR-L3包含SEQ ID NO:45的氨基酸序列,所述HVR-H1包含SEQ ID NO:58的氨基酸序列,所述HVR-H2包含SEQ ID NO:71的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:84的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域,所述轻链可变结构域包含选自SEQ ID NO:189-318、449-461和484-489的氨基酸序列;和/或重链可变结构域,所述重链可变结构域包含选自SEQ ID NO:319-448、462-474和490-496的氨基酸序列。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含单克隆抗体的轻链可变结构域,所述单克隆抗体选自:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8;和/或单克隆抗体的重链可变结构域,所述单克隆抗体选自:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体与选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的一种或多种抗体竞争结合至Siglec-7。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,所述抗Siglec-7抗体与选自以下的单克隆抗体结合基本相同的Siglec-7表位:1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8。本公开的其它方面涉及一种分离的单克隆抗Siglec-7抗体,其中所述抗Siglec-7抗体包含轻链可变结构域和重链可变结构域,其中所述轻链可变结构域包含:(a)HVR-L1,其包含选自SEQ ID NO:7-19和476的氨基酸序列,或与选自SEQ ID NO:7-19和476的氨基酸序列具有至少约90%同源性的氨基酸序列;(b)HVR-L2,其包含选自SEQ ID NO:20-32和477的氨基酸序列,或与选自SEQ ID NO:20-32和477的氨基酸序列具有至少约90%同源性的氨基酸序列;以及(c)HVR-L3,其包含选自SEQ ID NO:33-45和478的氨基酸序列,或与选自SEQ ID NO:33-45和478的氨基酸序列具有至少约90%同源性的氨基酸序列;和/或其中所述重链可变结构域包含:(a)HVR-H1,其包含选自SEQ ID NO:46-58和479的氨基酸序列,或与选自SEQ ID NO:46-58和479的氨基酸序列具有至少约90%同源性的氨基酸序列;(b)HVR-H2,其包含选自SEQ ID NO:59-71和480-482的氨基酸序列,或与选自SEQ ID NO:59-71和480-482的氨基酸序列具有至少约90%同源性的氨基酸序列;以及(c)HVR-H3,其包含选自SEQ ID NO:72-84和483的氨基酸序列,或与选自SEQ ID NO:72-84和483的氨基酸序列具有至少约90%同源性的氨基酸序列。

[0031] 在可与前述实施方案中的任一项组合的一些实施方案中，所述抗体具有IgG类、IgM类或IgA类。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体具有IgG1、IgG2、IgG3或IgG4同种型。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗体结合抑制性Fc受体。在可与前述实施方案中的任一项组合的一些实施方案中，所述抑制性Fc受体是抑制性Fc-γ受体IIB(FcγIIB)。在可与前述实施方案中的任一项组合的一些实施方案中：(a)所述抗Siglec-7抗体具有人或小鼠IgG1同种型，并且包含在Fc区中在选自以下的残基位置处的一种或多种氨基酸取代：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以及其任何组合，其中所述残基的编号根据EU或Kabat编号，或包含在Fc区中在对应于甘氨酸236的位置处的氨基酸缺失；(b)所述抗Siglec-7抗体具有IgG1同种型并且包含IgG2同种型重链恒定结构域1(CH1)和铰链区，任选地其中所述IgG2同种型CH1和铰链区包含ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVERKCCVECPPCP(SEQ ID NO:475)的氨基酸序列，并且任选地其中所述抗体Fc区包含S267E氨基酸取代、L328F氨基酸取代或两者，和/或N297A或N297Q氨基酸取代，其中所述残基的编号根据EU编号；(c)所述抗Siglec-7抗体具有IgG2同种型并且包含在Fc区中在选自以下的残基位置处的一种或多种氨基酸取代：P238S、V234A、G237A、H268A、H268Q、V309L、A330S、P331S、C214S、C232S、C233S、S267E、L328F、M252Y、S254T、T256E、H268E、N297A、N297Q、A330L以及其任何组合，其中所述残基的编号根据EU或Kabat编号；(d)所述抗Siglec-7抗体具有人或小鼠IgG4同种型并且包含在Fc区中在选自以下的残基位置处的一种或多种氨基酸取代：L235A、G237A、S228P、L236E、S267E、E318A、L328F、M252Y、S254T、T256E、E233P、F234V、L234A/F234A、S228P、S241P、L248E、T394D、N297A、N297Q、L235E以及其任何组合，其中所述残基的编号根据EU或Kabat编号；或(e)所述抗Siglec-7抗体具有杂合IgG2/4同种型，并且任选地其中所述抗体包含氨基酸序列，所述氨基酸序列包含人IgG2的氨基酸118至260和人IgG4的氨基酸261至447，其中所述残基的编号根据EU或Kabat编号。在可与前述实施方案中的任一项组合的一些实施方案中：(a)所述抗Siglec-7抗体具有人或小鼠IgG1同种型，并且包含在Fc区中在选自以下的残基位置处的一种或多种氨基酸取代：N297A、N297Q、D270A、D265A、L234A、L235A、C226S、C229S、P238S、E233P、L234V、P238A、A327Q、A327G、P329A、K322A、L234F、L235E、P331S、T394D、A330L、M252Y、S254T、T256E以及其任何组合，其中所述残基的编号根据EU或Kabat编号；(b)所述抗Siglec-7抗体具有IgG2同种型并且包含在Fc区中在选自以下的残基位置处的一种或多种氨基酸取代：P238S、V234A、G237A、H268A、H268Q、H268E、V309L、N297A、N297Q、A330S、P331S、C232S、C233S、M252Y、S254T、T256E以及其任何组合，其中所述残基的编号根据EU或Kabat编号；或(c)所述抗Siglec-7抗体具有IgG4同种型并且包含在Fc区中在选自以下的残基位置处的一种或多种氨基酸取代：E233P、F234V、L234A/F234A、L235A、G237A、E318A、S228P、L236E、S241P、L248E、T394D、M252Y、S254T、T256E、N297A、N297Q以及其任何组合，其中所述残基的编号根据EU或Kabat编号。在可与前述实施方案中的任一项组合的一些实施方案中：(a)所述Fc区还包含在选自A330L、L234F、L235E、P331S以及其任何组合的位置处的一种或多种另外的氨基酸取

代,其中所述残基的编号根据EU或Kabat编号;(b)所述Fc区还包含在选自M252Y、S254T、T256E以及其任何组合的位置处的一种或多种另外的氨基酸取代,其中所述残基的编号根据EU或Kabat编号;或(c)所述Fc区还包含根据EU或Kabat编号的S228P氨基酸取代。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗体具有IgG4同种型。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体包含在残基位置228处的S228P氨基酸取代,在残基位置234处的F234A氨基酸取代,以及在残基位置235处的L235A氨基酸取代,其中所述残基位置的编号根据EU编号。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗体具有IgG4同种型并且包含在残基位置228处的S228P氨基酸取代,在残基位置234处的F234A氨基酸取代,以及在残基位置235处的L235A氨基酸取代,其中所述残基位置的编号根据EU编号。在可与前述实施方案中的任一项组合的一些实施方案中,所述Siglec-7蛋白是哺乳动物蛋白或人蛋白。在可与前述实施方案中的任一项组合的一些实施方案中,所述Siglec-7蛋白是野生型蛋白。在可与前述实施方案中的任一项组合的一些实施方案中,所述Siglec-7蛋白是天然存在的变体。在可与前述实施方案中的任一项组合的一些实施方案中,所述Siglec-7蛋白在选自以下的一种或多种细胞上表达:人树突细胞、人巨噬细胞、人嗜中性粒细胞、人NK细胞、人单核细胞、人破骨细胞、人T细胞、人T辅助细胞、人细胞毒性T细胞、人粒细胞以及人小神经胶质细胞。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体特异性地结合至哺乳动物Siglec-7蛋白、人Siglec-7蛋白或两者。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体以pH依赖性方式结合Siglec-7。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体在5.5至8.0范围内的pH下结合Siglec-7。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体在小于5.0的pH下从Siglec-7解离。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体是结合至包含人Siglec-7或哺乳动物Siglec-7蛋白上的氨基酸残基的表位的抗体片段。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体是与选自以下的一种或多种人蛋白质结合的抗体片段:人Siglec-7、人Siglec-7的天然存在的变体和人Siglec-7的疾病变体。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗体片段与第二抗体片段交联,所述第二抗体片段与选自以下的一种或多种人蛋白质结合:人Siglec-7、人Siglec-7的天然存在的变体和人Siglec-7的疾病变体。在可与前述实施方案中的任一项组合的一些实施方案中,所述片段是Fab、Fab′、Fab′-SH、F(ab′)2、Fv或scFv片段。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体是鼠抗体。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体是人源化抗体、双特异性抗体、单克隆抗体、多价抗体、缀合抗体或嵌合抗体。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体是识别第一抗原和第二抗原的双特异性抗体。在可与前述实施方案中的任一项组合的一些实施方案中,所述第一抗原是Siglec-7,并且所述第二抗原是:(a)促进跨血脑屏障的转运的抗原;(b)选自以下的促进跨血脑屏障的转运的抗原:转铁蛋白受体(TR)、胰岛素受体(HIR)、胰岛素样生长因子受体(IGFR)、低密度脂蛋白受体相关蛋白1和2(LPR-1和2)、白喉毒素受体、CRM197、美洲驼单结构域抗体、TMEM 30(A)、蛋白质转导结构域、TAT、Syn-B、穿膜肽、聚精氨酸肽、血管肽以及ANG1005;(c)选自致病肽或蛋白或致病核酸的致病因子,其中所述致病核酸是反义GGCCCC

(G2C4)重复序列-扩增RNA,所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽;(d)在免疫细胞上表达的配体和/或蛋白质,其中所述配体和/或蛋白质选自PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG以及磷脂酰丝氨酸;以及(e)在一种或多种肿瘤细胞上表达的蛋白质、脂质、多糖或糖脂。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体是缀合抗体。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体缀合至可检测标记、毒素或治疗剂。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体缀合至选自以下的毒素:蓖麻毒素、蓖麻毒素A链、多柔比星、道诺霉素、类美登素、紫杉醇、溴化乙锭、丝裂霉素、依托泊苷、替尼泊苷、长春新碱、长春花碱、秋水仙碱、二羟基炭疽菌素二酮、放线菌素、白喉毒素、假单胞菌外毒素(PE)A、PE40、相思豆毒素、相思豆毒素A链、蒴莲根毒素A链、α-八叠球菌素、白树毒素、丝林霉素(mitogellin)、局限曲菌素(retstrictocin)、酚霉素、伊诺霉素、麻疯树逆境蛋白、巴豆毒素、加利车霉素、肥皂草抑制剂、糖皮质激素、奥瑞斯他汀、金霉素(auromycin)、钇、铋、康普瑞汀(combrestatin)、倍癌霉素(duocarmycins)、多拉司他汀、cc1065以及顺铂。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体与一种或多种特异性地结合致病因子的抗体组合使用,所述致病因子选自致病肽、致病蛋白、淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽,以及其任何组合;或与结合选自以下的免疫调节蛋白的一种或多种抗体组合使用:PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、TREM1、TREM2、CD33、Siglec-5、Siglec-9、Siglec-11、磷脂酰丝氨酸、致病核酸、反义GGCCCC(G2C4)重复序列-扩增RNA以及其任何组合。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体对于人Siglec-7和哺乳动物Siglec-7具有在约10nM至约10pM或小于

10pM范围内的解离常数(K_D)。在一些实施方案中,解离常数(K_D)在大约25℃的温度下测定。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体对于人Siglec-7具有在约9.5nM至约17pM或小于17pM范围内的解离常数(K_D)。在一些实施方案中,解离常数(K_D)在大约25℃的温度下测定。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体以在2nM至100pM范围内的EC_{50}结合至人树突细胞。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体以在1.4nM至300pM范围内的EC_{50}结合至人树突细胞。在一些实施方案中,结合至人树突细胞的EC_{50}在大约4℃的温度下测定。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体以在500pM至18pM范围内的EC_{50}降低Siglec-7的细胞水平。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体以在350pM至33pM范围内的EC_{50}降低Siglec-7的细胞水平。在一些实施方案中,EC_{50}在大约37℃的温度下测定。

[0032] 本公开的其它方面涉及一种分离的核酸,所述分离的核酸包含编码前述实施方案中的任一项的抗Siglec-7抗体的核酸序列。本公开的其它方面涉及一种载体,所述载体包含前述实施方案中的任一项的核酸。本公开的其它方面涉及一种分离的宿主细胞,所述宿主细胞包含前述实施方案种的任一项的载体。本公开的其它方面涉及一种产生抗Siglec-7抗体的方法,所述方法包括培养前述实施方案中的任一项的宿主细胞,以使得产生抗Siglec-7抗体。在一些实施方案中,所述方法还包括回收由所述宿主细胞产生的抗Siglec-7抗体。本公开的其它方面涉及一种通过前述实施方案中的任一项的方法产生的分离的抗Siglec-7抗体。本公开的其它方面涉及一种药物组合物,所述药物组合物包含前述实施方案中的任一项的抗Siglec-7抗体和药学上可接受的载体。

[0033] 本公开的其它方面涉及一种预防疾病、病症或损伤、降低疾病、病症或损伤的风险或治疗疾病、病症或损伤的方法,所述疾病、病症或损伤选自痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病和癌症、膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、表达一种或多种Siglec-7配体的肿瘤、甲状腺癌、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV以及流感嗜血杆菌,所述方法包括向有需要的个体施用治疗有效量的药剂,所述药剂降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者。在一些实

施方案中，所述癌症选自由以下各项组成的组：膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)以及多发性骨髓瘤。本公开的其它方面涉及一种用于预防疾病、病症或损伤、降低疾病、病症或损伤的风险或治疗疾病、病症或损伤的药剂，所述药剂降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者，所述疾病、病症或损伤选自痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病和癌症、膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、表达一种或多种Siglec-7配体的肿瘤、甲状腺癌、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV以及流感嗜血杆菌。本公开的其它方面涉及一种药剂在制造用于预防疾病、病症或损伤、降低疾病、病症或损伤的风险或治疗疾病、病症或损伤的药物中的用途，所述药剂降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者，所述疾病、病症或损伤选自痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病和癌症、膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、表达一种或多种Siglec-7配体的肿瘤、甲状腺癌、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感

染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV以及流感嗜血杆菌。在一些实施方案中，所述药剂选自抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、反义分子、siRNA、小分子抑制剂、蛋白质以及肽。在一些实施方案中，所述药剂是分离的抗Siglec-7抗体。在一些实施方案中，所述抗Siglec-7抗体是前述实施方案中的任一项的抗Siglec-7抗体。在一些实施方案中，所述一种或多种免疫细胞选自树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、小神经胶质细胞、T细胞、T辅助细胞、细胞毒性T细胞以及其任何组合。本公开的其它方面涉及一种预防疾病、病症或损伤、降低疾病、病症或损伤的风险或治疗疾病、病症或损伤的方法，所述疾病、病症或损伤选自痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、Tau蛋白病、感染以及癌症，所述方法包括向有需要的个体施用治疗有效量的降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者的药剂。本公开的其它方面涉及一种用于预防疾病、病症或损伤、降低疾病、病症或损伤的风险或治疗疾病、病症或损伤的药剂，所述药剂降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者，所述疾病、病症或损伤选自痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、Tau蛋白病、感染以及癌症。本公开的其它方面涉及一种药剂在制造用于预防疾病、病症或损伤、降低疾病、病症或损伤的风险或治疗疾病、病症或损伤的药物中的用途，所述药剂降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者，所述疾病、病症或损伤选自痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、Tau蛋白病、感染以及癌症。

[0034] 在可与前述实施方案中的任一项组合的一些实施方案中，所述疾病、病症或损伤是癌症，并且其中所述药剂抑制选自以下的一种或多种Siglec-7活性：(a)促进以下中的一种或多种的增殖、成熟、迁移、分化和/或功能性：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关抑制嗜中性粒细胞、肿瘤相关抑制NK细胞以及调控性T细胞；(b)增强以下中的一种或多种浸润到肿瘤中：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关抑制嗜中性粒细胞、肿瘤相关抑制NK细胞以及调控性T细胞；(c)增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量；(d)增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性；(e)增加肿瘤或外周血液中肿瘤促进细胞因子的表达，任选地其中所述肿瘤促进细胞因子是TGF-β或IL-10；(f)增加肿瘤促进FoxP3+调控性T淋巴细胞的肿瘤浸润；(g)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化；(h)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润；(i)减少具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润；(j)降低NK细胞的肿瘤杀伤潜力；(k)减少具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润；(l)增加肿瘤体积；(m)增加肿瘤生长速率；(n)增加转移；(o)增加肿瘤复发率；(p)降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效，任选地其中所述一种或多种免疫疗法是靶向一种或多种靶蛋白的免疫疗法，所述一种或多种靶蛋白选自PD1/PDL1、CTLA4、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5以及其任何组合；(q)抑制PLCγ/PKC/钙动员；以及(r)抑制PI3K/Akt、Ras/MAPK信号传导。在可与前述实施方案中的任一项组合的一些实

施方案中，所述癌症表达Siglec-7或一种或多种Siglec-7配体。在可与前述实施方案中的任一项组合的一些实施方案中，所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)以及多发性骨髓瘤。在可与前述实施方案中的任一项组合的一些实施方案中，所述药剂展示一种或多种选自由以下各项组成的组的活性：(a)增加肿瘤浸润$CD3^+$ T细胞的数量；(b)抑制Siglec-7与一种或多种Siglec-7配体的结合；(c)降低外周免疫细胞中Siglec-7的细胞水平；(d)减少非致瘤性$CD14^+$骨髓细胞的数量，任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞，或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于血液中；(e)减少非致瘤性$CD14^+$骨髓细胞的数量，任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞，或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于肿瘤中；(f)降低一种或多种细胞中的PD-L1水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(g)降低一种或多种细胞中的PD-L2水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(h)降低一种或多种细胞中的CD11b水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(i)降低一种或多种细胞中的B7-H3水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(j)降低一种或多种细胞中的CD200R水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(k)降低一种或多种细胞中的CD163水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(l)降低一种或多种细胞中的CD206水平，任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC)；(m)降低实体肿瘤的肿瘤生长速率；(n)减小肿瘤体积；(o)提高一种或多种PD-1抑制剂的功效；(p)提高一种或多种检查点抑制剂疗法和/或免疫调节疗法的功效，任选地其中所述一种或多种检查点抑制剂疗法和/或免疫调节疗法靶向以下中的一种或多种：CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3、LAG3或其任何组合；(q)抑制非致瘤性骨髓源性抑制细胞的(MDSC)分化、存活和/或一种或多种功能；(r)诱导一种或多种骨髓源性抑制细胞(MDSC)的细胞死亡；以及(s)在非致瘤性骨髓源性抑制细胞(MDSC)存在下增加T细胞的增殖。

[0035] 本公开的其它方面涉及一种诱导或促进有需要的个体中一种或多种免疫细胞的存活、成熟、功能性、迁移或增殖的方法，所述方法包括向所述个体施用治疗有效量的降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者的药剂。本公开的其它方面涉及一种用于诱导或促进有需要的个体中一种或多种免疫细胞的存活、成熟、功能性、迁移或增殖的药剂，所述药剂降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者。本公开的其它方面涉及一种药剂在制造用于诱导或促进有需要的个体中一种或多种免疫细胞的存活、成熟、功能性、迁移或增殖的药物中的用途，所述药剂降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者。在一些实施方案中，所述药剂选自抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、反义分子、siRNA、小分子抑制剂、蛋白质以及肽。在一些实施方案中，所述药剂是分离的抗Siglec-7抗体。在一些实施方案中，所述抗Siglec-7抗体是前述实施方案中的任一项的抗Siglec-7抗体。在一些实施方案中，所述一种或多种免疫细胞选自树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、小神经胶质细胞、T

细胞、T辅助细胞、细胞毒性T细胞以及其任何组合。

[0036] 本公开的其它方面涉及一种降低以下各项的活性、功能性或存活的方法：调控性T细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、急性骨髓性白血病(AML)细胞、慢性淋巴细胞性白血病(CLL)细胞或慢性骨髓性白血病(CML)细胞，所述方法包括向所述个体施用治疗有效量的与Siglec-7结合或相互作用的试剂。本公开的其它方面涉及一种药剂用于降低以下各项的活性、功能性或存活的用途，所述药剂与Siglec-7结合或相互作用：调控性T细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、急性骨髓性白血病(AML)细胞、慢性淋巴细胞性白血病(CLL)细胞或慢性骨髓性白血病(CML)细胞。本公开的其它方面涉及一种药剂在制造用于降低以下各项的活性、功能性或存活的药物中的用途，所述药剂与Siglec-7结合或相互作用：调控性T细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、急性骨髓性白血病(AML)细胞、慢性淋巴细胞性白血病(CLL)细胞或慢性骨髓性白血病(CML)细胞。在一些实施方案中，所述药剂是分离的抗Siglec-7抗体或抗Siglec-7抗体缀合物。在一些实施方案中，所述抗Siglec-7抗体是前述实施方案中的任一项的抗Siglec-7抗体。

[0037] 本公开的其它方面涉及一种降低有需要的个体中一种或多种细胞上的Siglec-7的细胞水平的方法，所述方法包括向所述个体施用治疗有效量的分离的抗Siglec-7抗体。本公开的其它方面涉及分离的抗Siglec-7抗体用于降低有需要的个体中一种或多种细胞上的Siglec-7的细胞水平的用途。本公开的其它方面涉及分离的抗Siglec-7抗体在制造用于降低有需要的个体中一种或多种细胞上的Siglec-7的细胞水平的药物中的用途。在一些实施方案中，所述抗Siglec-7抗体降低体内Siglec-7的细胞水平。在一些实施方案中，所述抗Siglec-7抗体以在500pM至18pM范围内的EC_{50}降低Siglec-7的细胞水平。在一些实施方案中，所述抗Siglec-7抗体以在350pM至33pM范围内的EC_{50}降低Siglec-7的细胞水平。在一些实施方案中，EC_{50}在大约37℃的温度下测定。在一些实施方案中，所述抗Siglec-7抗体对于人Siglec-7具有在约10nM至10pM或小于10pM范围内的解离常数(K_D)。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体对于人Siglec-7具有在约9.5nM至约17pM或小于17pM范围内的解离常数(K_D)。在一些实施方案中，解离常数(K_D)在大约25℃的温度下测定。在一些实施方案中，所述抗Siglec-7抗体以在2nM至100pM范围内的EC_{50}结合至人树突细胞。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体以在1.4nM至300pM范围内的EC_{50}结合至人树突细胞。在一些实施方案中，结合至人树突细胞的EC_{50}在大约4℃的温度下测定。在一些实施方案中，所述抗Siglec-7抗体是前述实施方案中的任一项的抗Siglec-7抗体。

[0038] 在可与前述实施方案中的任一项组合的一些实施方案中，所述方法还包括向所述个体施用至少一种特异性地结合至抑制性检查点分子的抗体，和/或一种或多种标准或研究性抗癌疗法。在可与前述实施方案中的任一项组合的一些实施方案中，所述至少一种特异性地结合至抑制性检查点分子的抗体与所述抗Siglec-7抗体组合施用。在可与前述实施方案中的任一项组合的一些实施方案中，所述至少一种特异性地结合至抑制性检查点分子的抗体选自抗PD-L1抗体、抗CTLA4抗体、抗PD-L2抗体、抗PD-1抗体、抗B7-H3抗体、抗B7-H4抗体和抗HVEM抗体、抗B-和T-淋巴细胞衰减子(BTLA)抗体、抗杀伤抑制性受体(KIR)抗体、

抗GAL9抗体、抗TIM3抗体、抗A2AR抗体、抗LAG-3抗体、抗磷脂酰丝氨酸抗体、抗CD27抗体、抗TNFa抗体、抗CD33抗体、抗Siglec-5抗体、抗Siglec-9抗体、抗Siglec-11抗体、拮抗性抗TREM1抗体、拮抗性抗TREM2抗体以及其任何组合。在可与前述实施方案中的任一项组合的一些实施方案中，所述一种或多种标准或研究性抗癌疗法选自放射疗法、细胞毒性化学疗法、靶向疗法、伊马替尼疗法、曲妥珠单抗疗法、依那西普疗法、过继细胞转移(ACT)疗法、嵌合抗原受体T细胞转移(CAR-T)疗法、疫苗疗法以及细胞因子疗法。在可与前述实施方案中的任一项组合的一些实施方案中，所述方法还包括向所述个体施用至少一种特异性地结合至抑制性细胞因子的抗体。在可与前述实施方案中的任一项组合的一些实施方案中，所述至少一种特异性地结合至抑制性细胞因子的抗体与所述抗Siglec-7抗体组合施用。在可与前述实施方案中的任一项组合的一些实施方案中，所述至少一种特异性地结合至抑制性细胞因子的抗体选自抗CCL2抗体、抗CSF-1抗体、抗IL-2抗体以及其任何组合。在可与前述实施方案中的任一项组合的一些实施方案中，所述方法还包括向所述个体施用至少一种特异性地结合至刺激性检查点蛋白的激动性抗体。在可与前述实施方案中的任一项组合的一些实施方案中，所述至少一种特异性地结合至刺激性检查点蛋白的激动性抗体与所述抗Siglec-7抗体组合施用。在可与前述实施方案中的任一项组合的一些实施方案中，所述至少一种特异性地结合至刺激性检查点蛋白的激动性抗体选自激动剂抗CD40抗体、激动剂抗OX40抗体、激动剂抗ICOS抗体、激动剂抗CD28抗体、激动性抗TREM1抗体、激动性抗TREM2抗体、激动剂抗CD137/4-1BB抗体、激动剂抗CD27抗体、激动剂抗糖皮质激素诱导的TNFR相关蛋白GITR抗体以及其任何组合。在可与前述实施方案中的任一项组合的一些实施方案中，所述方法还包括向所述个体施用至少一种刺激下细胞因子。在可与前述实施方案中的任一项组合的一些实施方案中，所述至少一种刺激细胞因子与所述抗Siglec-7抗体组合施用。在可与前述实施方案中的任一项组合的一些实施方案中，所述至少一种刺激性细胞因子选自IFN-a4、IFN-b、IL-1β、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-23、CXCL10、IL-33、MCP-1、MIP-1-β以及其任何组合。

[0039] 本公开的其它方面涉及一种评估个体对与Siglec-7结合或相互作用的药剂的应答性的方法，所述方法包括：a)测量在向所述个体施用与Siglec-7结合或相互作用的药剂之前从所述个体获得的血液样品中非致瘤性骨髓细胞上$CD45^+$和$CD14^+$的表达水平；b)向所述个体施用治疗有效量的所述药剂；以及c)测量在施用所述药剂后从所述个体获得的血液样品中非致瘤性骨髓细胞上$CD45^+$和$CD14^+$的表达水平。在一些实施方案中，在施用与Siglec-7结合或相互作用的药剂后，非致瘤性骨髓细胞上$CD45^+$和$CD14^+$的水平降低表明所述个体对所述药剂应答。在一些实施方案中，所述方法还包括施用一种或多种另外的治疗有效量的所述药剂。在一些实施方案中，所述药剂选自由以下各项组成的组：抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、反义分子、siRNA、小分子抑制剂、蛋白质以及肽。在一些实施方案中，所述药剂是分离的抗Siglec-7抗体或抗Siglec-7抗体-缀合物。在一些实施方案中，所述抗Siglec-7抗体是本文公开的抗Siglec-7抗体中的任一种。

[0040] 附图简述

[0041] 图1A描绘人Siglec-7(SEQ ID NO:1)、普通黑猩猩Siglec-7(SEQ ID NO:2)、矮小

黑猩猩Siglec-7(SEQ ID NO:3)、猩猩Siglec-7(SEQ ID NO:4)、大猩猩Siglec-7(SEQ ID NO:5)以及长臂猿Siglec-7(SEQ ID NO:6)之间的氨基酸序列比对。星号(“*”)表示具有单个完全保守的残基的位置;冒号(“:”)表示具有强相似性质的组之间的保守性-在Gonnet PAM 250矩阵中得分＞0.5;并且句点(“.”)表示具有弱相似性质的组之间的保守性-在Gonnet PAM 250矩阵中得分＝＜0.5。图1B描绘Siglec-7的3D结构。草图中描绘了SEQ ID NO:1的Siglec-7氨基酸序列的氨基酸残基19-150。还描绘了抗体4A1的表位的草图呈现。图中列出了结合区^{113}ARMSDAGRYFFRM^{125}(SEQ ID NO:1)。Siglec-7的蛋白质表面显示为网状。

[0042] 图1C描绘抗体2G4、3E11、10B5、2G1和7F12的不连续表位的结合位点的草图呈现。在图中列出了不连续结合区^{60}PVHGYWFRAG^{69}(SEQ ID NO:1)和^{117}DAGRYFFRMEK^{127}(SEQ ID NO:1)。图1D描绘抗体10G8、抗体2G4、3E11、10B5、2G1和7F12的不连续表位的结合位点的草图呈现。在图中列出了不连续结合区^{60}PVHGYWFRAG^{69}(SEQ ID NO:1)和^{84}AWAVQEETRDRF^{95}(SEQ ID NO:1)。图1E描绘了抗体4A1的表位的草图呈现。图中列出了结合区^{113}ARMSDAGRYFFRM^{125}(SEQ ID NO:1)。还描绘了抗体7E11的构象表位的结合位点。图中列出了结合区^{68}AGNDISWKAPV^{78}(SEQ ID NO:1)。图1F描绘了本公开的抗体的野生型Siglec-7(%WT)与所示Siglec-7突变体的结合反应性(百分比)。图1G描绘指示参与抗体结合的氨基酸残基的Sigdec-7的模型。用于结合的关键残基用红球表示;用于结合的二级残基用粉球表示。

[0043] 图2示出人Siglec蛋白如Siglec-7的聚糖结合特异性。此图示出最常被研究的唾液酸化聚糖的最常报道的特异性的总结。在每种Siglec的研究内的相对结合被表示为++,强结合;+,可检测的结合;以及-,非常弱或不可检测的结合。未示出最近报道的hSiglec-8和mSiglec-F对6′-硫酸化-唾液酸-路易斯x(sLex)以及hSiglec-9对6-硫酸化-sLex的强结合偏好。除少数例外情况(CD22和MAG)外,不同研究者使用不同测定对人Siglec进行的结合特异性研究的结果显著不同。除了测定形式和聚糖接头问题之外,所研究的配体的密度和排列可能是造成这种变化的原因(Varki等人,(2006)Glycobiol.16:1R-27R)。

[0044] 图3示出哺乳动物脑中的双唾液酸神经节苷脂的结构和代谢。所述图中的双唾液酸神经节苷脂的命名遵循Svennerholm(1964)J.Lipid Res.5:145-155(Ariga T等人(2008)J.Lipid Res.49:1157-1175)的系统。

[0045] 图4描绘显示人原代免疫细胞中的Siglec-7表达的FACS分析的结果。

[0046] 图5A描绘与同种型对照相比,Siglec-7抗体与人原代树突细胞的结合的FACS分析。图5B描绘评估结合的12点滴定曲线,并计算Siglec-7抗体4E3和10B5与原代人树突细胞的表面的结合的半最大有效浓度值(EC_{50})。

[0047] 图6A描绘示出本公开的Siglec-7抗体与纯化的Siglec-7-his标记的蛋白的结合亲和力的Biacore传感图。图6B示出用于组合抗Siglec-7抗体4E3(mAb S7-4E3)的人源化型式的抗体轻链可变区(VL)序列的示意图。在每个序列下方列出了另外的变体。所述图包括人源化抗体4E3的型式的序列。IGKV3-11*01(SEQ ID NO:497);连接区(SEQ ID NO:498);S7-4E3(SEQ ID NO:499);3-11*01(SEQ ID NO:500);h4E3-L1(SEQ ID NO:501);h4E3-L2(SEQ ID NO:502);h4E3-L3(SEQ ID NO:503)。图6C示出用于组合抗Siglec-7抗体4E3(mAb S7-4E3)的人源化型式的抗体重链可变区(VH)序列的示意图。在每个序列下方列出了另外的变体。所述图包括人源化抗体4E3的型式的序列。IGHV3-21*01(SEQ ID NO:504);连接区(SEQ ID NO:505);S7-4E3(SEQ ID NO:506);3-21*01(SEQ ID NO:507);h4E3-H1(SEQ ID

NO:508);h4E3-H2(SEQ ID NO:509);h4E3-H3(SEQ ID NO:510)。图6D示出用于组合抗Siglec-7抗体10B5(mAb S7-10B5)的人源化型式的抗体轻链可变区(VL)序列的示意图。在每个序列下方列出了另外的变体。所述图包括人源化抗体10B5的型式的序列。IGKV1-39*01(SEQ ID NO:511);连接区(SEQ ID NO:512);S7-10B5.1(SEQ ID NO:513);1-39*01(SEQ ID NO:514);h10B5-L1(SEQ ID NO:515);h10B5-L2(SEQ ID NO:516);h10B5-L3(SEQ ID NO:517)。图6E示出用于组合抗Siglec-7抗体10B5(mAb S7-10B5)的人源化型式的抗体重链可变区(VH)序列的示意图。在每个序列下方列出了另外的变体。所述图包括人源化抗体10B5的型式的序列。IGHV1-46*01(SEQ ID NO:518);连接区(SEQ ID NO:519);S7-10B5.1(SEQ ID NO:520);1-46*01(SEQ ID NO:521);h10B5-H1(SEQ ID NO:522);h10B5-H2(SEQ ID NO:523);h10B5-H3(SEQ ID NO:524);h10B5-H4(SEQ ID NO:525)。对于图6B-6E,CDR序列以粗体描绘;残基编号显示为顺序的(seq)或根据Chothia;“b”是指隐藏的侧链;“p”是指部分隐藏;“i”是指在VH与VL结构域之间的界面处的侧链;星号(*)表示人与鼠种系之间的序列差异;在序列下方标出框架中的潜在额外突变;CDR序列中的潜在变化在每个CDR序列下方标出(此类变化可防止天冬酰胺(N)脱酰胺,色氨酸(W)氧化或异天冬氨酸(DG)形成)。

[0048] 图7A-7N描绘在体外和体内细胞表面Siglec-7受体的抗体依赖性下调。图7A描绘U937组织细胞淋巴瘤。图7B描绘人原代单核细胞。图7C描绘人原代树突细胞。图7D描绘人原代巨噬细胞。图7E描绘人原代天然杀伤(NK)细胞。图7F描绘人原代单核细胞源性的小神经胶质细胞。图7G描绘与无抗体对照相比,用抗Siglec-7抗体10B5或同种型对照抗体处理后人树突细胞上Siglec-7表面表达和TREM2表面表达的水平。图7H描绘在用抗Siglec-7抗体10B5处理后人树突细胞上CD11c表面表达、Siglec-7表面表达和TREM2表面表达的水平。图7I描绘在用本公开的抗Siglec-7抗体处理14天后来自人源化NOG小鼠的外周血样品中的Siglec-7和CD33表达。图7J示出在体内抗体处理后Siglec-7的细胞表面水平的体内降低。图7K示出不相关的受体CD33的表达。使用CD33作为对照。在体内抗体处理后,CD33的细胞表面水平未显著降低。图7L示出在用本公开的抗Siglec-7抗体处理14天后来自人源化NOG小鼠的血液样品的FACS门控策略。图7M描绘12点滴定曲线,其示出用于降低Siglec-7的细胞表面表达的Siglec-7抗体4E3和10B5的半最大有效浓度(EC_{50})。图7N描绘12点滴定曲线,其示出用于降低CD11c的细胞表面表达的Siglec-7抗体4E3和10B5的半最大有效浓度(EC_{50})。

[0049] 图8描绘证明本公开的Siglec-7抗体能够阻断在红细胞上表达的Siglec-7配体与板固定的Siglec-7-Fc蛋白的结合的结果。

[0050] 图9描绘FACS分析,其显示树突细胞上的唾液酸配体在与人原代细胞的混合淋巴细胞反应期间限制T细胞增殖。

[0051] 图10描绘显示树突细胞上的唾液酸Siglec-7配体在混合淋巴细胞反应期间限制T细胞增殖。

[0052] 图11A-11H描绘显示由各种刺激诱导的人骨髓细胞上的Siglec-7受体和增加的Siglec-7配体表达的结果。图11A和11B描绘显示在用肿瘤上清液处理后人原代树突细胞上的Siglec-7受体和增加的Siglec-7配体表达的结果。图11C和11D描绘显示在用肿瘤上清液处理后人原代树突细胞上的增加的Siglec-7配体表达的结果。图11E和11F描绘显示在LPS诱导的炎症过程中人树突细胞上Siglec-7受体表达的结果。图11G和11H描绘显示在LPS诱导的炎症过程中人骨髓细胞上唾液酸表达增加的结果。这些发现表明肿瘤可通过上调肿瘤

细胞和免疫细胞上针对Siglec-7的抑制性配体的水平来逃避免疫监视。

[0053] 图12描绘显示唾液酸酶处理以从大肠杆菌除去Siglec-7配体增加人原代树突细胞的吞噬的结果。

[0054] 图13A和13B描绘来自阿尔茨海默氏病脑(AD)和健康脑(非AD)的脑切片中的Siglec-7配体表达。图13A描绘来自两个供体(供体1和供体2)的AD和非AD脑样品中Siglec-7-Fc的免疫组织化学染色。图13B描绘来自5个AD和5个非AD脑样品的Siglec-7-Fc染色的单向ANOVA统计分析的结果,从而表明抑制性Siglec-7配体上调并促成AD病理学。

[0055] 图14描绘显示抑制性Siglec-7配体的表达在肺肿瘤细胞、黑色素瘤细胞和结肠癌细胞中增加的结果。所述结果表明抑制性Siglec-7配体在这些肿瘤类型中促成癌症病理学。

[0056] 图15描绘注射人外周血细胞的NOG小鼠细胞中Siglec-7的表达。在植入人胚胎肝$CD34^+$细胞12周后,将人源化小鼠移植患者来源的黑色素瘤。分离外周血、脾和肿瘤组织并分析免疫细胞标志物和Siglec-7表达。对于FACS分析,通过CD45表达、然后门控CD14+、CD3+群体鉴定人造血细胞。所述结果表明抑制性Siglec-7配体在这种肿瘤类型中促成癌症病理学。

[0057] 图16A描绘用于免疫人源化小鼠中患者来源的癌症的小鼠模型的PD-1/Siglec-7组合抗体治疗方案。图16B描绘移植人免疫干细胞的个体小鼠中在抗体处理后的肿瘤体积。将小鼠用单独或与抗Siglec-7抗体10B5组合的Keytruda®(派姆单抗)抗PD-1抗体处理。图16C描绘在移植人免疫干细胞的小鼠中用单独或与抗Siglec-7抗体10B5组合的Keytruda®(派姆单抗)抗PD-1抗体处理28天后的平均肿瘤体积。对于Keytruda®(派姆单抗)+10B5对Keytruda®(派姆单抗),*:$p<0.05$;**:$p<0.01$;***:$p<0.001$。呈现每个处理组的平均值误差棒代表SEM。图16D描绘在移植来自人供体984480112的人免疫干细胞的小鼠中用单独或与抗Siglec-7抗体10B5组合的Keytruda®(派姆单抗)抗PD-1抗体处理28天后的平均肿瘤体积。呈现每个处理组的平均值误差棒代表SEM。图16E描绘在移植来自人供体165547112或17509112的人免疫干细胞的小鼠中用单独或与抗Siglec-7抗体10B5组合的Keytruda®(派姆单抗)抗PD-1抗体处理28天后的平均肿瘤体积。对于Keytruda®(派姆单抗)+10B5对Keytruda®(派姆单抗),**:$p<0.01$。呈现每个处理组的平均值误差棒代表SEM。图16F描绘来自用单独或与抗Siglec-7抗体10B5组合的Keytruda®(派姆单抗)抗PD-1抗体处理的小鼠的外周血人(h)$CD45^+CD14^+$骨髓细胞中Siglec-7的细胞表面水平的体内降低。对于Keytruda®(派姆单抗)+10B5对Keytruda®(派姆单抗),***:$p<0.001$,从而校正供体和动物处死日。+:平均值;箱形图中线:中值;框的上下边界对应于第一和第三四分位数(第25和第75百分位数)。图16G描绘来自用单独或与抗Siglec-7抗体10B5组合的Keytruda®(派姆单抗)抗PD-1抗体处理的小鼠的肿瘤浸润人(h)$CD45^+CD14^+$骨髓细胞中的体内降低。对于Keytruda®(派姆单抗)+10B5对Keytruda®(派姆单抗),***:$p<0.001$,从而针对供体校正。+:平均值;箱形图中线:中值;框的上下边界对应于第一和第三四分位数(第25和第75百分位数)。图16H描绘来自用单独或与抗Siglec-7抗体10B5组合的Keytruda®(派姆单抗)抗PD-1抗体处理的小鼠的肿瘤浸润人(h)$CD45^+$ $CD3^+$ T细胞中的体

内增加。对于Keytruda®(派姆单抗)+10B5对Keytruda®(派姆单抗),***:p<0.001,从而针对供体校正。+:平均值;箱形图中线:中值;框的上下边界对应于第一和第三四分位数(第25和第75百分位数)。图16I描绘来自用单独或与抗Siglec-7抗体10B5组合的Keytruda®(派姆单抗)抗PD-1抗体处理的小鼠的外周血人(h)$CD45^+CD14^+$骨髓细胞中的体内降低。对于Keytruda®(派姆单抗)+10B5对Keytruda®(派姆单抗),**:p<0.01,从而针对供体校正。+:平均值;箱形图中线:中值;框的上下边界对应于第一和第三四分位数(第25和第75百分位数)。

[0058] 图17A描绘通过与用抗Siglec-7抗体10B5处理的细胞相比,用同种型对照抗体(mIgG1)处理的骨髓来源的抑制细胞(MDSC)之间PD-L1、PD-L2、CD200R、B7-H3、Siglec-7和CD206的平均荧光强度(MFI)量化的表达的变化。图17B描绘通过与用抗Siglec-7抗体4E3处理的细胞相比,用同种型对照抗体(mIgG1)处理的骨髓来源的抑制细胞(MDSC)之间CD200R、CD163、PD-L2、B7-H3、PD-L1、CD11b和Siglec-7的平均荧光强度(MFI)量化的表达的变化。图17C描绘在不存在和存在共培养的骨髓来源的抑制细胞(MDSC)的情况下活化的T细胞增殖的百分比。另外,共培养的T细胞/MDSC不进行处理,或用抗Siglec-7抗体4E3、小鼠同种型对照抗体(mIgG1)或抗PD-L1抗体(PDL1)处理。****:p<0.00001。图17D描绘在不存在和存在共培养的骨髓来源的抑制细胞(MDSC)的情况下培养的用成胶质细胞瘤条件培养基处理的T细胞的活化的T细胞增殖的百分比。另外,共培养的T细胞/MDSC不进行处理,或用抗Siglec-7抗体4E3、小鼠同种型对照抗体(mIgG1)或抗PD-L1抗体(PDL1)处理。**:p<0.01;***:p<0.001。

[0059] 图18描绘显示抗Siglec-7抗体4E3和10B5选择性杀死骨髓来源的抑制细胞(MDSC)的子集的结果。顶行:细胞形态的活门/死门:使用S7-4E3和S7-10B5死细胞门的增加。中间行:使用染色对活/死细胞进行门控:染色高阳性细胞是死亡,染色低细胞是存活。直方图:以直方图格式显示活/死细胞染色。

[0060] 发明详述

[0061] 一般技术

[0062] 本文描述或引用的技术和程序通常被本领域技术人员熟知并且通常使用常规方法学来采用,例如像描述于以下中的广泛使用的方法:Sambrook等人,Molecular Cloning:A Laboratory Manual第3版(2001)Cold Spring Harbor Laboratory Press,Cold Spring Harbor,N.Y.;Current Protocols in Molecular Biology(F.M.Ausubel,等人编,(2003));系列Methods in Enzymology(Academic Press,Inc.):PCR 2:A Practical Approach(M.J.MacPherson,B.D.Hames和G.R.Taylor编(1995)),Harlow和Lane,编(1988)Antibodies,A Laboratory Manual,和Animal Cell Culture(R.I.Freshney,编(1987));Oligonucleotide Synthesis(M.J.Gait,编,1984);Methods in Molecular Biology,Humana Press;Cell Biology:A Laboratory Notebook(J.E.Cellis,编,1998)Academic Press;Animal Cell Culture(R.I.Freshney),编,1987);Introduction to Cell and Tissue Culture(J.P.Mather和P.E.Roberts,1998)Plenum Press;Cell and Tissue Culture:Laboratory Procedures (A.Doyle,J.B.Griffiths,和D.G.Newell,编,1993-8)J.Wiley和Sons;Handbook of Experimental Immunology(D.M.Weir和C.C.Blackwell,

编);Gene Transfer Vectors for Mammalian Cells(J.M.Miller和M.P.Calos,编,1987);PCR:The Polymerase Chain Reaction,(Mullis等人,编,1994);Current Protocols in Immunology(J.E.Coligan等人,编,1991);Short Protocols in Molecular Biology(Wiley和Sons,1999);Immunobiology(C.A.Janeway和P.Travers,1997);Antibodies(P.Finch,1997);Antibodies:A Practical Approach(D.Catty.,编,IRL Press,1988-1989);Monoclonal Antibodies:A Practical Approach(P.Shepherd和C.Dean,编,Oxford University Press,2000);Using Antibodies:A Laboratory Manual(E.Harlow和D.Lane(Cold Spring Harbor Laboratory Press,1999);The Antibodies(M.Zanetti和J.D.Capra,编,Harwood Academic Publishers,1995);以及Cancer:Principles and Practice of Oncology(V.T.DeVita等人,编,J.B.Lippincott Company,1993)。

[0063] 定义

[0064] 如本文所用,术语“预防”包括关于个体的特定疾病、病症或病况的发生或复发提供预防。个体可能易患、易感特定疾病、病症或病况,或处于发展这种疾病、病症或病况的风险中,但尚未被诊断患有所述疾病、病症或病况。

[0065] 如本文所用,处于发展特定疾病、病症或病况的“风险”的个体在本文描述的治疗方法之前可能具有或可能不具有可检测到的疾病或疾病症状,并且可能已显示或可能未显示可检测到的疾病或疾病症状。“处于风险”表示个体具有一种或多种风险因素,所述风险因素是如本领域中所已知与特定疾病、病症或病况的发展有关的可测量的参数。与没有这些风险因素中的一种或多种的个体相比,具有这些风险因素中的一种或多种的个体发展特定疾病、病症或病况的可能性更高。

[0066] 如本文所用,术语“治疗”是指设计用来在临床病理学过程中改变所治疗的个体的天然过程的临床介入。治疗的合意作用包括降低特定疾病、病症或病况的进展速率、改善或缓解特定疾病、病症或病况的病理状态以及缓和或改善特定疾病、病症或病况的预后。例如当与特定疾病、病症或病况相关的一种或多种症状得到减轻或消除时,个体得到成功“治疗”。

[0067] “有效量”是指在必需剂量下且持续必需的时期,至少有效实现所需治疗或预防结果的量。有效量可在一次或多次施用中提供。本文的有效量可根据多种因素而不同,如个体的疾病状态、年龄、性别以及重量和治疗在个体体内引发所希望的应答的能力。有效量还是其中治疗有益作用超过治疗的任何毒性或有害作用的量。对于预防性用途,有利或所需的结果包括诸如以下的结果:消除或减少风险、减轻严重性或延缓疾病(包括所述疾病的生物化学的、组织学的和/或行为的症状、在所述疾病发展期间存在的所述疾病的并发症和中间病理表型)的发作。对于治疗性用途,有利或所需的结果包括诸如以下的临床结果:减少由疾病引起的一种或多种症状、提高患有疾病的患者的生活质量、减少治疗疾病所需的其它药物的剂量、诸如通过靶向来增强另一种药物的作用、延缓疾病进展和/或延长存活。药物、化合物或药物组合物的有效量是足以直接地或间接地完成预防性或治疗性治疗的量。在临床背景中所理解的是,与另一种药物、化合物或药物组合物结合,药物、化合物或药物组合物的有效量可以或可以不实现。因此,可认为“有效量”处于施用一种或多种治疗剂的背景中,并且如果与一种或多种其它药剂结合可实现或实现了理想结果,那么可认为单一药剂是以有效量给予的。

[0068] “治疗有效量”是实现特定病症、病症或病况的可测量的改善所需要的至少最低浓度。本文中的治疗有效量可根据以下因素而变化，如患者的疾病状态、年龄、性别和重量以及Siglec-7蛋白拮抗剂在个体体内引发所需应答的能力。治疗有效量还是治疗有益作用胜过Siglec-7蛋白拮抗剂的任何毒性或有害作用的量。

[0069] 如本文所用，与另一种化合物或组合物“联合”施用包括同时施用和/或在不同时间施用。联合施用还包括作为共同制剂施用或作为独立组合物施用，包括以不同的给药频率或间隔并且使用相同的施用途径或不同的施用途径。

[0070] 出于治疗、预防或降低风险目的的“个体”是指被归类为哺乳动物的任何动物，包括人、家养动物和农场动物，以及动物园动物、运动动物或宠物动物，如狗、马、兔、牛、猪、仓鼠、沙鼠、小鼠、雪貂、大鼠、猫等。优选地，所述个体是人。

[0071] 术语“免疫球蛋白”(Ig)在本文中可与“抗体”互换使用。本文中的术语“抗体”是广义上使用的并且特定地涵盖单克隆抗体、多克隆抗体、由至少两种完整的抗体形成的多特异性抗体(例如，双特异性抗体)和抗体片段，只要它们展示所需的生物活性。

[0072] 基本的4链抗体单元是主要由两条相同的轻(L)链和两条相同的重(H)链组成的异四聚糖蛋白。V_H和V_L的配对一起形成单一抗原结合位点。关于不同类别的抗体的结构和性质，参见例如，Basic and Clinical Immunology，第8版，Daniel P.Stites，Abba I.Terr和Tristram G.Parslow(编)，Appleton&Lange，Norwalk，CT，1994，第71页和第6章。

[0073] 来自任何脊椎动物物种的L链可基于其恒定结构域的氨基酸序列指定为两种明显不同类型(称为卡帕(“κ”)和拉姆达(“λ”))中的一者。取决于其重链的恒定结构域(CH)的氨基酸序列，免疫球蛋白可归属于不同的类别或同种型。存在五种类别的免疫球蛋白：IgA、IgD、IgE、IgG和IgM，其分别具有指定为阿尔法(“α”)、德尔塔(“δ”)、艾普斯龙(“ε”)、伽马(“γ”)和缪(“μ”)的重链。基于CH序列和功能的相对小的差异，γ和α类别被进一步分成亚类(同种型)，例如，人表达以下亚类：IgG1、IgG2、IgG3、IgG4、IgA1和IgA2。不同类别的免疫球蛋白的亚基结构和三维构型是众所周知的，并且通常描述于例如Abbas等人，Cellular and Molecular Immunology，第4版(W.B.Saunders Co.，2000)中。

[0074] 天然抗体通常是约150,000道尔顿的异四聚体糖蛋白，由两条相同的轻(L)链和两条相同的重(H)链组成。每条轻链都借助一个共价二硫键连接到一条重链，但不同免疫球蛋白同种型的重链中二硫键链的数量不同。每条重链和轻链还具有规律性间隔的链内二硫桥。每条重链在一端具有一个可变结构域(V_H)，之后跟随多个恒定结构域。每条轻链在一端具有一个可变结构域(V_L)并且在另一端具有一个恒定结构域；轻链的恒定结构域与重链的第一恒定结构域对准，并且轻链的可变结构域与重链的可变结构域对准。据悉，具体的氨基酸残基形成了轻链可变结构域与重链可变结构域之间的界面。

[0075] “分离的”抗体(如本公开的抗Siglec-7抗体)是已经从其生产环境的组分(例如，天然或重组地)鉴定、分离和/或回收的抗体。优选地，分离的多肽不与来自其生产环境的所有其它污染物组分缔合。来自其生产环境的污染组分(如由重组转染的细胞产生的那些污染组分)是通常将干扰抗体的研究、诊断或治疗用途的物质，并且可包括酶、激素以及其它蛋白质或非蛋白质溶质。在优选实施方案中，所述多肽将：(1)被纯化至如通过例如劳立法(Lowry method)所测定大于95重量％的抗体且在一些实施方案中纯化至大于99重量％；(2)被纯化至足以通过使用旋杯式测序仪获得N端或内部氨基酸序列的至少15个残基的程

度;或(3)通过使用考马斯蓝(Coomassie blue)或优选银染色,在非还原或还原条件下进行SDS-PAGE被纯化至均质。分离的抗体包括重组T细胞内的原位抗体,因为抗体的天然环境的至少一种组分将不存在。然而,通常将通过至少一个纯化步骤来制备分离的多肽或抗体。

[0076] 抗体(如本公开的抗Siglec-7抗体)的"可变区"或"可变结构域"是指抗体的重链或轻链的氨基末端结构域。重链和轻链的可变结构域可分别称为"V_H"和"V_L"。这些结构域通常是抗体中最可变的部分(相对于同一类别的其它抗体)并含有抗原结合位点。

[0077] 术语"可变"是指以下事实:可变结构域的某些区段在抗体(如本公开的抗Siglec-7抗体)之间的序列中存在广泛差异。V结构域介导抗原结合并限定特定抗体对其特定抗原的特异性。然而,可变性并不是均匀分布在整个可变结构域的范围内。而是,在轻链和重链可变结构域中,可变性集中在三个称为高变区(HVR)的区段中。可变结构域的更高度保守的部分称为框架区(FR)。天然重链和轻链的可变结构域各自包含由三个HVR连接的四个FR区域,所述四个FR基本上采用β-片层构型,所述三个HVR形成连接β-片层结构的环并且在一些情况下形成β-片层结构的部分。在每个链中的HVR由FR区保持紧靠在一起,并且与来自另一条链的HVR促成抗体的抗原结合位点的形成(参见Kabat等人,Sequences of Immunological Interest,第5版,National Institute of Health,Bethesda,MD(1991))。虽然恒定结构域并不直接参与抗体与抗原的结合,但表现各种效应子功能,诸如抗体参与抗体依赖性细胞毒性。

[0078] 如本文所用,术语"单克隆抗体"是指从基本上同质抗体的群体获得的抗体(如本公开的抗Siglec-7抗体),即构成所述群体的单独抗体是相同的,除了可能以微量存在的可能的天然存在的突变和/或翻译后修饰(例如,异构化,酰胺化)。单克隆抗体是高度特异性的,从而针对一个或多个抗原位点。在一些实施方案中,本公开的单克隆抗体可以是双特异性抗体。与通常包括针对不同决定簇(表位)的不同抗体的多克隆抗体制剂不同,各单克隆抗体针对一个或多个抗原位点上的单一决定簇。修饰语"单克隆"指示抗体是从实质上均质的抗体群体获得的特性,且不应解释为需要通过任何特定方法来产生所述抗体。例如,待根据本公开使用的单克隆抗体可通过各种技术来制备,所述技术包括例如噬菌体展示技术(参见例如,Clackson等人,Nature,352:624-628(1991);Marks等人,J.Mol.Biol.222:581-597(1992);Sidhu等人,J.Mol.Biol.338(2):299-310(2004);Lee等人,J.Mol.Biol.340(5):1073-1093(2004);Fellouse,Proc.Nat'l Acad.Sci.USA 101(34):12467-472(2004);以及Lee等人,J.Immunol.Methods 284(1-2):119-132(2004)、杂交瘤方法(例如,,Kohler和Milstein.,Nature,256:495-97(1975);Hongo等人,Hybridoma,14(3):253-260(1995);Harlow等人,Antibodies:A Laboratory Manual,(Cold Spring Harbor Laboratory Press,第2版1988);Hammerling等人,in:Monoclonal Antibodies and T-Cell Hybridomas 563-681(Elsevier,N.Y.,1981))、重组DNA方法(参见例如,美国专利号4,816,567)以及用于在具有部分或全部人免疫球蛋白基因座或编码人免疫球蛋白序列的基因的动物中产生人或人样抗体的技术(参见例如,WO 1998/24893;WO 1996/34096;WO 1996/33735;WO 1991/10741;Jakobovits等人,Proc.Nat'l Acad.Sci.USA 90:2551(1993);Jakobovits等人,Nature 362:255-258(1993);Bruggemann等人,Year in Immunol.7:33(1993);美国专利号5,545,807;5,545,806;5,569,825;5,625,126;5,633,425;以及5,661,016;Marks等人,Bio/Technology 10:779-783(1992);Lonberg等人,Nature 368:856-859

(1994);Morrison,Nature 368:812-813(1994);Fishwild等人,Nature Biotechnol.14:845-851(1996);Neuberger,Nature Biotechnol.14:826(1996);以及Lonberg和Huszar,Intern.Rev.Immunol.13:65-93(1995)。

[0079] 术语“全长抗体”、“完整抗体”或“全抗体”可互换使用来指与抗体片段相反,呈其基本上完整形式的抗体,如本公开的抗Siglec-7抗体。具体地说,全抗体包括具有重链和轻链(包括Fc区)的抗体。恒定结构域可为天然序列恒定结构域(例如人天然序列恒定结构域)或其氨基酸序列变体。在一些情况下,完整抗体可具有一种或多种效应子功能。

[0080] “抗体片段”包含完整抗体的一部分,优选地所述完整抗体的抗原结合区和/或可变区。抗体片段的实例包括Fab、Fab′、F(ab′)$_2$和Fv片段;双抗体;线性抗体(参见美国专利5,641,870,实施例2;Zapata等人,Protein Eng.8(10):1057-1062(1995));单链抗体分子以及由抗体片段形成的多特异性抗体。

[0081] 抗体(如本公开的抗Siglec-7抗体)的木瓜蛋白酶消化产生称为“Fab”片段的两个相同的抗原结合片段和反映容易结晶的能力名称的残余“Fc”片段。Fab片段由整条L链连同H链的可变区结构域(V_H)以及一条重链的第一个恒定结构域(C_H1)组成。每个Fab片段相对于抗原结合是单价的,即它具有单个抗原结合位点。抗体的胃蛋白酶处理产生单个大F(ab′)$_2$片段,所述片段大致对应于具有不同抗原结合活性且仍能够交联抗原的两个二硫化物连接的Fab片段。Fab′片段与Fab片段的不同之处在于在C_H1结构域的羧基末端处具有一些另外的残基,包括来自抗体铰链区的一个或多个半胱氨酸。Fab′-SH是本文中的Fab′的名称,其中恒定结构域的一个或多个半胱氨酸残基带有游离硫醇基。F(ab′)$_2$抗体片段最初以其之间具有铰链半胱氨酸的Fab′片段对形式产生。抗体片段的其它化学偶联也是已知的。

[0082] Fc片段包含通过二硫化物结合在一起的两条H链的羧基末端部分。抗体的效应子功能由Fc区中的序列决定,所述区域也被某些类型的细胞上发现的Fc受体(FcR)识别。

[0083] “Fv”是含有完全抗原识别和结合位点的最小抗体片段。此片段由处于紧密、非共价缔合的一个重链可变区结构域和一个轻链可变区结构域的二聚体组成。从这两个结构域的折叠发出六个高变环(各自来自H和L链的3个环),所述高变环贡献氨基酸残基以用于抗原结合并赋予抗体以抗原结合特异性。然而,甚至单个可变结构域(或仅包含三个对抗原有特异性的HVR的一半Fv)具有识别和结合抗原的能力,尽管与整个结合位点相比,处于较低的亲和力下。

[0084] “单链Fv”也缩写为“sFv”或“scFv”是包含连接成单条多肽链的VH和VL抗体结构域的抗体片段。优选地,sFv多肽还包含V_H与V_L结构域之间的多肽接头,所述接头使得sFv能够形成抗原结合所需的结构。关于sFv的综述,参见Pluckthun in The Pharmacology of Monoclonal Antibodies,第113卷,Rosenburg和Moore编,Springer-Verlag,New York,第269-315页(1994)。

[0085] 抗体(如本公开的抗Siglec-7抗体)的“功能片段”包含完整抗体的一部分,通常包括完整抗体的抗原结合区或可变区或抗体的F区,所述F区保留或具有改变的FcR结合能力。抗体片段的实例包括线性抗体、单链抗体分子和由抗体片段形成的多特异性抗体。

[0086] 术语“双抗体”是指通过在V_H与V_L结构域之间用短接头(约5-10个残基)构建sFv片段(参见前面的段落)制备的小抗体片段,以使得实现V结构域的链间而非链内配对,由此产生二价片段,即具有两个抗原结合位点的片段。双特异性双抗体是两种“交叉”sFv片段的异

二聚体,其中两种抗体的V_H和V_L结构域存在于不同的多肽链上。双抗体更详细地描述于例如EP 404,097;WO 93/11161;Hollinger等人,Proc.Nat'l Acad.Sci.USA 90:6444-48(1993)中。

[0087] 如本文所用,"嵌合抗体"是指抗体(免疫球蛋白),如本公开的抗Siglec-7抗体,其中重链和/或轻链的一部分与来源于特定物种或属于特定抗体类型或亚类的抗体中的对应序列同一或同源,而所述一条或多条链的其余部分与来源于另一物种或属于另一个抗体类型或亚类的抗体、以及此类抗体的片段中的对应序列同一或同源,只要它们展示出所需的生物活性(美国专利号4,816,567;Morrison等人,Proc.Nat'l Acad.Sci.USA,81:6851-55(1984))。本文中的目标嵌合抗体包括PRIMATIZED®抗体,其中所述抗体的抗原结合区源自通过例如用目标抗原免疫猕猴产生的抗体。如本文所用,"人源化抗体"用于"嵌合抗体"的子集。

[0088] "人源化"形式的非人(例如鼠类)抗体(如本公开的抗Siglec-7抗体)是含有源自非人免疫球蛋白的最小序列的嵌合抗体。在一个实施方案中,人源化抗体是人免疫球蛋白(接受者抗体),其中来自接受者的HVR的残基被来自诸如小鼠、大鼠、兔或非人类灵长类动物的非人物种(供体抗体)的HVR的具有所需特异性、亲和力和能力的残基置换。在一些情况下,人免疫球蛋白的FR残基被相应的非人残基置换。另外,人源化抗体可包含在接受者抗体中或在供体抗体中没有见到的残基。可产生这些修饰来进一步细化抗体性能,如结合亲和力。通常,人源化抗体将包含至少一个且通常两个可变结构域的基本全部,其中全部或基本全部的高变环对应于非人免疫球蛋白序列的那些高变环且全部或基本全部的FR区为人免疫球蛋白序列的那些FR区,但是FR区可包含一个或多个单独的FR残基取代,所述取代提高抗体性能,如结合亲和力、异构化、免疫原性等。FR中这些氨基酸取代的数目在H链中通常不超过6个,并且在L链中不超过3个。所述人源化抗体可任选地还应当至少包括免疫球蛋白恒定区(Fc)的一部分,典型地人免疫球蛋白的一部分。关于进一步细节,参见例如,Jones等人,Nature 321:522-525(1986);Riechmann等人,Nature 332:323-329(1988);以及Presta,Curr.Op.Struct.Biol.2:593-596(1992)。还参见例如,Vaswani和Hamilton,Ann.Allergy,Asthma&Immunol.1:105-115(1998);Harris,Biochem.Soc.Transactions 23:1035-1038(1995);Hurle和Gross,Curr.Op.Biotech.5:428-433(1994);以及美国专利号6,982,321和7,087,409。

[0089] "人抗体"是具有对应于由人产生的抗体(如本公开的抗Siglec-7抗体)的氨基酸序列的氨基酸序列和/或已使用如本文公开的用于制备人抗体的任一种技术制造的抗体。人抗体的定义特异性地排除了包括非人抗原结合残基的人源化抗体。可使用本领域中已知的各种技术(包括噬菌体展示文库)产生人抗体。Hoogenboom和Winter,J.Mol.Biol.,227:381(1991);Marks等人,J.Mol.Biol.,222:581(1991)。也可用于制备人单克隆抗体的方法是描述于Cole等人,Monoclonal Antibodies and Cancer Therapy,Alan R.Liss,第77页(1985);Boerner等人,J.Immunol.,147(1):86-95(1991)中的方法。还参见van Dijk和van de Winkel,Curr.Opin.Pharmacol.5:368-74(2001)。人抗体可通过将抗原施用于转基因动物来制备,所述转基因动物已经被修饰以响应于抗原激发而产生此类抗体,但其内源基因座已经失效,例如免疫的异种小鼠(关于XENOMOUSE™技术,参见例如,美国专利号6,075,181和6,150,584)。关于经由人B细胞杂交瘤技术产生的人抗体,还参见例如,Li等人,

Proc.Nat′l Acad.Sci.USA,103:3557-3562(2006)。

[0090] 当在本文中使用时,术语“高变区”、“HVR”或“HV”是指抗体可变结构域的区域,如本公开的抗Siglec-7抗体的区域,所述区域在序列中是高变的和/或形成结构限定的环。一般来说,抗体包含六个HVR;三个在VH中(H1、H2、H3),且三个在VL中(L1、L2、L3)。在天然抗体中,H3和L3展示6种HVR的最多样化,并且特别是认为H3在赋予针对抗体的良好特异性方面发挥独特作用。参见例如,Xu等人,Immunity 13:37-45(2000);Johnson和Wu,Methods in Molecular Biology 248:1-25(Lo,编,Human Press,Totowa,NJ,2003))。实际上,由重链组成的天然存在的骆驼科抗体仅在没有轻链的情况下是功能性且稳定的。参见例如,Hamers-Casterman等人,Nature 363:446-448(1993)和Sheriff等人,Nature Struct.Biol.3:733-736(1996)。

[0091] 许多HVR描述正在使用中,并包含在本文中。作为EU或Kabat互补决定区(CDR)的HVR是基于序列变异性并且是最常用的(Kaba等人,同上)。而Chothia是指结构环的位置(Chothia和Lesk J.Mol.Biol.196:901-917(1987))。AbM HVR表示EU或Kabat CDR与Chothia结构化环之间的折衷,并且是通过Oxford Molecular的AbM抗体建模软件来使用。“接触”HVR是基于分析可用复合物晶体结构的。来自这些HVR中的每一个的残基如下所述。

[0092]

环	Kabat	AbM	Chothia	接触
L1	L24-L34	L24-L34	L26-L32	L30-L36
L2	L50-L56	L50-L56	L50-L52	L46-L55
L3	L89-L97	L89-L97	L91-L96	L89-L96
H1	H31-H35B	H26-H35B	H26-H32	H30-H35B (Kabat编号)
H1	H31-H35	H26-H35	H26-H32	H30-H35 (Chothia编号)
H2	H50-H65	H50-H58	H53-H55	H47-H58
H3	H95-H102	H95-H102	H96-H101	H93-H101

[0093] HVR可包含如下的“延伸的HVR”:VL中的24-36或24-34(L1)、46-56或50-56(L2)以及89-97或89-96(L3),以及VH中的26-35(H1)、50-65或49-65(优选的实施方案)(H2)以及93-102、94-102或95-102(H3)。对于这些延伸的HVR定义中的每一个,可变结构域残基是根据EU或Kaba等人,同上进行编号。

[0094] “框架”或“FR”残基是除如本文所定义的HVR残基以外的那些可变结构域残基。

[0095] 短语“如EU或Kaba中的可变结构域残基编号”或“如EU或Kabat中的氨基酸位置编号”及其变化形式是指用于EU或Kabat等人,上文中的抗体编译的重链可变结构域或轻链可变结构域的编号系统。使用此编号系统,实际线性氨基酸序列可含有较少或另外的氨基酸,其对应于可变结构域的FR或HVR的缩短或对其进行的插入。例如,重链可变结构域可包括H2的残基52之后的单个氨基酸插入(根据Kabat的残基52a)和重链FR残基82之后的插入残基(例如根据Kabat的残基82a、82b和82c等)。可通过在抗体序列的同源区处与“标准”Kabat编号序列比对来确定给定抗体的残基的EU或Kabat编号。

[0096] 当提及可变结构域中的残基时,通常使用EU或Kabat编号系统(大约轻链的残基1-107和重链的残基1-113)(例如,Kabat等人,Sequences of Immunological Interest.第5版.Public Health Service,National Institutes of Health,Bethesda,Md.(1991))。“EU或Kabat编号系统”或“EU索引”通常在提及免疫球蛋白重链恒定区中的残基时使用(例如,Kabat等人,上文中报告的EU索引)。“如Kabat中的EU索引”是指人IgG1 EU抗体的残基编

号。除非本文另有说明，否则对抗体的可变结构域中的残基编号的提及是指由Kabat编号系统编号的残基。除非本文另有说明，否则对抗体的恒定结构域中的残基编号的提及是指由EU或Kabat编号系统编号的残基(例如，参见美国专利公布号2010-280227)。

[0097] 如本文所用的“受体人框架”是包含源自人免疫球蛋白框架或人共有框架的VL或VH框架的氨基酸序列的框架。“源自”人免疫球蛋白框架或人共有框架的受体人框架可包含其相同的氨基酸序列，或者其可含有预先存在的氨基酸序列变化。在一些实施方案中，预先存在的氨基酸变化的数目是10或更小，9或更小，8或更小，7或更小，6或更小，5或更小，4或更小，3或更小，或2或更小。当在VH中存在预先存在的氨基酸变化时，优选那些变化仅在位置71H、73H和78H中的三个、两个或一个处发生；例如，那些位置处的氨基酸残基可以是71A、73T和/或78A。在一个实施方案中，VL受体人框架在序列上与VL人免疫球蛋白框架序列或人共有框架序列相同。

[0098] “人共有框架”是代表在人免疫球蛋白VL或VH框架序列的选择中最常存在的氨基酸残基的框架。一般来说，人免疫球蛋白VL或VH序列选自可变结构域序列的亚组。一般来说，所述序列亚组是如在Kabat等人，Sequences of Proteins of Immunological Interest，第5版Public Health Service，National Institutes of Health，Bethesda，MD(1991)中的亚组。实例包括对于VL，所述亚组可以是如Kabat等人，同上中的亚组κI、κII、κIII或κIV。此外，对于VH，所述亚组可以是如Kabat等人，同上的亚组I、亚组II或亚组III。

[0099] 例如本公开的抗Siglec-7抗体的指定位置处的“氨基酸修饰”是指指定残基的取代或缺失，或邻近指定残基插入至少一个氨基酸残基。“邻近”指定残基的插入是指在其一个至两个残基内插入。插入可为指定残基的N末端或C末端。本文优选的氨基酸修饰是取代。

[0100] “亲和力成熟”抗体(如本公开的抗Siglec-7抗体)是一个或多个HVR中具有一个或多个改变的抗体，所述变化导致与不具有那些改变的亲本抗体相比，抗体对于抗原的亲和力提高。在一个实施方案中，亲和力成熟抗体对靶抗原具有纳摩尔或甚至皮摩尔亲和力。亲和力成熟抗体是通过本领域中已知的程序产生。例如，Marks等人，Bio/Technology 10:779-783(1992)描述了通过VH-和VL-结构域改组的亲和力成熟。对HVR和/或框架残基的随机诱变由例如以下文献描述：Barbas等人Proc Nat.Acad.Sci.USA 91:3809-3813(1994)；Schier等人Gene 169:147-155(1995)；Yelton等人J.Immunol.155:1994-2004(1995)；Jackson等人，J.Immunol.154(7):3310-9(1995)；以及Hawkins等人，J.Mol.Biol.226:889-896(1992)。

[0101] 如本文所用，术语“特异性地识别”或“特异性地结合”是指可测量的和可再现的相互作用，诸如靶标与抗体(如本公开的抗Siglec-7抗体)之间的吸引或结合，所述吸引或结合在存在包括生物分子的分子的异源群体的情况下确定靶标的存在。例如，特异性或优先结合靶标或表位的抗体(如本公开的抗Siglec-7抗体)是以比它结合至其它靶标或靶标的其它表位更大的亲和力、亲合力、更容易和/或更大的持续时间结合至靶标或表位。通过阅读这个定义还应理解，例如，特异性或优先结合至第一靶标的抗体(或部分)可以或可以不特异性或优先结合至第二靶标。因此，“特异性结合”或“优先结合”并不一定需要(尽管其可包括)排外的结合。特异性地结合至靶标的抗体可具有至少约$10^{3}M^{-1}$或$10^{4}M^{-1}$，有时约$10^{5}M^{-1}$或$10^{6}M^{-1}$，在其它情况下$10^{6}M^{-1}$或$10^{7}M^{-1}$、约$10^{8}M^{-1}$至$10^{9}M^{-1}$或约$10^{10}M^{-1}$至$10^{11}M^{-1}$或更高的缔合常数。多种免疫测定形式可用于选择与特定蛋白质特异性免疫反应的抗体。例如，固相

ELISA免疫测定常规地用于选择与蛋白质特异性免疫反应的单克隆抗体。关于可用来确定特异性免疫反应的免疫测定形式和条件的描述，参见例如Harlow和Lane(1988) Antibodies,A Laboratory Manual,Cold Spring Harbor Publications,New York。

[0102] 如本文所用，Siglec-7蛋白与第二种蛋白质之间的“相互作用”包括但不限于蛋白质-蛋白质相互作用、物理相互作用、化学相互作用、结合、共价结合和离子结合。如本文所用，当抗体破坏、减少或完全消除两种蛋白质之间的相互作用时，抗体“抑制两种蛋白质之间的相互作用”。当本公开的抗体或其片段结合至两种蛋白质中的一种时，所述抗体或其片段“抑制两种蛋白质之间的相互作用”。

[0103] “激动剂”抗体或“活化”抗体是在抗体结合抗原后诱导(例如增加)所述抗原的一种或多种活性或功能的抗体，如本公开的激动剂抗Siglec-7抗体。

[0104] “阻断”抗体、“拮抗剂”抗体或“抑制性”抗体是在抗体结合抗原后抑制或减少(例如降低)抗体与一种或多种配体的结合和/或在抗体结合抗原后抑制或减少(例如降低)所述抗原的一种或多种活性或功能的抗体，如本公开的抗Siglec-7抗体。在一些实施方案中，阻断抗体、拮抗剂抗体或抑制性抗体基本上或完全抑制抗原与所述抗原的一种或多种配体的结合和/或所述抗原的一种或多种活性或功能。

[0105] 抗体“效应子功能”是指可归因于抗体的Fc区(天然序列Fc区或氨基酸序列变体Fc区)的那些生物活性，并且随抗体同种型变化。

[0106] 本文的术语“Fc区”用于定义免疫球蛋白重链的C末端区，其包括天然序列Fc区和变体Fc区。尽管免疫球蛋白重链的Fc区的边界可能变化，但是人IgG重链Fc区通常被定义为从位置Cys226或Pro230处的氨基酸残基延伸至其羧基末端。例如，Fc区的C-末端赖氨酸(根据EU或Kabat编号系统的残基447)可例如在抗体的生产或纯化期间或通过重组改造编码抗体重链的核酸。因此，完整抗体的组合物可包含除去所有K447残基的抗体群体，不除去K447残基的抗体群体和具有有或无K447残基的抗体混合物的抗体群体。用于本公开的抗体的合适的天然序列Fc区包括人IgG1、IgG2、IgG3和IgG4。

[0107] “天然序列Fc区”包含的氨基酸序列与自然界中所存在的Fc区的氨基酸序列相同。天然序列人Fc区包括天然序列人IgG1 Fc区(非A和A同种异型)；天然序列人IgG2 Fc区；天然序列人IgG3 Fc区；以及天然序列人IgG4 Fc区以及其天然存在的变体。

[0108] “变体Fc区”所包含的氨基酸序列与天然序列Fc区的氨基酸序列的不同之处在于至少一个氨基酸修饰，优选一个或多个氨基酸序列。优选地，与天然序列Fc区或亲本多肽的Fc区相比，变体Fc区具有至少一个氨基酸取代，例如，在天然序列Fc区中或在亲本多肽的Fc区中约1至约10个氨基酸取代，并且优选约1至约5个氨基酸取代。本文中的变体Fc区将优选与天然序列Fc区和/或与亲本多肽的Fc区具有至少约80％同源性，并且最优选与其具有至少约90％同源性，更优选与其具有至少约95％同源性。

[0109] “Fc受体”或“FcR”描述结合至抗体Fc区的受体。优选的FcR是天然序列人FcR。此外，优选的FcR是结合IgG抗体(γ受体)并且包括FcγRI、FcγRII和FcγRIII亚类的受体的FcR，包括这些受体的等位基因变体和可变剪接形式，FcγRII受体包括FcγRIIA(“活化受体”)和FcγRIIB(“抑制受体”)，它们具有主要在其细胞质结构域中不同的相似氨基酸序列。活化受体FcγRIIA在其细胞质域中含有免疫受体酪氨酸基活化基序(“ITAM”)。抑制受体FcγRIIB在其细胞质域中含有免疫受体酪氨酸基抑制基序(“ITIM”)。(参见例如，M.

Daëron,Annu.Rev.Immunol.15:203-234(1997))。FcR在以下各项中进行综述:Ravetch和Kinet,Annu.Rev.Immunol.9:457-92(1991);Capel等人,Immunomethods 4:25-34(1994);以及de Haas等人,J.Lab.Clin.Med.126:330-41(1995)。本文中的术语"FcR"涵盖其它FcR,包括将来待鉴定的那些FcR。FcR也可增加抗体的血清半衰期。

[0110] 可例如在转基因小鼠或表达人FcRn的转染的人细胞系中或者在施用了具有变体Fc区的多肽的灵长类动物中测定与体内FcRn的结合以及人FcRn高亲和力结合多肽的血清半衰期。WO 2004/42072(Presta)描述了具有提高的或减弱的与FcR的结合的抗体变体。参见例如Shields等人,J.Biol.Chem.9(2):6591-6604(2001)。

[0111] 如本文所用,就肽、多肽或抗体序列而言的"氨基酸序列同一性百分比(%)"和"同源性"是指,在比对序列并且引入缺口(如果需要的话)以获得最大序列同一性百分比之后,候选序列中与特定肽或多肽序列中氨基酸残基相同的氨基酸残基的百分比,而不考虑任何保守取代作为序列同一性的一部分。用于测定氨基酸序列同一性百分比的目的的比对可以属于本领域中的技能的多种方式实现,所述方式例如使用可公开获得的计算机软件,诸如BLAST、BLAST-2、ALIGN或MEGALIGN™(DNASTAR)软件。本领域技术人员可确定用于测量比对的适当参数,包括对所比较的序列的全长获得最大比对所需的本领域中已知的任何算法。

[0112] "分离的"细胞是从在产生其的环境中通常与其缔合的至少一种污染细胞鉴定并且分离的分子或细胞。在一些实施方案中,分离的细胞不与同生产环境相关的所有组分缔合。分离的细胞呈不同于它在自然界中所存在的形式或配置的形式。分离的细胞与组织、器官或个体中天然存在的细胞不同。在一些实施方案中,分离的细胞是本公开的宿主细胞。

[0113] 编码抗体(如本公开的抗Siglec-7抗体)的"分离的"核酸分子是从在产生其的环境中通常与其缔合的至少一种污染核酸分子鉴定并且分离的核酸分子。优选地,分离的核酸不与同生产环境相关的所有组分缔合。编码本文的多肽和抗体的分离的核酸分子呈不同于它在自然界中所存在的形式或配置的形式。分离的核酸分子因此不同于在细胞中天然存在的编码本文的多肽和抗体的核酸。

[0114] 如本文所用的术语"载体"意指能够转运其已连接的另一核酸的核酸分子。一种类型的载体是"质粒",所述质粒是指可将额外的DNA区段连接到其中的环状双链DNA。另一种类型的载体是噬菌体载体。另一种类型的载体是病毒载体,其中额外的DNA区段可被连接到病毒基因组中。某些载体能够在它们被引入至其中的宿主细胞中自主复制(例如,具有细菌复制起点的细菌载体以及附加型哺乳动物载体)。其它载体(例如,非附加型哺乳动物载体)可以在引入到宿主细胞中后整合到宿主细胞的基因组中,并且由此与宿主基因组一起复制。此外,某些载体能够指导它们所可操作地连接的基因的表达。所述载体在本文中称为"重组表达载体"或简称为"表达载体"。一般而言,可用于重组DNA技术中的表达载体经常呈质粒形式。在本说明书中,"质粒"和"载体"可互换地使用,因为质粒是载体的最通常使用形式。

[0115] 如本文可互换使用的"多核苷酸"或"核酸"是指具有任何长度的核苷酸的聚合物,并且包括DNA和RNA。所述核苷酸可以是脱氧核糖核苷酸、核糖核苷酸、修饰的核苷酸或碱基和/或它们的类似物、或可通过DNA或RNA聚合酶或通过合成反应并入聚合物中的任何底物。多核苷酸可包含修饰的核苷酸,如甲基化核苷酸及其类似物。如果存在,那么可在聚合物组装之前或之后赋予对核苷酸结构的修饰。核苷酸的序列可由非核苷酸组分间断。多核苷酸

可包含在合成后进行的修饰，如缀合至标记。其它类型的修饰包括，例如，“加帽(cap)”、用类似物取代一种或多种天然存在的核苷酸、核苷酸间修饰，例如像，具有不带电荷的键联(例如，膦酸甲酯、磷酸三酯、磷酰胺酸酯(phosphoamidate)、氨基甲酸酯(carbamate)，等等)和具有带电荷的键联(例如，硫代磷酸酯、二硫代磷酸酯，等等)的那些、含有侧悬部分(例如像，蛋白质(例如，核酸酶、毒素、抗体、信号肽、聚-L-赖氨酸，等等))的那些、具有嵌入剂(例如，吖啶、补骨脂素)的那些、含有螯合剂(例如，金属、放射性金属、硼、氧化金属，等等)的那些、含有烷化剂(alkylator)的那些、具有修饰的键联(例如，α端基异构核酸，等等)的那些、以及一种或多种多核苷酸未修饰形式。此外，通常存在于糖类中的任何羟基可被(例如)膦酸酯基、磷酸酯基置换、被标准保护基保护或被活化以提供与另外核苷酸的另外键联，或可与固体或半固体载体缀合。5′和3′末端OH可以被磷酸化或被胺或具有1至20个碳原子的有机加帽基团部分而取代。其它羟基也可衍生成标准保护基。多核苷酸还可以包含本领域众所周知的核糖或脱氧核糖的类似形式，包括，例如，2′-O-甲基-、2′-O-烯丙基、2′-氟-或2′-叠氮基-核糖、碳环糖类似物、α-端基异构糖、差向异构糖(如阿拉伯糖、木糖或来苏糖)、吡喃糖糖、呋喃糖糖、景天庚酮糖、无环类似物以及碱性核苷类似物(如甲基核苷)。一个或多个磷酸二酯键联可由替代连接基团来置换。这些替代连接基团包括，但不限于，其中磷酸酯被P(O)S(“硫代酸酯(thioate)”)、P(S)S(“二硫代酸酯(dithioate)”)、(O)NR2(“酰胺化物(amidate)”)、P(O)R、P(O)OR′、CO或CH2(“甲缩醛(formacetal)”)置换的实施方案，其中每个R或R′独立地是H或任选含有醚(-O-)键联的取代的或未取代的烷基(1-20个C)、芳基、烯基、环烷基、环烯基或芳烷基(araldyl)。多核苷酸中并非所有键联都需要相同。前文描述适用于本文所提及的所有多核苷酸，包括RNA和DNA。

[0116] “宿主细胞”包括可以是或已成为用于并入多核苷酸插入物的载体的接受者的个别细胞或细胞培养物。宿主细胞包括单一宿主细胞的子代，并且子代可由于天然、偶然或故意突变而不一定与初始亲本细胞完全相同(在形态方面或在基因组DNA互补体方面)。宿主细胞包括用本公开的多核苷酸体内转染的细胞。

[0117] 如本文所用的“载体”包括在所采用的剂量和浓度下对暴露于其的细胞或哺乳动物无毒的药学上可接受的载体、赋形剂或稳定剂。通常生理学上可接受的载体是pH缓冲水溶液。生理学上可接受的载体的实例包括缓冲剂，如磷酸盐、柠檬酸盐以及其它有机酸；抗氧化剂，包括抗坏血酸；低分子量(小于约10个残基)多肽；蛋白质，如血清白蛋白、明胶或免疫球蛋白；亲水性聚合物，如聚乙烯吡咯烷酮；氨基酸，如甘氨酸、谷氨酰胺、天冬酰胺、精氨酸或赖氨酸；单糖、二糖以及其它碳水化合物，包括葡萄糖、甘露糖或糊精；螯合剂，如EDTA；糖醇，如甘露糖醇或山梨糖醇；成盐抗衡离子，如钠；和/或非离子型表面活性剂类，如TWEEN™、聚乙二醇(PEG)以及PLURONICS™。

[0118] 如本文所用，术语“细胞凋亡”是指细胞内细胞破坏的基因定向过程。细胞凋亡不同于坏死；它包括细胞骨架断裂、细胞质收缩和浓缩、细胞膜外表面上磷脂酰丝氨酸的表达以及起泡，从而导致细胞膜结合囊泡或凋亡小体的形成。所述过程也被称为“程序性细胞死亡”。在细胞凋亡期间，观察到特征性现象，如弯曲的细胞表面、核染色质的浓缩、染色体DNA的片段化以及线粒体功能的丧失。可使用各种已知的技术来检测细胞凋亡，如用膜联蛋白V、碘化丙啶、DNA片段化测定和YO-PRO-1(Invitrogen)染色细胞。在一些实施方案中，可使用用膜联蛋白V和碘化丙啶染色，并且膜联蛋白V+/PI+、膜联蛋白V+/PI-和膜联蛋白V-/PI+

群体的组合百分比被认为是死细胞。

[0119] 如本文所用，术语“降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者的药剂”是指减少(包括显著)、降低、阻断、抑制或干扰体外、原位和/或体内Siglec-7(哺乳动物，如人Siglec-7)生物活性的分子。术语“药剂”意味着没有任何特定的生物作用机制，并且明确地包括并涵盖与Siglec-7的所有可能的药理学、生理学和生物化学相互作用，无论是直接的还是间接的以及是与Siglec-7、一种或多种其配体还是通过另一种机制相互作用，并且其后果可通过各种不同的且化学相异的组合物来实现。示例性药剂包括但不限于特异性地结合至Siglec-7的抗Siglec-7抗体、可溶性Siglec-7受体蛋白、可溶性Siglec-7-Fc融合蛋白(例如，Siglec-7免疫粘附素)、结合至Siglec-7配体的可溶性Siglec受体、结合至Siglec-7配体的Siglec-Fc融合蛋白(例如，Siglec免疫粘附素)、针对编码Siglec-7的核酸的反义分子、针对编码Siglec-7的核酸的短干扰RNA(“siRNA”)分子、Siglec-7抑制性化合物、结合至Siglec-7的RNA或DNA适体以及Siglec-7结构类似物。在一些实施方案中，Siglec-7抑制剂(例如抗体)结合降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者的药剂(或与其物理相互作用)，结合至Siglec-7配体和/或抑制(减少)Siglec-7合成或产生。在其它实施方案中，本公开抑制剂的药剂结合Siglec-7并防止其与一种或多种其配体的结合。在其它实施方案中，本公开的药剂减少或消除Siglec-7的表达(即转录或翻译)。本文提供了降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者的药剂的类型的实例。

[0120] 如本文所用，术语“与Siglec-7结合或相互作用的药剂”是指与Siglec-7蛋白直接或间接相互作用的分子。术语“药剂”意味着没有任何特定生物作用的机制，并且明确地包括并涵盖与Siglec-7的所有可能的药理学、生理学和生物化学相互作用，无论是直接的还是间接的以及是与Siglec-7还是通过另一种机制相互作用，并且其后果可通过各种不同的且化学相异的组合物来实现。示例性药剂包括但不限于特异性地结合至Siglec-7的抗Siglec-7抗体。

[0121] 如本文所用，术语“RNA干扰”或“RNAi”通常是指其中双链RNA分子或短发夹RNA分子减少或抑制双链或短发夹RNA分子与其具有基本上或完全同源性的核酸序列表达的过程。术语“短干扰RNA”或“siRNA”或“RNAi剂”是指引发RNA干扰的RNA序列。参见Kreutzer等人，WO 00/44895;Zernicka-Goetz等人，WO 01/36646;Fire，WO 99/32619;Mello和Fire，WO 01/29058。如本文所用，siRNA分子包括包含化学修饰的核苷酸和非核苷酸的RNA分子。术语“ddRNAi剂”是指从外源载体转录的DNA定向的RNAi剂。术语“短发夹RNA”或“shRNA”是指具有双链体区和环区的RNA结构。在某些实施方案中，ddRNAi剂初始表达为shRNA。

[0122] 如本文所用，术语“适体”是指能够与所需分子靶标紧密且特异性结合的异源寡核苷酸，例如像常见的代谢辅因子(例如辅酶A、S-腺苷甲硫氨酸等)、蛋白质(例如补体蛋白C5、抗体等)或核酸分子中的保守结构元件(例如，对转录因子等的结合重要的结构)。适体通常包含长度在约10至约100个核苷酸、约10至约75个核苷酸、约10至约50个核苷酸、约10至约35个核苷酸以及约10至约25个核苷酸的范围内的DNA或RNA核苷酸序列。合成DNA或RNA寡核苷酸可使用标准固相亚磷酰胺方法和设备来制备，如通过使用可获自Applied Biosystems(Foster City，CA)的3900高通量DNA Synthesizer™。适体经常并入在DNA和RNA

中发现的常见核苷酸的衍生物或类似物(例如,A、G、C和T/U),包括主链或键联修饰(例如,肽核酸(PNA)或硫代磷酸酯键联)以增加对核酸酶的抗性、结合亲合力或以其它方式改变其药代动力学性质。示例性修饰阐述于美国专利号6,455,308;4,469,863;5,536,821;5,541,306;5,637,683;5,637,684;5,700,922;5,717,083;5,719,262;5,739,308;5,773,601;5,886,165;5,929,226;5,977,296;6,140,482;以及WIPO公布WO 00/56746和WO 01/14398中。用于合成包含此类类似物或衍生物的寡核苷酸的方法公开于例如以上引用的专利公布以及美国专利号6,455,308;5,614,622;5,739,314;5,955,599;5,962,674;6,117,992;以及WO 00/75372中。

[0123] 如本文所用的术语"约"是指本技术领域的技术人员容易知道的相应值的通常误差范围。本文中对"约"某一个值或参数的提及包括(以及描述)针对所述值或参数本身的实施方案。

[0124] 如本文中和所附权利要求中所使用,单数形式"一个/种(a/an)"和"所述"包括复数提及物,除非上下文另外清楚地指示。例如,对一种"抗体"的引用是对一种至许多抗体(如摩尔量)的引用,并且包括本领域技术人员已知的其等效物等。

[0125] 应理解,本文中描述的本公开的方面和实施方案包括"包含"方面和实施方案、"由方面和实施方案组成"和/或"主要由方面和实施方案组成"。

[0126] 综述

[0127] 本公开涉及降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂(例如抗Siglec-7抗体);制备和使用此类试剂(例如,抗Siglec-7抗体)的方法;含有此类药剂(例如抗Siglec-7抗体)的药物组合物;编码此类试剂(例如抗Siglec-7抗体)的核酸;以及含有编码此类试剂(例如抗Siglec-7抗体)的核酸的宿主细胞。

[0128] 在一些实施方案中,本公开的抗Siglec-7抗体具有一种或多种拮抗活性,所述拮抗活性至少部分是由于抗体抑制Siglec-7与一种或多种天然聚糖配体之间的相互作用的能力。在一些实施方案中,本公开的抗-Siglec-7抗体可具有一种或多种拮抗活性,所述拮抗活性至少部分是由于抗体通过诱导Siglec-7的降解、下调、裂解、受体脱敏和/或溶酶体靶向而降低Siglec-7的细胞表达(例如细胞表面表达)的能力。

[0129] 在一些实施方案中,抗体诱导的Siglec-7活性可通过本文公开的任何技术(参见例如实施例1-5)在体外测定或测试,包括但不限于测试全长抗Siglec-7抗体的板结合以增加暴露于Siglec-7的抗体的密度、使抗Siglec-7抗体与二级抗体交联、使抗Siglec-7抗体与表达一种或多种Fcg受体(例如FcgRIIB)的细胞交联,使用溶液中的Siglec-7抗体以及使用Siglec-7抗体的Fab片段。

[0130] 在一些实施方案中,本公开的抗Siglec-7抗体具有一种或多种拮抗活性,所述拮抗活性至少部分是由于抗体抑制Siglec-7与一种或多种天然聚糖配体之间的相互作用的能力。在一些实施方案中,本公开的抗-Siglec-7抗体可具有一种或多种拮抗活性,所述拮抗活性至少部分是由于抗体通过诱导Siglec-7的降解、下调、裂解、受体脱敏和/或溶酶体靶向而降低Siglec-7的细胞表达(例如细胞表面表达)的能力。在一些实施方案中,所述抗Siglec-7抗体表现出以下性质中的一种或多种:a.以比抗Siglec-7抗体Mab1138(R&D Systems;目录号MAB 1138)低的半最大有效浓度(EC_{50})降低Siglec-7的细胞水平;b.与抗

Siglec-7抗体Mab1138(R&D Systems;目录号MAB 1138)相比,使红细胞与Siglec-7-Fc的结合降低有效达10倍;c.对人Siglec-7具有可在10nM至10pM范围内的解离常数(K_D),例如当在大约25℃的温度下测定K_D时;d.对人细胞如人树突细胞具有可在2nM至100pM范围内的解离常数(K_D),例如当在大约4℃的温度下测定K_D时;e.以可在2nM至100pM范围内的半最大有效浓度(EC_{50})结合至人细胞,如人树突细胞,例如当在大约4℃的温度下测定EC_{50}时;或f.以可在350pM至33pM范围内的半最大有效浓度(EC_{50})降低Siglec-7的细胞水平。如本文所公开,半最大有效浓度(EC_{50})是指本公开的抗Siglec-7抗体降低细胞上或细胞中的Siglec-7的细胞水平的浓度,或者抗体在细胞上达到与Siglec-7的半最大结合的浓度。

[0131] 有利地,本公开的抗Siglec-7抗体与商业抗Siglec-7抗体如Mab1138(R&D Systems;目录号MAB 1138)相比对于结合Siglec-7具有提高的EC_{50},比商业抗Siglec-7抗体如Mab1138(R&D Systems;目录号MAB 1138)更有效地(例如,更低的EC_{50})降低细胞表面表达,并且与商业抗Siglec-7抗体如Mab1138(R&D Systems;目录号MAB 1138)相比更有效地(达10倍)降低红细胞与Siglec-7-Fc的结合(参见例如,实施例3和4)。

[0132] 本公开的某些方面至少部分基于鉴定表现出与一种或多种Siglec-7配体竞争结合至Siglec-7的能力和/或降低细胞上Siglec-7的细胞表面水平、从而导致一种或多种Siglec-7活性的降低、中和、预防或遏制的能力的药剂,如抗Siglec-7抗体示例性Siglec-7活性包括但不限于,通过Src家族酪氨酸激酶如Syk、LCK、FYM和/或ZAP70磷酸化Tyr-437和Tyr-460;募集并结合至酪氨酸特异性蛋白磷酸酶SHP1和SHP2;募集并结合至PLC-γ1,其充当发动蛋白-1(Dynamini-1)的鸟嘌呤核苷酸交换因子;募集并结合至含SH2结构域的蛋白质(例如Crk1);募集并结合至脾酪氨酸激酶Syk;募集并结合至SH3-SH2-SH3生长因子受体结合蛋白2(Grb2);募集并结合至多种含SH2的蛋白质;调节一种或多种促炎性细胞因子的表达,所述促炎性细胞因子如IF IFN-a4、IFN-β、IL-1β、IL-1α、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-33、MCP-1以及MIP-1-β;调节一种或多种细胞中的一种或多种促炎性细胞因子的表达,所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞;增加一种或多种抗炎细胞因子的表达,所述抗炎细胞因子如IL-4、IL-10、IL-13、IL-35、IL-16、TGF-β、IL-1Ra、G-CSF以及TNF、IFN-β1a、IFN-β1b或IL-6的可溶性受体;调节一种或多种细胞中的一种或多种抗炎细胞因子的表达,所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞;调节一种或多种选自以下的蛋白质的表达:C1qa、C1qB、C1qC、C1s、C1R、C4、C2、C3、ITGB2、HMOX1、LAT2、CASP1、CSTA、VSIG4、MS4A4A、C3AR1、GPX1、TyroBP、ALOX5AP、ITGAM、SLC7A7、CD4、ITGAX、以及PYCARD;抑制细胞外信号调控激酶(ERK)磷酸化;降低一种或多种细胞蛋白上的酪氨酸磷酸化,任选地,其中所述一种或多种细胞蛋白包含ZAP-70并且所述酪氨酸磷酸化发生在ZAP-70的Tyr-319上;调节C-C趋化因子受体7(CCR7)的表达;抑制针对表达CCL19的细胞和表达CCL21的细胞的小神经胶质细胞趋化性;减少由一种或多种细胞诱导的T细胞增殖,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞、M2小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细

胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞以及M2 NK细胞;抑制破骨细胞产生,降低破骨细胞生成速率或两者;降低一种或多种细胞的存活,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;降低一种或多种细胞的增殖,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;抑制一种或多种细胞的迁移,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;抑制一种或多种细胞的一种或多种功能,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;抑制一种或多种细胞的成熟,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;抑制一种或多种类型的清除,所述清除选自凋亡神经元清除、神经组织碎片清除、功能障碍性突触清除、非神经组织碎片清除、细菌清除、其它异物清除、致病蛋白清除、致病肽清除、致病核酸清除以及肿瘤细胞清除;任选地,其中所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽,所述致病核酸是反义GGCCCC(G2C4)重复序列-扩增RNA,并且所述肿瘤细胞来自癌症,所述癌症选自膀胱癌、脑癌、乳腺

癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌;抑制以下中的一种或多种的吞噬:凋亡神经元、神经组织碎片、功能障碍性突触、非神经组织碎片、细菌、其它异物、致病蛋白、致病肽、致病核酸或肿瘤细胞;任选地其中所述致病核酸是反义GGCCCC(G2C4)重复序列-扩增RNA,所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽,并且所述肿瘤细胞来自癌症,所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤或甲状腺癌;与肿瘤细胞上的Siglec-7配体结合;与细胞上的Siglec-7配体结合,所述细胞选自嗜中性粒细胞、树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞以及NK细胞;通过以下中的一种或多种抑制肿瘤细胞杀伤:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;抑制以下中的一种或多种的抗肿瘤细胞增殖活性:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;抑制以下中的一种或多种的抗肿瘤细胞转移活性:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;抑制一种或多种含ITAM基序的受体,任选地其中所述一种或多种含ITAM基序的受体选自TREM1、TREM2、Sirpβ、FcgR、DAP10以及DAP12;通过一种或多种模式识别受体(PRR)抑制信号传导,任选地其中所述一种或多种PRR选自鉴定病原体相关分子模式(PAMP)的受体、鉴定损伤相关分子模式(DAMP)的受体以及其任何组合;抑制包含基序D/Ex$_{0-2}$YxxL/IX$_{6-8}$YxxL/I(SEQ ID NO:537)的一种或多种受体;通过一种或多种Toll样受体抑制信号传导;抑制JAK-STAT信号传导途径;抑制活化的B细胞的核因子κ-轻链增强子(NFêB);含有ITAM基序的受体的去磷酸化;调节一种或多种炎性受体的表达,任选地其中所述一种或多种炎性受体包含CD86并且所述一种或多种炎性受体在以下中的一种或多种上表达:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突状细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;增加一种或多种Siglec-7依赖性基因的表达;破坏的Siglec-7依赖性基因表达的正常化;降低一种或多种ITAM依赖性基因的表达,任选地其中所述一种或多种ITAM依赖性基因通过活化T细胞(NFAT)转录因子的核因子活化;促进或挽救以下中的一种或多种的功能性:免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞;增加以下中的一种或多种浸润到肿瘤中:免疫抑制树突细胞、免疫抑制巨

噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞;增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量;增强骨髓源性抑制细胞的肿瘤促进活性;增加肿瘤或外周血液中肿瘤促进细胞因子的表达,任选地其中所述肿瘤促进细胞因子是TGF-β或IL-10;增加肿瘤促进FoxP3+调控性T淋巴细胞的肿瘤浸润;增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性;减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化;减少具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润;降低NK细胞的肿瘤杀伤潜力;减少具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润;减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润;增加肿瘤体积;增加肿瘤生长速率;增加转移;增加肿瘤复发率;降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效,任选地其中所述一种或多种免疫疗法是靶向一种或多种靶蛋白的免疫疗法,所述一种或多种靶蛋白选自PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、TREM1、TREM2、CSF-1受体以及其任何组合;抑制PLCã/PKC/钙动员;以及抑制PI3K/Akt、Ras/MAPK信号传导。

[0133] 在一些实施方案中,用诸如Siglec-7阻断抗体的药剂治疗癌症:(i)直接或间接降低在癌症患者的肿瘤、外周血和淋巴器官中累积的肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的存活、增殖、成熟、分化和/或功能性;(ii)减少癌症患者的肿瘤、外周血和其它淋巴器官中的肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量;(iii)阻断骨髓来源的抑制细胞(MDSC)的肿瘤促进活性;(iv)降低癌症患者的肿瘤和外周血中的肿瘤促进细胞因子如TGF-β和IL-10的表达;(v)降低肿瘤中的肿瘤促进FoxP3+调控性T淋巴细胞浸润;(vi)增加具有肿瘤杀伤潜力的T淋巴细胞的浸润和活化;(vii)增加具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润;(viii)增加NK细胞的杀瘤潜力;(ix)增加具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润;(x)减少肿瘤体积;(xi)降低肿瘤生长速度;(xii)减少和/或抑制转移;(xiii)降低肿瘤复发率;(xiv)提高调节抗肿瘤T细胞应答的免疫疗法和癌症疫苗的功效,所述免疫疗法如PD1/PDL1、CTLA4、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5;(xv)诱导、活化或以其它方式增加PLCã/PKC/钙动员;以及(xvi)诱导、活化或以其它方式增加PI3K/Akt、Ras/MAPK信号传导。

[0134] 免疫抑制细胞有时也被称为骨髓来源的抑制细胞(MDSC)。在人中,MDSC可通过以下标志物组合中的一种来定义:(1)$CD14^+$ $HLA\text{-}DR^{低/-}$,(2)$CD14^+$ $IL4R\alpha^+$,(3)$CD14^+$ $HLA\text{-}DR^-$ $IL4R\alpha^+$,(4)$CD34^+$ $CD14^+$ $CD11b^+$ $Siglec\text{-}7^+$,(5)$CD11b^+$ $CD14^+$ $Siglec\text{-}7^+$,(6)$Siglec\text{-}7^+$ $HLA\text{-}DR^-$,(7)Lin^- $HLA\text{-}DR^-$,(8)Lin^- $HLA\text{-}DR^-$ $Siglec\text{-}7^+$,(9)Lin^- $HLA\text{-}DR^-$ $Siglec\text{-}7^+$ $CD11b^+$,(10)Lin^- $Siglec\text{-}7^+$ $CD11b^+$ $CD15^+$,(11)Lin^- $HLA\text{-}DR^-$ $Siglec\text{-}7^+$ $CD11b^+$ $CD14^-$ $CD15^+$,(12)$CD11b^+$ $CD14^-$ $Siglec\text{-}7^+$,(13)$CD11b^+$ $CD14^-$ $HLA\text{-}DR^-$ $Siglec\text{-}7^+$ $CD15^+$,(14)$Siglec\text{-}7^+$ $HLA\text{-}DR^-$ $CD15^+$,(15)$CD15^+$ $IL4R\alpha^+$,(16)$CD11b^+$ $CD15^+$ $CD66b^+$,(17)$CD15^+$ $FSC^{低}$ $SSC^{高}$,(18)$CD15^{高}$ $Siglec\text{-}7^+$,(19)CD11b+ $CD14^-$ $CD15^+$,(20)$CD66b^+$ $SSC^{高}$,以及(21)$CD11b^+$ $CD15^+$(还参见Solito S等人Annals of the NY Academy of Sciences,2014)。在小鼠中,MDSC可通过表面标志物$CD45^+$、$CD11b^+$、$Gr1^+$和/或$Il4Ra^+$的表达来定义。另外的示例性免疫抑制性单核细胞谱系是$CD45^+$、$CD11b^+$、$Gr1^{低}$;以及$CD45^+$、$CD11c^+$。

[0135] 本公开还涉及与Siglec-7结合或相互作用的药剂，如抗Siglec-7抗体。在某些实施方案中，所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平，和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。

[0136] Siglec-7蛋白

[0137] 在一个方面，本公开提供与本公开的Siglec-7蛋白内的区域如表位相互作用或以其它方式结合至所述区域的分离的(例如单克隆)抗体。在一些实施方案中，本公开的药剂，如本公开的抗Siglec-7抗体结合至Siglec-7蛋白并在与Siglec-7蛋白结合后调节一种或多种Siglec-7活性，例如，与细胞中Siglec-7表达相关的活性。本公开的Siglec-7蛋白包括但不限于哺乳动物Siglec-7蛋白、人Siglec-7蛋白、小鼠Siglec-7蛋白和大鼠Siglec-7蛋白。

[0138] Siglec-7被不同地称为Siglec-7分子、结合唾液酸的Ig样凝集素7、AIRM1、CD328、CDw328、D-Siglec、QA79、SIGLEC19P、SIGLECP2、p75以及p75/AIRM1。

[0139] Siglec-7是主要在免疫细胞和造血细胞上表达的免疫球蛋白样受体，所述细胞包括但不限于单核细胞、巨噬细胞、树突细胞、嗜中性粒细胞、肥大细胞、小神经胶质细胞、淋巴细胞、天然杀伤细胞以及T细胞亚群。

[0140] 已知各种Siglec-7同系物，包括但不限于人Siglec-7、普通黑猩猩Siglec-7、矮小黑猩猩Siglec-7、猩猩Siglec-7、大猩猩Siglec-7以及长臂猿Siglec-7。人Siglec-7的氨基酸序列在下文中列出为SEQ ID NO:1：

[0141]
```
          10          20          30          40          50
MLLLLLLPLL WGRERVEGQK SNRKDYSLTM QSSVTVQEGM CVHVRCSFSY
          60          70          80          90         100
PVDSQTDSDP VHGYWFRAGN DISWKAPVAT NNPAWAVQEE TRDRFHLLGD
         110         120         130         140         150
PQTKNCTLSI RDARMSDAGR YFFRMEKGNI KWNYKYDQLS VNVTALTHRP
         160         170         180         190         200
NILIPGTLES GCFQNLTCSV PWACEQGTPP MISWMGTSVS PLHPSTTRSS
         210         220         230         240         250
VLTLIPQPQH HGTSLTCQVT LPGAGVTTNR TIQLNVSYPP QNLTVTVFQG
         260         270         280         290         300
EGTASTALGN SSSLSVLEGQ SLRLVCAVDS NPPARLSWTW RSLTLYPSQP
         310         320         330         340         350
SNPLVLELQV HLGDEGEFTC RAQNSLGSQH VSLNLSLQQE YTGKMRPVSG
         360         370         380         390         400
VLLGAVGGAG ATALVFLSFC VIFIVVRSCR KKSARPAADV GDIGMKDANT
         410         420         430         440         450
IRGSASQGNL TESWADDNPR HHGLAAHSSG EEREIQYAPL SFHKGEPQDL
         460
SGQEATNNEY SEIKIPK
```

[0142] 在一些实施方案中，所述Siglec-7是包含信号序列的前蛋白。在一些实施方案中，所述Siglec-7是成熟蛋白质。在一些实施方案中，所述成熟Siglec-7蛋白不包含信号序列。在一些实施方案中，所述成熟Siglec-7蛋白在细胞上表达。在一些实施方案中，所述成熟Siglec-7蛋白在细胞，如细胞表面上表达，所述细胞包括但不限于人树突细胞、人巨噬细胞、人单核细胞、人破骨细胞、人嗜中性粒细胞、人T细胞、人辅助T细胞、人细胞毒性T细胞、人粒细胞以及人小神经胶质细胞。本公开的药剂(如本公开的抗Siglec-7抗体)可结合在本文公开的任何细胞上表达的本公开的任何Siglec-7蛋白。

[0143] 本公开的Siglec-7蛋白如人Siglec-7包含若干结构域，包括但不限于位于SEQ ID

NO:1的氨基酸残基1-18处的信号序列,位于SEQ ID NO:1的氨基酸残基39-122处的细胞外免疫球蛋白样可变型(IgV)结构域,位于SEQ ID NO:1的氨基酸残基150-233和240-336的两个Ig-样C2-型结构域,位于SEQ ID NO:1的氨基酸残基354-376处的跨膜结构域,位于SEQ ID NO:1的氨基酸残基435-440处的ITIM基序1以及位于SEQ ID NO:1的氨基酸残基459-463处的ITIM基序2。如本领域技术人员将理解,本公开的结构域的起始和结束残基可根据所使用的计算机建模程序或用于确定结构域的方法而变化。

[0144] 本公开的某些方面提供与人Siglec-7或其同系物(包括但不限于来自其它物种的哺乳动物Siglec-7蛋白和Siglec-7直向同源物)结合的抗Siglec-7抗体。示例性Siglec-7同系物和直向同源物列于表A中。

[0145] 表A:Siglec-7同系物和直向同源物

[0146]

生物体	Siglec-7登录号
普通黑猩猩(泛类人猿)	NCBI登录号XP_009434417.1
矮小黑猩猩(倭黑猩猩)	NCBI登录号XP_008964443.1
猩猩(苏门答腊猩猩)	NCBI登录号XP_009231247
大猩猩(西部低地大猩猩)	NCBI登录号XP_004061321.1
长臂猿(白颊长臂猿)	NCBI登录号XP_003269883.1

[0147] 因此,如本文所用,本公开的"Siglec-7"蛋白包括但不限于哺乳动物Siglec-7蛋白、人Siglec-7蛋白和灵长类动物Siglec-7蛋白。此外,本公开的抗Siglec-7抗体可结合哺乳动物Siglec-7蛋白、人Siglec-7蛋白和灵长类动物Siglec-7中的一种或多种内的表位。在一些实施方案中,本公开的抗Siglec-7抗体可特异性地结合至哺乳动物Siglec-7蛋白、人Siglec-7蛋白或两者。在某些实施方案中,本公开的抗Siglec-7抗体可特异性地结合至人Siglec-7、灵长类动物Siglec-7或两者。

[0148] 在一些实施方案中,本公开的降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或与Siglec-7结合或相互作用的药剂,如本公开的抗Siglec-7抗体可以pH依赖性方式结合Siglec-7。在一些实施方案中,本公开的药剂(如抗Siglec-7抗体)可在中性pH下结合至Siglec-7并被内化而不与Siglec-7蛋白解离。或者,在酸性pH下,本公开的药剂,如抗Siglec-7抗体一旦被内化并随后通过内体/溶酶体途径降解就可从Siglec-7解离。在某些实施方案中,抗Siglec-7抗体在5.5至8.0、5.5至7.5、5.5至7.0、5.5至6.5、5.5至6.0、6.0至8.0、6.5至8.0、7.0至8.0、7.5至8.0、6.0至7.5、6.0至7.0、6.5至7.5范围内的pH下结合Siglec-7。在某些实施方案中,抗Siglec-7抗体在小于6.0、小于5.5、小于5.0、小于4.5、小于4.0、小于3.5、小于3.0、小于2.5或小于2.0的pH下从Siglec-7解离。

[0149] 在一些实施方案中,本公开的降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或与Siglec-7结合或相互作用的药剂,如本公开的抗Siglec-7抗体结合至本公开的野生型Siglec-7蛋白、其天然存在的变体和/或其疾病变体。

[0150] 在一些实施方案中,本公开的降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或与Siglec-7结合或相互作用的药剂,如本公开的

抗Siglec-7抗体结合人Siglec-7的变体。

[0151] 在一些实施方案中，本公开的降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或与Siglec-7结合或相互作用的药剂，如本公开的抗Siglec-7抗体与细胞表面上表达的Siglec-7蛋白结合，所述细胞包括但不限于人树突细胞、人巨噬细胞、人NK细胞、人单核细胞、人破骨细胞、人嗜中性粒细胞、人T细胞、人T辅助细胞、人细胞毒性T细胞、人粒细胞以及人小神经胶质细胞。在一些实施方案中，本公开的降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或与Siglec-7结合或相互作用的药剂，如本公开的抗Siglec-7抗体与细胞表面上表达的Siglec-7蛋白结合，并在与表面表达的Siglec-7蛋白结合后调节(例如诱导或抑制)本公开的至少一种Siglec-7活性。在本公开的一些实施方案中，所述抗Siglec-7抗体特异性地结合至Siglec-7蛋白。在本公开的一些实施方案中，所述抗Siglec-7抗体进一步结合至至少一种另外的Siglec蛋白。在一些实施方案中，所述抗Siglec-7抗体调节至少一种另外的Siglec蛋白或表达所述至少一种另外的Siglec蛋白的细胞的一种或多种活性。

[0152] Siglec-7配体

[0153] 本公开的Siglec-7蛋白可与一种或多种Siglec-7配体相互作用(例如结合)。

[0154] 示例性Siglec-7配体包括但不限于唾液酸、含唾液酸的糖脂、含唾液酸的糖蛋白、含α-2,8-二唾液酸的糖脂、含支链α-2,6-连接的唾液酸的糖蛋白、含末端α-2,6-连接的唾液酸的糖脂、含末端α-2,3-连接的唾液酸的糖蛋白、双唾液酸神经节苷脂(例如含有与唾液酸化聚糖连接的神经酰胺的神经节苷脂或糖脂)、分泌的粘蛋白、在红细胞上表达的Siglec-7配体、在细菌细胞上表达的Siglec-7配体、在凋亡细胞上表达的Siglec-7配体、在神经细胞上表达的Siglec-7配体、在神经胶质细胞上表达的Siglec-7配体、在小神经胶质细胞上表达的Siglec-7配体、在星形胶质细胞上表达的Siglec-7配体、在肿瘤细胞上表达的Siglec-7配体、在病毒上表达的Siglec-7配体、在树突细胞上表达的Siglec-7配体、与β淀粉样蛋白斑块结合的Siglec-7配体、与Tau缠结结合的Siglec-7配体、致病蛋白上的Siglec-7配体、致病肽上的Siglec-7配体、在巨噬细胞上表达的Siglec-7配体、在嗜中性粒细胞上表达的Siglec-7配体、在单核细胞上表达的Siglec-7配体、在天然杀伤细胞上表达的Siglec-7配体、在T细胞上表达的Siglec-7配体、在T辅助细胞上表达的Siglec-7配体、在细胞毒性T细胞上表达的Siglec-7配体、在B细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制树突细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制巨噬细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制嗜中性粒细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制NK细胞上表达的Siglec-7配体、在骨髓源性抑制细胞上表达的Siglec-7配体以及在调控性T细胞上表达的Siglec-7配体。在一些实施方案中，本公开的Siglec-7配体是神经节苷脂(例如，双唾液酸神经节苷脂)。双唾液酸神经节苷脂通常共有乳-神经酰胺核心和一个或多个唾液酸残基。

[0155] 合适的Siglec-7配体的其它实例描绘于图2中。

[0156] 合适的神经节苷脂(例如，双唾液酸神经节苷脂)配体的其它实例描绘于图3中并列于表B中。通常，神经节苷脂(例如，双唾液酸神经节苷脂)是由糖链上连接有一种或多种唾液酸(例如，n-乙酰基-神经氨酸，NANA)的鞘糖脂构成的分子。

[0157] 表B:示例性神经节苷脂Siglec-7配体的结构

[0158]

GM2-1 = aNeu5Ac(2-3)bDGalp(1-?)bDGalNAc(1-?)bDGalNAc(1-?)bDGlcp(1-1)Cer
GM3 = aNeu5Ac(2-3)bDGalp(1-4)bDGlcp(1-1)Cer
GM2,GM2a(?) = bDGalpNAc(1-4)[aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GM2b(?) = aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlcp(1-1)Cer
GM1,GM1a = bDGalp(1-3)bDGalNAc[aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
去唾液酸-GM1,GA1 = bDGalp(1-3)bDGalpNAc(1-4)bDGalp(1-4)bDGlcp(1-1)Cer
去唾液酸-GM2,GA2 = bDGalpNAc(1-4)bDGalp(1-4)bDGlcp(1-1)Cer
GM1b = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)bDGalp(1-4)bDGlcp(1-1)Cer
GD3 = aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlcp(1-1)Cer
GD2 = bDGalpNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GD1a = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GD1alpha = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-6)]bDGalp(1-4)bDGlcp(1-1)Cer
GD1b = bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GT1a = aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GT1,GT1b = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
OAc-GT1b = aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)aXNeu5Ac9Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GT1c = bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GT3 = aNeu5Ac(2-8)aNeu5Ac(2-8)aNeu5Ac(2-3)bDGal(1-4)bDGlc(1-1)CerGQ1b = aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-3)bDGalNAc(1-4)[aNeu5Ac(2-8)aNeu5Ac(2-3)]bDGalp(1-4)bDGlcp(1-1)Cer
GGal = aNeu5Ac(2-3)bDGalp(1-1)Cer
其中：
aNeu5Ac = 5-乙酰基-α-神经氨酸
aNeu5Ac9Ac = 5,9-二乙酰基-α-神经氨酸
bDGalp = β-D-吡喃半乳糖
bDGalpNAc = N-乙酰基-β-D-吡喃半乳糖
bDGlcp = β-D-吡喃葡萄糖
Cer = 神经酰胺(一般N-酰化鞘氨醇)

[0159] Siglec-7剂

[0160] 本公开的某些方面涉及降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂(例如,Siglec-7药剂)。本公开的其它方面涉及与Siglec-7结合或相互作用的药剂(例如Siglec-7药剂)。在一些实施方案中,本公开的药剂阻断、抑制、降低或干扰体外、原位和/或体内Siglec-7蛋白的一种或多种活性。在一些实施方案中,本公开的药剂不会阻断、抑制、降低或干扰体外、原位和/或体内Siglec-7蛋白的一种或多种活性。在一些实施方案中,本公开的药剂增加、活化或诱导体外、原位和/或体内Siglec-7蛋白的一种或多种活性。

[0161] 在某些实施方案中,本公开的药剂是降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂(例如,Siglec-7药剂)。本公开的降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂是具有一种或多种以下特征的分子:(1)抑制或降低一种或更多Siglec-7活性;(2)抑制或降低Siglec-7与一种或多种其配体结合的能力;(3)降低表达Siglec-7的细胞中的Siglec-7表达(如在mRNA水平和/或在蛋白质水平下)的能力;(4)与Siglec-7蛋白相互作用、结合或识别Siglec-7蛋白的能力;(5)与Siglec-7蛋白特异性地相互作用或结合的能力;以及(6)治疗、改善或预防本文描述或考虑的疾病或病症的任何方面的能力。

[0162] 抑制Siglec-7产生的示例性药剂包括但不限于特异性地抑制Siglec-7合成和/或释放的化合物、针对Siglec-7的反义分子或针对编码Siglec-7的核酸的短干扰RNA(siRNA)分子。抑制一种或多种Siglec-7活性的其它示例性药剂包括但不限于,特异性地结合至Siglec-7蛋白的抗Siglec-7抗体、特异性地抑制一种或多种Siglec-7活性的化合物(如小分子抑制剂和/或肽抑制剂)、特异性地抑制Siglec-7与一种或多种配体的结合的化合物、Siglec-7结构类似物或结合Siglec-7的RNA或DNA适体。在一些实施方案中,降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂是变构抑制剂。在一些实施方案中,降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种

Siglec-7配体之间的相互作用的药剂是正构抑制剂。

[0163] 在某些实施方案中，降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂是小分子抑制剂，包括但不限于小肽或肽样分子、可溶性肽和合成的非肽基有机或无机化合物。小分子抑制剂可具有约100至约20,000道尔顿(Da)、约500至约15,000Da、约1000至约10,000Da中的任一个的分子量。用于制备和测试小分子对一种或多种Siglec-7活性的抑制作用的方法在本领域中是熟知的，并且此类方法可用于评估小分子抑制剂对Siglec-7活性的影响。例如，本文公开的任何方法和测定都可用于筛选降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的小分子抑制剂。

[0164] 在某些实施方案中，降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂是与Siglec-7结合或物理相互作用的抗Siglec-7抗体。所述抗体可对靶抗原(例如，Siglec-7)具有纳摩尔或甚至皮摩尔亲和力。在某些实施方案中，所述抗体的Kd是约0.002至约100nM。在某些实施方案中，所述抗体的Kd是约0.05至约100nM。在某些实施方案中，所述抗体的Kd是约0.05至约50nM。在某些实施方案中，所述抗体的Kd是约0.05至约10nM。在某些实施方案中，所述抗体的Kd是约0.05至约2nM。在某些实施方案中，所述抗体的Kd是约0.1至约2nM。例如，所述抗体的Kd是以下中的任一个：约100nM、约90nM、约80nM、约70nM、约60nM、约50nM、约45nM、约40nM、约35nM、约30nM、约25nM、约20nM、约15nM、约10nM、约9nM、约8nM、约7nM、约6nM、约5nM、约4nM、约3nM、约2nM、约1nM、约900pM、约800pM、约700pM、约600pM、约500pM、约400pM、约300pM、约200pM、约100pM、约75pM或约50pM至以下中的任一个：约2pM、约5pM、约10pM、约15pM、约20pM、约25pM、约50pM、约75pM、约100pM、约200pM、约300pM、约400pM、约500pM、约600pM、约700pM、约800pM、约900pM、约1nM或约2nM。在一些实施方案中，Siglec-7的解离常数(K_D)在大约25℃的温度下测定。在一些实施方案中，使用单价抗体(例如，Fab)或单价形式的全长抗体来测定K_D。本文描述了用于制备和选择与Siglec-7特异性相互作用和/或结合的抗体的方法。(例如，参见实施例1)。

[0165] 在某些实施方案中，降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂包含至少一种能够通过靶向编码Siglec-7的核酸而阻断或降低功能性Siglec-7的表达的反义分子。Siglec-7的核酸序列在本领域中是已知的。例如，人Siglec-7可具有如NCBI登录号NM_014385.3中所示的核酸序列，并且普通黑猩猩Siglec-7可具有如NCBI登录号XM_009436142.1中所示的核酸序列。已知用于制备反义寡核苷酸分子的方法，并且此类方法可用于制备将特异性地结合一种或多种Siglec-7 mRNA而不与其它多核苷酸交叉反应的反义寡核苷酸。靶向的示例性位点包括但不限于起始密码子、5′调控区、编码序列(包括任何保守的共有区)以及3′非翻译区。在某些实施方案中，反义寡核苷酸的长度是约10至约100个核苷酸、约15至约50个核苷酸、约18至约25个核苷酸或更多。在某些实施方案中，所述寡核苷酸还包含化学修饰以增加核酸酶抗性等，例如像本领域的普通技术人员已知的硫代磷酸酯键联和2′-O-糖修饰。

[0166] 在某些实施方案中，降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂包含至少一种能够通过靶向编码Siglec-7的核酸而阻断或降低功能性Siglec-7的表达的siRNA分子。用于制备siRNA分子的方法在本领域中是熟知的，并且此类方法可用于制备将特异性地靶向Siglec-7 mRNA而不与其它多核苷酸交

叉反应的siRNA分子。siRNA分子可通过诸如通过典型固相寡核苷酸合成的方法产生，并且通常将并入化学修饰以增加siRNA药剂的半衰期和/或功效，和/或允许更稳健的递送制剂。或者，使用编码用于siRNA的细胞内转录的表达盒的载体来递送siRNA分子。

[0167] 在某些实施方案中，降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂是与Siglec-7结合或物理相互作用的RNA或DNA适体，并阻断Siglec-7与一种或多种其配体之间的相互作用。在某些实施方案中，所述适体包含至少一种结合至成熟形式的Siglec-7的RNA或DNA适体。

[0168] 在某些实施方案中，降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂包含至少一种Siglec-7结构类似物。术语Siglec-7结构类似物是指具有与Siglec-7的三维结构的一部分类似的三维结构并且在生理条件下在体外或体内结合至一种或多种CD3配体的化合物，其中所述结合至少部分地抑制Siglec-7生物活性。合适的Siglec-7结构类似物可通过Siglec-7与本公开的配体(如Siglec-7配体)的结合的分子建模来设计和合成。Siglec-7结构类似物可以是相同或不同结构的任何所需组合的单体、二聚体或更高级多聚体，以获得改善的亲和力和生物作用。在一些实施方案中，所述药剂与Siglec-7的氨基酸序列结合或相互作用。

[0169] 在某些实施方案中，降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂包含可溶性Siglec-7受体蛋白、可溶性Siglec-7-Fc融合蛋白(例如，Siglec-7免疫粘附素)、结合至Siglec-7配体的可溶性Siglec受体、结合至Siglec-7配体的Siglec-Fc融合蛋白(例如，Siglec免疫粘附素)。在某些实施方案中，此类药剂结合一种或多种Siglec-7配体，且由此防止给定Siglec-7配体与功能性Siglec-7受体之间的相互作用。

[0170] 在某些实施方案中，本公开的药剂是与Siglec-7结合或相互作用的药剂(例如，Siglec-7药剂)。与Siglec-7结合或相互作用的示例性药剂包括但不限于惰性抗Siglec-7抗体、激动剂抗Siglec-7抗体、Siglec-7配体、Siglec-7配体激动剂片段、Siglec-7免疫粘附素、Siglec-7可溶性受体、Siglec-Fc融合蛋白(例如，Siglec免疫粘附素)、可溶性Siglec受体、Siglec-7配体模拟物以及小分子化合物。小分子化合物可具有约100至约20,000道尔顿(Da)、约500至约15,000Da、约1000至约10,000Da中的任一个的分子量。用于制备和测试药剂对一种或多种Siglec-7活性的作用的方法在本领域中是熟知的，并且此类方法可用于评估小分子抑制剂对Siglec-7活性的影响。例如，本文公开的任何方法和测定可用于筛选与Siglec-7结合或相互作用的小分子抑制剂。

[0171] 测定

[0172] 降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂可使用本领域中熟知的方法鉴定和/或表征，例如放射性标记的抑制剂测定、光学测定、蛋白质结合测定、生物化学筛选测定、免疫测定、质量偏移测量测定、荧光测定和/或荧光肽裂解测定。

[0173] 结合测定和其它测定

[0174] 在某些实施方案中，降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的药剂可通过本领域中熟知的用于检测Siglec-7药剂候选物与Siglec-7的相互作用和/或结合亲和力的存在的技术来鉴定。

[0175] 在某些实施方案中，可使用放射性标记的抑制剂测定来鉴定与Siglec-7相互作用的药剂。例如，已知量的放射性标记药剂候选物可与已知量的固定化Siglec-7和缓冲液一起孵育。随后，可用缓冲液洗涤固定化的Siglec-7，并且可使用本领域中已知的技术(例如像γ计数器)来测量固定化的Siglec-7的放射性标记的Siglec-7药剂候选物的剩余存在。指示放射性标记物质的存在的测量可指示放射性标记的药剂候选物能够与Siglec-7相互作用和/或结合。

[0176] 在某些实施方案中，可使用光学技术来鉴定与Siglec-7相互作用的药剂。用于检测Siglec-7药剂的示例性光学技术可包括例如将Siglec-7连接至比色共振接枝表面、从而由于光必须采取的光学路径的变化而改变反射光的波长，并且随后在允许候选药剂与Siglec-7相互作用时测量反射光波长的另外变化。例如，当将药剂与Siglec-7一起孵育时，反射光的测量波长没有变化可能表明药剂候选物不能与Siglec-7相互作用。当药剂候选物与Siglec-7一起孵育时，反射光的测量波长的变化可表明所述药剂候选物能够与Siglec-7结合和/或相互作用。

[0177] 在某些实施方案中，可使用蛋白质结合测定来鉴定与Siglec-7相互作用的药剂。用于检测Siglec-7药剂的示例性蛋白质结合测定可包括例如在药剂候选物存在下对Siglec-7的免疫共沉淀。例如，可将Siglec-7与药剂候选物一起在缓冲液中孵育，且随后可使用对捕获Siglec-7具有特异性的固定化分子(例如像抗Siglec-7抗体)来在药剂候选物存在下捕获Siglec-7并且在本领域中已知的洗涤程序期间结合Siglec-7，可能具有相互作用药剂候选物。随后，可释放可能具有相互作用药剂候选物的Siglec-7，并且可基于药剂候选特征通过例如像质谱和/或蛋白质印迹的技术来检测药剂候选物的存在。

[0178] 在某些实施方案中，可使用本领域中熟知的生物化学和/或免疫测定测定来鉴定与Siglec-7相互作用的药剂。示例性技术可包括例如使用技术(例如像蛋白质印迹、免疫染色和免疫共沉淀)定量测量Siglec-7浓度和/或蛋白质半衰期的变化的测定。例如，可将药剂候选物与含有Siglec-7的样品(如表达Siglec-7的细胞)一起孵育，且随后可在时程研究期间的点处测量Siglec-7蛋白的量和/或细胞水平。与对照治疗相比，蛋白质量、细胞水平和/或蛋白质半衰期的变化可表明Siglec-7药剂候选物可能能够改变Siglec-7半衰期和/或活性。

[0179] 在某些实施方案中，质量偏移测量测定可用于鉴定与Siglec-7相互作用的药剂。示例性质量偏移测量测定可包括例如通过使用仪器(如但不限于质谱仪)当药剂候选物与Siglec-7相互作用时测量Siglec-7质量的变化来检测强和/或共价结合的Siglec-7药剂的存在。例如，取决于药剂候选物相互作用的性质，可对整个蛋白质和/或基于肽的分析进行质量偏移测定。检测与向Siglec-7添加所述药剂候选物相关的质量偏移可表明药剂候选物可能能够与Siglec-7相互作用或以其它方式抑制Siglec-7。另外，示例性质量偏移测量测定可包括例如使用技术(例如像表面等离子体共振)当药剂候选物与Siglec-7相互作用时检测向Siglec-7添加与相应药剂候选物质量相关的质量。例如，可测量光的折射率的变化并且将其与传感器表面附着的Siglec-7的质量变化相关联。

[0180] 在某些实施方案中，化学交联测定可用于鉴定与Siglec-7相互作用的Siglec-7试剂。例如，药剂候选物可与Siglec-7在体内或体外与能够将与Siglec-7相互作用的药剂候选物共价连接至所述Siglec-7分子的分子交联剂一起孵育。随后，可使用诸如但不限于质

谱法和/或蛋白质印迹的技术来鉴定能够与Siglec-7相互作用或以其它方式抑制Siglec-7的药剂候选物。例如，检测与药剂候选物共价交联的Siglec-7可表明所述药剂候选物可能能够与Siglec-7相互作用或以其它方式抑制Siglec-7。

[0181] 在某些实施方案中，可使用荧光测定来鉴定与Siglec-7相互作用的药剂。例如，已知量的荧光药剂候选物可与已知量的固定化Siglec-7和缓冲液一起孵育。随后，可用缓冲液洗涤固定化的Siglec-7，并且可使用本领域中已知的技术(如但不限于荧光检测)来测量固定化的Siglec-7的荧光Siglec-7药剂候选物的剩余存在。指示荧光物质的存在的测量可指示荧光药剂候选物能够与Siglec-7相互作用和/或结合。

[0182] 活性测定

[0183] 本领域已知和本文描述的测定(例如实施例1-10)可用于鉴定和测试本公开的Siglec-7药剂的生物活性。在一些实施方案中，提供了用于测试Siglec-7药剂调节一种或多种Siglec-7活性的能力的测定。

[0184] 抗Siglec-7抗体

[0185] 本公开的某些方面涉及降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如，结合)的抗Siglec-7抗体。在一些实施方案中，所述抗Siglec-7抗体降低Siglec-7的细胞水平而不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如，结合)。在一些实施方案中，所述抗Siglec-7抗体抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如，结合)。在一些实施方案中，所述抗Siglec-7抗体降低Siglec-7的细胞水平并抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如，结合)。

[0186] Siglec-7的细胞水平可指但不限于Siglec-7的细胞表面水平、Siglec-7的细胞内水平和Siglec-7的总水平。在一些实施方案中，Siglec-7的细胞水平的降低包括Siglec-7的细胞表面水平的降低。如本文所用，如果抗Siglec-7抗体诱导Siglec-7的细胞表面水平降低21％或更多，如通过本文所述或本领域中已知的任何体外基于细胞的测定或合适的体内模型所测量，例如利用流式细胞术如荧光活化的细胞分选(FACS)来测量Siglec-7的细胞表面水平，则所述抗Siglec-7抗体降低Siglec-7的细胞表面水平。在一些实施方案中，Siglec-7的细胞水平的降低包括Siglec-7的细胞内水平的降低。如本文所用，如果抗Siglec-7抗体诱导Siglec-7的细胞内水平降低21％或更多，如通过本文所述或本领域中已知的任何体外基于细胞的测定或合适的体内模型(例如免疫染色、蛋白质印迹分析、免疫共沉淀以及细胞计数)所测量，则所述抗Siglec-7抗体降低Siglec-7的细胞内水平。在一些实施方案中，Siglec-7的细胞水平的降低包括Siglec-7的总水平的降低。如本文所用，如果抗Siglec-7抗体诱导Siglec-7的总水平降低21％或更多，如通过本文所述或本领域中已知的任何体外基于细胞的测定或合适的体内模型(例如免疫染色、蛋白质印迹分析、免疫共沉淀以及细胞计数)所测量，则所述抗Siglec-7抗体降低Siglec-7的总水平。在一些实施方案中，所述抗Siglec-7抗体诱导Siglec-7降解、Siglec-7裂解、Siglec-7内化、Siglec-7脱落和/或Siglec-7表达的下调。在一些实施方案中，利用体外细胞测定在原代细胞(例如树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞和巨噬细胞)上或细胞系上测量Siglec-7的细胞水平。

[0187] 在一些实施方案中，与在抗Siglec-7抗体不存在下Siglec-7的细胞水平相比，本

公开的抗Siglec-7抗体使Siglec-7的细胞水平降低至少21％、至少22％、至少23％、至少24％、至少25％、至少26％、至少27％、至少28％、至少29％、至少30％、至少31％、至少32％、至少33％、至少34％、至少35％、至少36％、至少37％、至少38％、至少39％、至少40％、至少41％、至少42％、至少43％、至少44％、至少45％、至少46％、至少47％、至少48％、至少49％、至少50％、至少51％、至少52％、至少53％、至少54％、至少55％、至少56％、至少57％、至少58％、至少59％、至少60％、至少61％、至少62％、至少63％、至少64％、至少65％、至少66％、至少67％、至少68％、至少69％、至少70％、至少71％、至少72％、至少73％、至少74％、至少75％、至少76％、至少77％、至少78％、至少79％、至少80％、至少81％、至少82％、至少83％、至少84％、至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或更多。

[0188] 在一些实施方案中，本公开的抗Siglec-7抗体以可小于10nM、小于9.5nM、小于9nM、小于8.5nM、小于8nM、小于7.5nM、小于7nM、小于6.5nM、小于6nM、小于5.5nM、小于5nM、小于4.5nM、小于4nM、小于3.5nM、小于3nM、小于2.5nM、小于2nM、小于1.5nM、小于1.4nM、小于1.3nM、小于1.2nM、小于1.1nM、小于1nM、小于500pM、小于450pM、小于400pM、小于350pM、小于300pM、小于250pM、小于200pM、小于175pM、小于170pM、小于169pM、小于168pM、小于167pM、小于166pM、小于166.2pM、小于165pM、小于164pM、小于163pM、小于162pM、小于161pM、小于160pM、小于150pM、小于145pM、小于140pM、小于139pM、小于138pM、小于138.2pM、小于137pM、小于136pM、小于135pM、小于134pM、小于133pM、小于132pM、小于131pM、小于130pM、小于120pM、小于110pM、小于100pM、小于90pM、小于80pM、小于70pM、小于60pM、小于50pM、小于40pM、小于35pM、小于33pM、小于30pM、小于20pM、小于19pM、小于18pM、小于17pM、小于16pM、小于15pM、小于14pM、小于13pM、小于12pM、小于11pM或小于10pM的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。在一些实施方案中，本公开的抗Siglec-7抗体以在约10nM至约10pM或小于10pM范围内的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。在一些实施方案中，本公开的抗Siglec-7抗体以在约10nM至约100pM或小于100pM范围内的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。在一些实施方案中，本公开的抗Siglec-7抗体以在约10nM至约300pM或小于300pM范围内的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。在一些实施方案中，本公开的抗Siglec-7抗体以在约2nM至约10pM或小于10pM范围内的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。在一些实施方案中，本公开的抗Siglec-7抗体以在约2nM至约100pM或小于100pM范围内的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。在一些实施方案中，本公开的抗Siglec-7抗体以在约2nM至约300pM或小于300pM范围内的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。在一些实施方案中，本公开的抗Siglec-7抗体以在约1.4nM至约10pM或小于10pM范围内的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。在一些实施方案中，本公开的抗Siglec-7抗体以在约1.4nM至约100pM或小于100pM范围内的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。在一些实施方案中，本公开的抗Siglec-7抗体以在约1.4nM至约300pM或小于300pM范围内的半最大有效浓度(EC_{50})结合至人细胞，如原代树突细胞。本文所述的任何合适的方法(例如参见实施例1-3)可用于计算结合至人细胞如原代树突细胞的本公开的抗Siglec-7抗体的半最大有效浓度(EC_{50})。在一些实施方案中，半最大有效浓度(EC_{50})在大约4℃的温度下测定。

[0189] 在一些实施方案中，本公开的抗Siglec-7抗体以可小于500pM、小于450pM、小于400pM、小于350pM、小于300pM、小于250pM、小于200pM、小于175pM、小于170pM、小于169pM、小于168pM、小于167pM、小于166pM、小于166.2pM、小于165pM、小于164pM、小于163pM、小于162pM、小于161pM、小于160pM、小于150pM、小于145pM、小于140pM、小于139pM、小于138pM、小于138.2pM、小于137pM、小于136pM、小于135pM、小于134pM、小于133pM、小于132pM、小于131pM、小于130pM、小于120pM、小于110pM、小于100pM、小于90pM、小于80pM、小于70pM、小于60pM、小于50pM、小于40pM、小于35pM、小于33pM、小于30pM、小于20pM、小于19pM、小于18pM、小于17pM、小于16pM、小于15pM、小于14pM、小于13pM、小于12pM、小于11pM或小于10pM的半最大有效浓度(EC_{50})降低Siglec-7的细胞水平。在一些实施方案中，本公开的抗Siglec-7抗体以在约500pM至约18pM或小于18pM范围内的半最大有效浓度(EC_{50})降低Siglec-7的细胞水平。在一些实施方案中，本公开的抗Siglec-7抗体以在约500pM至约33pM或小于33pM范围内的半最大有效浓度(EC_{50})降低Siglec-7的细胞水平。在一些实施方案中，本公开的抗Siglec-7抗体以在约350pM至约18pM或小于18pM范围内的半最大有效浓度(EC_{50})降低Siglec-7的细胞水平。在一些实施方案中，本公开的抗Siglec-7抗体以在约350pM至约33pM或小于33pM范围内的半最大有效浓度(EC_{50})降低Siglec-7的细胞水平。可使用任何合适的方法(例如，参见实施例1-3)来测量本公开的抗Siglec-7抗体的半最大有效浓度(EC_{50})。在一些实施方案中，EC_{50}在大约37℃的温度下测定。

[0190] 本文描述的或本领域中已知的任何体外基于细胞的测定或合适的体内模型可用于测量Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)的抑制。在一些实施方案中，利用本文所述的或本领域中已知的任何体外测定或基于细胞的培养测定，在饱和抗体浓度(例如67nM)下，本公开的抗Siglec-7抗体将Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如，结合)抑制至少21％、至少22％、至少23％、至少24％、至少25％、至少26％、至少27％、至少28％、至少29％、至少30％、至少31％、至少32％、至少33％、至少34％、至少35％、至少36％、至少37％、至少38％、至少39％、至少40％、至少41％、至少42％、至少43％、至少44％、至少45％、至少46％、至少47％、至少48％、至少49％、至少50％、至少51％、至少52％、至少53％、至少54％、至少55％、至少56％、至少57％、至少58％、至少59％、至少60％、至少61％、至少62％、至少63％、至少64％、至少65％、至少66％、至少67％、至少68％、至少69％、至少70％、至少71％、至少72％、至少73％、至少74％、至少75％、至少76％、至少77％、至少78％、至少79％、至少80％、至少81％、至少82％、至少83％、至少84％、至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或更多。

[0191] 在一些实施方案中，本公开的抗Siglec-7抗体抑制Siglec-7的细胞表面簇集。在一些实施方案中，本公开的抗Siglec-7抗体抑制Siglec-7蛋白的一种或多种活性，包括但不限于，通过Src家族酪氨酸激酶如Syk、LCK、FYM和/或ZAP70磷酸化Tyr-437和Tyr-460；募集并结合至酪氨酸特异性蛋白磷酸酶SHP1和SHP2；募集并结合至PLC-γ1，其充当发动蛋白-1的鸟嘌呤核苷酸交换因子；募集并结合至含SH2结构域的蛋白质(例如Crk1)；募集并结合至脾酪氨酸激酶Syk；募集并结合至SH3-SH2-SH3生长因子受体结合蛋白2(Grb2)；募集并结合至多种含SH2的蛋白质；调节一种或多种促炎性细胞因子的表达，任选地其中所述一种或多种抗炎细胞因子选自由以下各项组成的组：IFN-a4、IFN-β、IL-1â、IL-1α、TNF-á、IL-

6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-33、MCP-1以及MIP-1-β;调节一种或多种细胞中的一种或多种促炎性细胞因子的表达,所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞;调节一种或多种抗炎细胞因子的表达,任选地其中所述一种或多种抗炎细胞因子选自IL-4、IL-10、IL-13、IL-35、IL-16、TGF-β、IL-1Ra、G-CSF以及TNF、IFN-β1a、IFN-β1b或IL-6的可溶性受体;调节一种或多种细胞中的一种或多种抗炎细胞因子的表达,所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞;调节一种或多种选自以下的蛋白质的表达:C1qa、C1qB、C1qC、C1s、C1R、C4、C2、C3、ITGB2、HMOX1、LAT2、CASP1、CSTA、VSIG4、MS4A4A、C3AR1、GPX1、TyroBP、ALOX5AP、ITGAM、SLC7A7、CD4、ITGAX以及PYCARD;抑制细胞外信号调控激酶(ERK)磷酸化;降低一种或多种细胞蛋白上的酪氨酸磷酸化,任选地,其中所述一种或多种细胞蛋白包含ZAP-70并且所述酪氨酸磷酸化发生在ZAP-70的Tyr-319上;调节C-C趋化因子受体7(CCR7)的表达;抑制针对表达CCL19的细胞和表达CCL21的细胞的小神经胶质细胞趋化性;减少由一种或多种细胞诱导的T细胞增殖,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞、M2小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞以及M2 NK细胞;抑制破骨细胞产生,降低破骨细胞生成速率或两者;降低一种或多种细胞的存活,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;降低一种或多种细胞的增殖,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;抑制一种或多种细胞的迁移,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;抑制一种或多种细胞的一种或多种功能,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;抑制一种或多种细胞的成熟,所述

一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；抑制一种或多种类型的清除，所述清除选自凋亡神经元清除、神经组织碎片清除、功能障碍性突触清除、非神经组织碎片清除、细菌清除、其它异物清除、致病蛋白清除、致病肽清除、致病核酸清除以及肿瘤细胞清除；任选地，其中所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽，所述致病核酸是反义GGCCCC(G2C4)重复序列-扩增RNA，并且所述肿瘤细胞来自癌症，所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌；抑制以下中的一种或多种的吞噬：凋亡神经元、神经组织碎片、功能障碍性突触、非神经组织碎片、细菌、其它异物、致病蛋白、致病肽、致病核酸或肿瘤细胞；任选地其中所述致病核酸是反义GGCCCC(G2C4)重复序列-扩增RNA，所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽，并且所述肿瘤细胞来自癌症，所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤或甲状腺癌；与肿瘤细胞上的Siglec-7配体结合；与细胞上的Siglec-7配体结合，所述细胞选自嗜中性粒细胞、树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞以及NK细胞；通过以下中的一种或多种抑制肿瘤细胞杀伤：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；抑制以下中的一种或多种的抗肿瘤细胞增殖活性：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、

T细胞、T辅助细胞或细胞毒性T细胞;抑制以下中的一种或多种的抗肿瘤细胞转移活性:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;抑制一种或多种含ITAM基序的受体,任选地其中所述一种或多种含ITAM基序的受体选自TREM1、TREM2、Sirpβ、FcgR、DAP10以及DAP12;通过一种或多种模式识别受体(PRR)抑制信号传导,任选地其中所述一种或多种PRR选自鉴定病原体相关分子模式(PAMP)的受体、鉴定损伤相关分子模式(DAMP)的受体以及其任何组合;抑制包含基序D/Ex_{0-2}YxxL/IX_{6-8}YxxL/I(SEQ ID NO:537)的一种或多种受体;通过一种或多种Toll样受体抑制信号传导;抑制JAK-STAT信号传导途径;抑制活化的B细胞的核因子κ-轻链增强子(NFêB);含有ITAM基序的受体的去磷酸化;调节一种或多种炎性受体的表达,任选地其中所述一种或多种炎性受体包含CD86并且所述一种或多种炎性受体在以下中的一种或多种上表达:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突状细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;增加一种或多种Siglec-7依赖性基因的表达;破坏的Siglec-7依赖性基因表达的正常化;降低一种或多种ITAM依赖性基因的表达,任选地其中所述一种或多种ITAM依赖性基因通过活化T细胞(NFAT)转录因子的核因子活化;促进或挽救以下中的一种或多种的功能性:免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞;增加以下中的一种或多种浸润到肿瘤中:免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞;增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量;增强骨髓源性抑制细胞的肿瘤促进活性;增加肿瘤或外周血中肿瘤促进细胞因子(如TGF-β或IL-10)的表达;增加肿瘤促进FoxP3+调控性T淋巴细胞的肿瘤浸润;增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性;减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化;减少具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润;降低NK细胞的肿瘤杀伤潜力;减少具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润;减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润;增加肿瘤体积;增加肿瘤生长速率;增加转移;增加肿瘤复发率;降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效,如免疫疗法是靶向一种或多种靶蛋白的免疫疗法,所述一种或多种靶蛋白选自PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、TREM1、TREM2、CSF-1受体以及其任何组合;抑制PLCã/PKC/钙动员;以及抑制PI3K/Akt、Ras/MAPK信号传导。

[0192] 在一些实施方案中,本公开的抗Siglec-7抗体表现出一种或多种活性,包括但不限于,增加肿瘤浸润$CD3^+$ T细胞的数量;抑制Siglec-7与一种或多种Siglec-7配体的结合;降低外周免疫细胞中Siglec-7的细胞水平;减少非致瘤性$CD14^+$骨髓细胞的数量,任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞,或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于血液中;减少非致瘤性$CD14^+$骨髓细胞的数量,任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞,或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于肿瘤中;降低一种或多种细胞中的PD-L1水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);降低一种或多种细胞中的PD-L2水平,任选地其中所述一种或多种细胞是非致瘤

性骨髓源性抑制细胞(MDSC);降低一种或多种细胞中的CD11b水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);降低一种或多种细胞中的B7-H3水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);降低一种或多种细胞中的CD200R水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);降低一种或多种细胞中的CD163水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);降低一种或多种细胞中的CD206水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);降低实体肿瘤的肿瘤生长速率;减小肿瘤体积;提高一种或多种PD-1抑制剂的功效;提高一种或多种检查点抑制剂疗法和/或免疫调节疗法的功效,任选地其中所述一种或多种检查点抑制剂疗法和/或免疫调节疗法靶向以下中的一种或多种:CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3、LAG3或其任何组合;抑制非致瘤性骨髓源性抑制细胞的(MDSC)分化、存活和/或一种或多种功能;诱导一种或多种骨髓源性抑制细胞(MDSC)的细胞死亡;以及在非致瘤性骨髓源性抑制细胞(MDSC)存在下增加T细胞的增殖。

[0193] 在一些实施方案中,所述抗Siglec-7抗体抑制本公开的Siglec-7蛋白与一种或多种Siglec-7配体之间的相互作用(例如结合),所述配体包括但不限于,在红细胞上表达的Siglec-7配体、在细菌细胞上表达的Siglec-7配体、在凋亡细胞上表达的Siglec-7配体、在神经细胞上表达的Siglec-7配体、在神经胶质细胞上表达的Siglec-7配体、在小神经胶质细胞上表达的Siglec-7配体、在星形胶质细胞上表达的Siglec-7配体、在肿瘤细胞上表达的Siglec-7配体、在病毒上表达的Siglec-7配体、在树突细胞上表达的Siglec-7配体、与β淀粉样蛋白斑块结合的Siglec-7配体、与Tau缠结结合的Siglec-7配体、致病蛋白上的Siglec-7配体、致病肽上的Siglec-7配体、在巨噬细胞上表达的Siglec-7配体、在嗜中性粒细胞上表达的Siglec-7配体、在单核细胞上表达的Siglec-7配体、在天然杀伤细胞上表达的Siglec-7配体、在T细胞上表达的Siglec-7配体、在T辅助细胞上表达的Siglec-7配体、在细胞毒性T细胞上表达的Siglec-7配体、在B细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制树突细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制巨噬细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制嗜中性粒细胞上表达的Siglec-7配体、在肿瘤包埋的免疫抑制NK细胞上表达的Siglec-7配体、在骨髓源性抑制细胞上表达的Siglec-7配体以及在调控性T细胞上表达的Siglec-7配体。在一些实施方案中,本公开的Siglec-7配体是神经节苷脂(例如,双唾液酸神经节苷脂)。

[0194] 在一些实施方案中,本公开的抗Siglec-7抗体结合至在细胞表面上表达的本公开的Siglec-7蛋白,并且裸抗体抑制Siglec-7蛋白与一种或多种Siglec-7配体之间的相互作用(例如,结合)。在一些实施方案中,结合至本公开的Siglec-7蛋白的本公开的抗Siglec-7抗体通过降低可用于在细胞表面上或细胞内与这些蛋白质相互作用的Siglec-7的有效水平来抑制Siglec-7蛋白与一种或多种Siglec-7配体之间的相互作用(例如结合)。在一些实施方案中,结合至本公开的Siglec-7蛋白的本公开的抗Siglec-7抗体通过诱导Siglec-7的降解来抑制Siglec-7蛋白与一种或多种Siglec-7配体之间的相互作用(例如结合)。

[0195] 本公开的其它方面涉及抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。

[0196] 如本文所用,利用本文所述的或本领域中已知的任何体外基于细胞的测定或合适

的体内模型，如果与不存在抗Siglec-7抗体的情况下Siglec-7的细胞水平相比，抗Siglec-7抗体使Siglec-7的细胞表面水平降低少于20％，则所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平。在一些实施方案中，与不存在抗Siglec-7抗体情况下Siglec-7的细胞水平相比，本公开的抗Siglec-7抗体使Siglec-7的细胞表面水平降低小于20％、小于19％、小于18％、小于17％、小于16％、小于15％、小于14％、小于13％、小于12％、小于11％、小于10％、小于9％、小于8％、小于7％、小于6％、小于5％、小于4％、小于3％、小于2％或小于1％。

[0197] 如本文所用，利用本文所述的或本领域中已知的任何体外测定或基于细胞的培养测定，如果抗Siglec-7抗体在饱和抗体浓度(例如，67nM)下使配体与Siglec-7的结合降低少于20％，则所述抗Siglec-7抗体不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)。在一些实施方案中，利用本文所述的或本领域中已知的任何体外测定或基于细胞的培养测定，在饱和抗体浓度(例如，67nM)下本公开的抗Siglec-7抗体将Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如，结合)抑制小于20％、小于19％、小于18％、小于17％、小于16％、小于15％、小于14％、小于13％、小于12％、小于11％、小于10％、小于9％、小于8％、小于7％、小于6％、小于5％、小于4％、小于3％、小于2％或小于1％。

[0198] 如本文所用，Siglec-7的水平可指编码Siglec-7的基因的表达水平；编码Siglec-7的一种或多种转录物的表达水平；Siglec-7蛋白的表达水平；和/或细胞内和/或细胞表面上存在的Siglec-7蛋白的量。本领域中用于测量基因表达、转录、翻译和/或蛋白质丰度或定位的水平的任何已知方法可用于测定Siglec-7的水平。

[0199] 另外，本公开的抗Siglec-7抗体可用于预防以下疾病、降低所述疾病的风险或治疗所述疾病：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和/或流感嗜血杆菌。在一些实施方案中，本公开的抗Siglec-7抗体可用于诱导或促进有需要的个体中一种或多种免疫细胞的存活、成熟、功能性、迁移或增殖；或用于降低有需要的个体中以下各项的活性、功能性或存活：调控性T细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、急性骨髓性白

血病(AML)细胞、慢性淋巴细胞性白血病(CLL)细胞和/或慢性骨髓性白血病(CML)细胞。在一些实施方案中,本公开的抗Siglec-7抗体是单克隆抗体。

[0200] 在一些实施方案中,本公开的分离的抗Siglec-7抗体降低Siglec-7的细胞水平(例如,细胞表面水平、细胞内水平和/或总水平)。在一些实施方案中,本公开的分离的抗Siglec-7抗体诱导Siglec-7的下调。在一些实施方案中,本公开的分离的抗Siglec-7抗体诱导Siglec-7的裂解。在一些实施方案中,本公开的分离的抗Siglec-7抗体诱导Siglec-7的内化。在一些实施方案中,本公开的分离的抗Siglec-7抗体诱导Siglec-7的脱落。在一些实施方案中,本公开的分离的抗Siglec-7抗体诱导Siglec-7的降解。在一些实施方案中,本公开的分离的抗Siglec-7抗体诱导Siglec-7的脱敏。在一些实施方案中,本公开的分离的抗Siglec-7抗体充当配体模拟物以瞬时活化Siglec-7。在一些实施方案中,本公开的分离的抗Siglec-7抗体充当配体模拟物并且在诱导Siglec-7的细胞水平降低和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)之前瞬时活化Siglec-7。在一些实施方案中,本公开的分离的抗Siglec-7抗体充当配体模拟物并且在诱导Siglec-7的降解之前瞬时活化Siglec-7。在一些实施方案中,本公开的分离的抗Siglec-7抗体充当配体模拟物并且在诱导Siglec-7的裂解之前瞬时活化Siglec-7。在一些实施方案中,本公开的分离的抗Siglec-7抗体充当配体模拟物并且在诱导Siglec-7的内化之前瞬时活化Siglec-7。在一些实施方案中,本公开的分离的抗Siglec-7抗体充当配体模拟物并且在诱导Siglec-7的脱落之前瞬时活化Siglec-7。在一些实施方案中,本公开的分离的抗Siglec-7抗体充当配体模拟物并且在诱导Siglec-7表达的下调之前瞬时活化Siglec-7。在一些实施方案中,本公开的分离的抗Siglec-7抗体充当配体模拟物并且在诱导Siglec-7的脱敏之前瞬时活化Siglec-7。

[0201] 在一些实施方案中,本公开的分离的抗Siglec-7抗体是鼠抗体。在一些实施方案中,本公开的分离的抗Siglec-7抗体是人抗体、人源化抗体、双特异性抗体、单克隆抗体、多价抗体或嵌合抗体。此类抗体的示例性描述在整个本公开中发现。

[0202] 在一些实施方案中,本公开的抗Siglec-7抗体结合至人Siglec-7或其同源物,包括但不限于哺乳动物Siglec-7蛋白、普通黑猩猩Siglec-7蛋白(NCBI登录号XP_009434417.1)、矮小黑猩猩Siglec-7蛋白(XP_008964443.1)、猩猩Siglec-7蛋白(NCBI登录号XP_009231247)、大猩猩Siglec-7蛋白(NCBI登录号XP_004061321.1)或长臂猿Siglec-7蛋白(NCBI登录号XP_003269883.1)。在一些实施方案中,本公开的抗Siglec-7抗体特异性地结合至人Siglec-7。在一些实施方案中,本公开的抗Siglec-7抗体特异性地结合至灵长类动物Siglec-7。在一些实施方案中,本公开的抗Siglec-7抗体特异性地结合至人Siglec-7和灵长类动物Siglec-7两者。

[0203] 在一些实施方案中,本公开的抗Siglec-7抗体是结合至在细胞表面上表达的本公开的Siglec-7蛋白并且在结合至表面表达的Siglec-7蛋白后调节(例如,诱导或抑制)本公开的一种或多种Siglec-7活性的激动剂抗体或拮抗剂抗体。在一些实施方案中,本公开的抗Siglec-7抗体是惰性抗体。

[0204] 在一些实施方案中,本公开的抗Siglec-7抗体不显著降低TREM2表达,包括但不限于TREM2的细胞表面水平、TREM2的细胞内水平和/或TREM2的总水平。在一些实施方案中,抗Siglec-7抗体不降低体内TREM2的细胞水平。在一些实施方案中,在选自树突细胞、骨髓源

性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞、嗜中性粒细胞和NK细胞的原代细胞上或在细胞系上测量TREM2的细胞水平，并且其中使用体外细胞测定来测量TREM2的细胞水平。如本文所用，利用本文所述的或本领域中已知的任何体外基于细胞的测定或合适的体内模型，如果与不存在抗Siglec-7抗体情况下的TREM2表达相比，抗Siglec-7抗体使TREM2降低少于20％，则所述抗Siglec-7抗体不显著降低cTREM2表达。在一些实施方案中，与不存在抗Siglec-7抗体情况下的TREM2表达相比，本公开的抗Siglec-7抗体使TREM2表达降低小于20％、小于19％、小于18％、小于17％、小于16％、小于15％、小于14％、小于13％、小于12％、小于11％、小于10％、小于9％、小于8％、小于7％、小于6％、小于5％、小于4％、小于3％、小于2％或小于1％。

[0205] 抗Siglec-7抗体结合区

[0206] 本公开的某些方面提供抗Siglec-7抗体，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基9-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353内的一个或多个氨基酸；或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基9-353、39-149、93-104、95-105、39-122、123-149、150-233、240-336、264-273、295-306、327-341或337-353的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和84-95的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和117-127的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基68-78内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基68-78的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基84-95的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122和282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122和282-291的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-123内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-123的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-125内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-125的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1

的氨基酸残基117-127的氨基酸残基内的一个或多个氨基酸。在一些实施方案中，所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基282-29的氨基酸残基内的一个或多个氨基酸。

[0207] 在一些实施方案中，本公开的抗Siglec-7抗体结合至一个或多个选自以下的氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、I72、W74、N81、T103、K104、T107以及R124，或哺乳动物Siglec-7蛋白上对应于选自以下的氨基酸残基的一个或多个氨基酸残基:SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、I72、W74、N81、T103、K104、T107以及R124。在一些实施方案中，本公开的抗Siglec-7抗体结合至选自SEQ ID NO:1的I72、W74、N81和R124的一个或多个、两个或更多个、三个或更多个或全部四个氨基酸残基，或者哺乳动物Siglec-7蛋白上对应于选自SEQ ID NO:1的I72、W74、N81和R124的氨基酸残基的一个或多个、两个或更多个、三个或更多个或全部四个氨基酸残基。在一些实施方案中，本公开的抗Siglec-7抗体结合至选自SEQ ID NO:1的R45、S47、T103、K104和T107的一个或多个、两个或更多个、三个或更多个、四个或更多或全部五个氨基酸残基，或哺乳动物Siglec-7蛋白上对应于选自SEQ ID NO:1的R45、S47、T103、K104和T107的氨基酸残基的一个或多个、两个或更多个、三个或更多个、四个或更多或全部五个氨基酸残基。在一些实施方案中，本公开的抗Siglec-7抗体结合至选自SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、T103、K104和T107的一个或多个、两个或更多个、三个或更多个、四个或更多个、五个或更多个、六个或更多个、七个或更多个、八个或更多个、九个或更多个或全部10个氨基酸残基，或哺乳动物Siglec-7蛋白上对应于选自SEQ ID NO:1的M30、Q31、V44、R45、S47、F48、Y50、T103、K104和T107的氨基酸残基的一个或多个、两个或更多个、三个或更多个、四个或更多个、五个或更多个、六个或更多个、七个或更多个、八个或更多个、九个或更多个或全部十个氨基酸残基。

[0208] 如表7B中所示，参与由抗体4E3结合的关键Siglec-7残基对应于SEQ ID NO:1的氨基酸残基I_{72}、W_{74}、N_{81}和R_{124}。参与由抗体10B5结合的关键Siglec-7残基对应于SEQ ID NO:1的氨基酸残基R_{45}、S_{47}、T_{103}、K_{104}和T_{107}；并且参与由抗体10B5结合的二级残基对应于SEQ ID NO:1的氨基酸残基M_{30}、Q_{31}、V_{44}、F_{48}和Y_{50}。

[0209] 本公开的其它方面提供了抗Siglec-7抗体，所述抗Siglec-7抗体降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)，并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体，所述抗Siglec-7抗体降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)，并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和84-95的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体，所述抗Siglec-7抗体降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)，并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和117-127的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体，所述抗Siglec-7抗体降低Siglec-7的细胞

水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基68-78内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基68-78的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基84-95的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122的氨基酸残基内的一个或多个氨基酸。在可与前述实施方案中的任一项组合的一些实施方案中,所述抗Siglec-7抗体结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122和282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122和282-291的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-123内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-123的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-125内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-125的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基117-127的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基282-29的氨基酸残基内的一个或多个氨基酸。

[0210] 本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和84-95的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7

抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基60-69和117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基60-69和117-127的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基68-78内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基68-78的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基84-95内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基84-95的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基111-122和282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基111-122和282-291的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-123内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-123的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基113-125内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基113-125的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基117-127内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基117-127的氨基酸残基内的一个或多个氨基酸。本公开的其它方面提供了抗Siglec-7抗体,所述抗Siglec-7抗体不显著降低Siglec-7的细胞表面水平和/或不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合),并且结合至人Siglec-7(SEQ ID NO:1)的氨基酸残基282-291内或Siglec-7同系物或直向同源物上对应于SEQ ID NO:1的氨基酸残基282-29的氨基酸残基内的一个或多个氨基酸。

[0211] 在一些实施方案中,本公开的抗Siglec-7抗体可结合构象表位。在一些实施方案中,本公开的抗Siglec-7抗体可结合不连续的Siglec-7表位。在一些实施方案中,所述不连续的Siglec-7表位可具有两种或更多种肽、三种或更多种肽、四种或更多种肽、五种或更多

种肽、六种或更多种肽、七种或更多种肽、八种或更多种肽、九种或更多种肽或10种或更多种肽。如本文所公开，Siglec-7表位可包含一种或多种肽，所述一种或多种肽包含SEQ ID NO:1的氨基酸序列的5个或更多个、6个或更多个、7个或更多个、8个或更多个、9个或更多个、10个或更多个、11个或更多个、12个或更多个、13个或更多个、14个或更多个、15个或更多个、16个或更多个、17个或更多个、18个或更多个、19个或更多个或20个或更多个氨基酸残基，或对应于SEQ ID NO:1的氨基酸序列的哺乳动物Siglec-7蛋白上的5个或更多个、6个或更多个、7个或更多个、8个或更多个、9个或更多个、10个或更多个、11个或更多个、12个或更多个、13个或更多个、14个或更多个、15个或更多个、16个或更多个、17个或更多个、18个或更多个、19个或更多个或20个或更多个氨基酸残基。

[0212] 在一些实施方案中，本公开的抗Siglec-7抗体竞争性地抑制至少一种选自表2A、2B、3A、3B、6A和6B中列出的任何抗体的抗体的结合。在一些实施方案中，本公开的抗Siglec-7抗体竞争性地抑制至少一种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体的结合。

[0213] 在一些实施方案中，本公开的抗Siglec-7抗体结合至人Siglec-7的表位，所述表位与由至少一种选自表2A、2B、3A、3B、6A和6B中列出的任何抗体的抗体结合的Siglec-7表位相同或重叠。在一些实施方案中，本公开的抗Siglec-7抗体结合至人Siglec-7的表位，所述表位与由至少一种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体结合的Siglec-7表位相同或重叠。

[0214] 在一些实施方案中，本公开的抗Siglec-7抗体基本上结合由至少一种选自表2A、2B、3A、3B、6A和6B中列出的任何抗体的抗体结合的相同Siglec-7表位。在一些实施方案中，本公开的抗Siglec-7抗体基本上结合由至少一种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体结合的相同Siglec-7表位。用于作图抗体所结合的表位的详细示例性方法提供于Morris(1996)“Epitope Mapping Protocols,”于Methods in Molecular Biology第66卷(Humana Press,Totowa,NJ)中。

[0215] 在一些实施方案中，本公开的抗Siglec-7抗体与一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体竞争结合至Siglec-7。

[0216] 在一些实施方案中，与不存在抗Siglec-7抗体的情况下与Siglec-7的结合相比，当本公开的抗Siglec-7抗体使一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体与Siglec-7的结合降低在约50％至100％范围内的量时，所述抗Siglec-7抗体与一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体竞争结合至Siglec-7。在一些实施方案中，与不存在抗Siglec-7抗体的情况下与Siglec-7的结合相比，当本公开的抗Siglec-7抗体使一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体与Siglec-7的结合降低至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％或100％时，所述抗Siglec-7抗体与一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、

4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体竞争结合至Siglec-7。在一些实施方案中，使一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体与Siglec-7的结合降低100％的本公开的抗Siglec-7抗体表明所述抗Siglec-7抗体基本上完全阻断一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体与Siglec-7的结合。在一些实施方案中，所述抗Siglec-7抗体和所述一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体以对应于10:1比率、9:1比率、8:1比率、7:1比率、6:1比率、5:1比率、4:1比率、3:1比率、2:1比率、1:1比率、0.75:1比率、0.5:1比率、0.25:1比率、0.1:1比率、0.075:1比率、0.050:1比率、0.025:1比率、0.01:1比率、0.0075:1比率、0.0050:1比率、0.0025:1比率、0.001:1比率、0.00075:1比率、0.00050:1比率、0.00025:1比率、0.0001:比率、1:10比率、1:9比率、1:8比率、1:7比率、1:6比率、1:5比率、1:4比率、1:3比率、1:2比率、1:0.75比率、1:0.5比率、1:0.25比率、1:0.1比率、1:0.075比率、1:0.050比率、1:0.025比率、1:0.01比率、1:0.0075比率、1:0.0050比率、1:0.0025比率、1:0.001比率、1:0.00075比率、1:0.00050比率、1:0.00025比率或1:0.0001比率的抗Siglec-7抗体与一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体的量存在。在一些实施方案中，所述抗Siglec-7抗体以与一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体的量相比超过在约1.5倍至100倍或大于100倍范围内的量存在。在一些实施方案中，所述抗Siglec-7抗体以与一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体的量相比约2倍、3倍、4倍、5倍、6倍、7倍、8倍、9倍、10倍、15倍、20倍、25倍、30倍、35倍、40倍、45倍、50倍、55倍、60倍、65倍、70倍、75倍、80倍、85倍、90倍、95倍或100倍过量的量存在。

[0217] 可使用本领域中已知的任何合适的竞争测定或Siglec-7结合测定(如BIAcore分析、ELISA测定或流式细胞术)来确定抗Siglec-7抗体是否与一种或多种选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体竞争结合至Siglec-7。在示例性竞争测定中，将固定的Siglec-7或细胞表面上表达Siglec-7的细胞在包含结合至Siglec-7的第一标记抗体(例如人或非人灵长类动物)和第二未标记抗体的溶液中孵育，所述第二未标记抗体正在针对其与所述第一抗体竞争结合至Siglec-7的能力进行测试。第二抗体可存在于杂交瘤上清液中。作为对照，将固定的Siglec-7或表达Siglec-7的细胞在包含第一标记抗体而不含第二未标记抗体的溶液中孵育。在容许第一抗体与Siglec-7结合的条件下孵育之后，移除过量未结合的抗体，并且测量与固定的Siglec-7或表达Siglec-7的细胞缔合的标记的量。如果相对于对照样品，与固定的Siglec-7或表达Siglec-7的细胞缔合的标记的量在测试样品中基本上降低，则然后指示第二抗体与第一抗体竞争结合至Siglec-7。参见Harlow和Lane(1988)Antibodies:A Laboratory Manual第14章(Cold Spring Harbor Laboratory,Cold Spring Harbor,NY)。

[0218] 抗Siglec-7抗体轻链和重链可变区

[0219] 在一些实施方案中，本公开的抗Siglec-7抗体包含(a)轻链可变区，其包含选自表

2A、2B、3A、3B、6A和6B中列出或选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的任一种抗体的HVR-L1、HVR-L2和HVR-L3的至少一个、两个或三个HVR;和/或(b)重链可变区,其包含选自表2A、2B、3A、3B、6A和6B中列出或选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的任一种抗体的HVR-H1、HVR-H2和HVR-H3的至少一个、两个或三个HVR。在一些实施方案中,所述HVR-L1、HVR-L2、HVR-L3、HVR-H1、HVR-H2以及HVR-H3包含如表2A、2B、3A、3B、6A和6B中所示或来自选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1、10G8以及其任何组合的抗体的EU或Kabat CDR、Chothia CDR或接触CDR序列。

[0220] 在一些实施方案中,本公开的抗Siglec-7抗体包含至少一个、两个、三个、四个、五个或六个选自以下的HVR:(i)HVR-L1,其包含在表2A、2B、3A、3B、6A和6B中所列出或来自选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体的HVR-L1序列中的任一个的氨基酸序列;(ii)HVR-L2,其包含在表2A、2B、3A、3B、6A和6B中所列出或来自选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体的HVR-L2序列中的任一个的氨基酸序列;(iii)HVR-L3,其包含在表2A、2B、3A、3B、6A和6B中所列出或来自选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体的HVR-L3序列中的任一个的氨基酸序列;(iv)HVR-H1,其包含在表2A、2B、3A、3B、6A和6B中所列出或来自选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体的HVR-H1序列中的任一个的氨基酸序列;(v)HVR-H2,其包含在表2A、2B、3A、3B、6A和6B中所列出或来自选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体的HVR-H2序列中的任一个的氨基酸序列;以及(vi)HVR-H3,其包含在表2A、2B、3A、3B、6A和6B中所列出或来自选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体的HVR-H3序列中的任一个的氨基酸序列。在一些实施方案中,本公开的抗Siglec-7抗体包含轻链可变结构域和重链可变结构域,其中(a)所述HVR-L1包含SEQ ID NO:7的氨基酸序列,所述HVR-L2包含SEQ ID NO:20的氨基酸序列,所述HVR-L3包含SEQ ID NO:33的氨基酸序列,所述HVR-H1包含SEQ ID NO:46的氨基酸序列,所述HVR-H2包含SEQ ID NO:59的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:72的氨基酸序列;(b)所述HVR-L1包含SEQ ID NO:8的氨基酸序列,所述HVR-L2包含SEQ ID NO:21的氨基酸序列,所述HVR-L3包含SEQ ID NO:34的氨基酸序列,所述HVR-H1包含SEQ ID NO:47的氨基酸序列,所述HVR-H2包含SEQ ID NO:60的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:73的氨基酸序列;(c)所述HVR-L1包含SEQ ID NO:9的氨基酸序列,所述HVR-L2包含SEQ ID NO:22的氨基酸序列,所述HVR-L3包含SEQ ID NO:35的氨基酸序列,所述HVR-H1包含SEQ ID NO:48的氨基酸序列,所述HVR-H2包含SEQ ID NO:61的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列;(d)所述HVR-L1包含SEQ ID NO:10的氨基酸序列,所述HVR-L2包含SEQ ID NO:23的氨基酸序列,所述HVR-L3包含SEQ ID NO:36的氨基酸序列,所述HVR-H1包含SEQ ID NO:49的氨基酸序列,所述HVR-H2包含SEQ ID NO:62的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:75的氨基酸序列;(e)所述HVR-L1包含SEQ ID NO:11

的氨基酸序列,所述HVR-L2包含SEQ ID NO:24的氨基酸序列,所述HVR-L3包含SEQ ID NO:37的氨基酸序列,所述HVR-H1包含SEQ ID NO:50的氨基酸序列,所述HVR-H2包含SEQ ID NO:63的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:76的氨基酸序列;(f)所述HVR-L1包含SEQ ID NO:12的氨基酸序列,所述HVR-L2包含SEQ ID NO:25的氨基酸序列,所述HVR-L3包含SEQ ID NO:38的氨基酸序列,所述HVR-H1包含SEQ ID NO:51的氨基酸序列,所述HVR-H2包含SEQ ID NO:64的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:77的氨基酸序列;(g)所述HVR-L1包含SEQ ID NO:13的氨基酸序列,所述HVR-L2包含SEQ ID NO:26的氨基酸序列,所述HVR-L3包含SEQ ID NO:39的氨基酸序列,所述HVR-H1包含SEQ ID NO:52的氨基酸序列,所述HVR-H2包含SEQ ID NO:65的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:78的氨基酸序列;(h)所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:66的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列;(i)所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:480的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:74的氨基酸序列;(j)所述HVR-L1包含SEQ ID NO:14的氨基酸序列,所述HVR-L2包含SEQ ID NO:27的氨基酸序列,所述HVR-L3包含SEQ ID NO:40的氨基酸序列,所述HVR-H1包含SEQ ID NO:53的氨基酸序列,所述HVR-H2包含SEQ ID NO:481的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:79的氨基酸序列;(k)所述HVR-L1包含SEQ ID NO:15的氨基酸序列,所述HVR-L2包含SEQ ID NO:28的氨基酸序列,所述HVR-L3包含SEQ ID NO:41的氨基酸序列,所述HVR-H1包含SEQ ID NO:54的氨基酸序列,所述HVR-H2包含SEQ ID NO:67的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:80的氨基酸序列;(l)所述HVR-L1包含SEQ ID NO:16的氨基酸序列,所述HVR-L2包含SEQ ID NO:29的氨基酸序列,所述HVR-L3包含SEQ ID NO:42的氨基酸序列,所述HVR-H1包含SEQ ID NO:55的氨基酸序列,所述HVR-H2包含SEQ ID NO:68的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:81的氨基酸序列;(m)所述HVR-L1包含SEQ ID NO:17的氨基酸序列,所述HVR-L2包含SEQ ID NO:30的氨基酸序列,所述HVR-L3包含SEQ ID NO:43的氨基酸序列,所述HVR-H1包含SEQ ID NO:56的氨基酸序列,所述HVR-H2包含SEQ ID NO:69的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:82的氨基酸序列;(n)所述HVR-L1包含SEQ ID NO:18的氨基酸序列,所述HVR-L2包含SEQ ID NO:31的氨基酸序列,所述HVR-L3包含SEQ ID NO:44的氨基酸序列,所述HVR-H1包含SEQ ID NO:57的氨基酸序列,所述HVR-H2包含SEQ ID NO:70的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列;(n)所述HVR-L1包含SEQ ID NO:476的氨基酸序列,所述HVR-L2包含SEQ ID NO:477的氨基酸序列,所述HVR-L3包含SEQ ID NO:478的氨基酸序列,所述HVR-H1包含SEQ ID NO:57的氨基酸序列,所述HVR-H2包含SEQ ID NO:70的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:83的氨基酸序列;(o)所述HVR-L1包含SEQ ID NO:18的氨基酸序列,所述HVR-L2包含SEQ ID NO:31的氨基酸序列,所述HVR-L3包含SEQ ID NO:44的氨基酸序列,所述HVR-H1包含SEQ ID NO:479的氨基酸序列,所述HVR-H2包含SEQ ID NO:482的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:483的氨基酸序列;或(p)所述HVR-L1包含SEQ ID NO:19的氨基酸序列,所述HVR-L2包含SEQ ID NO:32的氨基酸序列,所述HVR-L3包

含SEQ ID NO:45的氨基酸序列,所述HVR-H1包含SEQ ID NO:58的氨基酸序列,所述HVR-H2包含SEQ ID NO:71的氨基酸序列,并且所述HVR-H3包含SEQ ID NO:84的氨基酸序列。

[0221] 在一些实施方案中,本公开的抗Siglec-7抗体包含轻链可变结构域和重链可变结构域,其中所述轻链可变结构域包含以下中的一个或多个:(a)HVR-L1,其包含选自SEQ ID NO:7-19和476的氨基酸序列,或与选自SEQ ID NO:7-19和476的氨基酸序列具有至少约90%同源性的氨基酸序列;(b)HVR-L2,其包含选自SEQ ID NO:20-32和477的氨基酸序列,或与选自SEQ ID NO:20-32和477的氨基酸序列具有至少约90%同源性的氨基酸序列;以及(c)HVR-L3,其包含选自SEQ ID NO:33-45和478的氨基酸序列,或与选自SEQ ID NO:33-45和478的氨基酸序列具有至少约90%同源性的氨基酸序列;和/或其中所述重链可变结构域包含以下中的一个或多个:(a)HVR-H1,其包含选自SEQ ID NO:46-58和479的氨基酸序列,或与选自SEQ ID NO:46-58和479的氨基酸序列具有至少约90%同源性的氨基酸序列;(b)HVR-H2,其包含选自SEQ ID NO:59-71和480-482的氨基酸序列,或与选自SEQ ID NO:59-71和480-482的氨基酸序列具有至少约90%同源性的氨基酸序列;以及(c)HVR-H3,其包含选自SEQ ID NO:72-84和483的氨基酸序列,或与选自SEQ ID NO:72-84和483的氨基酸序列具有至少约90%同源性的氨基酸序列。

[0222] 在一些实施方案中,本公开的抗Siglec-7抗体包含在表2A、2B、3A、3B、6A和6B中列出或选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的任一种抗体的轻链可变区;和/或在表2A、2B、3A、3B、6A和6B中列出或选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的任一种抗体的重链可变区。在一些实施方案中,本公开的抗Siglec-7抗体包含轻链可变区,所述轻链可变区包含选自SEQ ID NO:189-318、449-461和484-489中的任一个的氨基酸序列;和/或重链可变结构域,所述重链可变结构域包含选自SEQ ID NO:319-448、462-474和490-496中的任一个的氨基酸序列。

[0223] 在一些实施方案中,所述抗Siglec-7抗体是抗Siglec-7单克隆抗体1A12。在一些实施方案中,所述抗Siglec-7抗体是与1A12结合基本相同的TREM2表位的分离的抗体。在一些实施方案中,所述抗Siglec-7抗体是包含单克隆抗体1A12的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中,所述抗Siglec-7抗体是包含单克隆抗体1A12的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中,所述抗Siglec-7抗体是包含单克隆抗体1A12的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0224] 在一些实施方案中,所述抗Siglec-7抗体是抗Siglec-7单克隆抗体1E8。在一些实施方案中,所述抗Siglec-7抗体是与1E8结合基本相同的TREM2表位的分离的抗体。在一些实施方案中,所述抗Siglec-7抗体是包含单克隆抗体1E8的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中,所述抗Siglec-7抗体是包含单克隆抗体1E8的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中,所述抗Siglec-7抗体是包含单克隆抗体1E8的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0225] 在一些实施方案中,所述抗Siglec-7抗体是抗Siglec-7单克隆抗体2G1。在一些实施方案中,所述抗Siglec-7抗体是与2G1结合基本相同的TREM2表位的分离的抗体。在一些

实施方案中，所述抗Siglec-7抗体是包含单克隆抗体2G1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体2G1的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体2G1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0226] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体2G4。在一些实施方案中，所述抗Siglec-7抗体是与2G4结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体2G4的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体2G4的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体2G4的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0227] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体3E11。在一些实施方案中，所述抗Siglec-7抗体是与3E11结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体3E11的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体3E11的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体3E11的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0228] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体4A1。在一些实施方案中，所述抗Siglec-7抗体是与4A1结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4A1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4A1的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4A1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0229] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体4D7。在一些实施方案中，所述抗Siglec-7抗体是与4D7结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4D7的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4D7的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4D7的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0230] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体4E3。在一些实施方案中，所述抗Siglec-7抗体是与4E3结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H2的重链可变结构域的HVR-H1、HVR-H2和HVR-H3

的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H3的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3L1的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3L2的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3L3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体4E3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H2的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体4E3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体4E3L1的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H2的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体4E3L2的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H2的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体4E3L3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H3的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体4E3L2的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体4E3H3的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体4E3L3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0231] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体7A3。在一些实施方案中，所述抗Siglec-7抗体是与7A3结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体7A3的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体7A3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体7A3的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0232] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体7E11。在一些实施方案中，所述抗Siglec-7抗体是与7E11结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体7E11的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体7E11的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体7E11的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0233] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体7F12。在一些实施方案中，所述抗Siglec-7抗体是与7F12结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体7F12的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体7F12的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体7F12的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0234] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体10B5。在一些实施方案中，所述抗Siglec-7抗体是与10B5结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H2的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H3的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H4的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5L1的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5L2的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5L3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体10B5的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H2的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体10B5的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体10B5L1的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H1的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体10B5L1的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H2的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体10B5L2的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H3的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体10B5L2的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H2的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体10B5L3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3

的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10B5H4的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及单克隆抗体10B5L3的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0235] 在一些实施方案中，所述抗Siglec-7抗体是抗Siglec-7单克隆抗体10G8。在一些实施方案中，所述抗Siglec-7抗体是与10G8结合基本相同的TREM2表位的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10G8的重链可变结构域的HVR-H1、HVR-H2和HVR-H3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10G8的轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。在一些实施方案中，所述抗Siglec-7抗体是包含单克隆抗体10G8的重链可变结构域的HVR-H1、HVR-H2和HVR-H3以及轻链可变结构域的HVR-L1、HVR-L2和HVR-L3的分离的抗体。

[0236] 本公开的任何抗体可由细胞系产生。在一些实施方案中，所述细胞系是哺乳动物细胞系。在某些实施方案中，所述细胞系是杂交瘤细胞系。在其它实施方案中，所述细胞系是可以是酵母细胞系。可使用本领域中已知的适用于抗体产生的任何细胞系来产生本公开的抗体。用于抗体产生的示例性细胞系在整个本公开中描述。

[0237] 在一些实施方案中，所述抗Siglec-7抗体是选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗Siglec-7单克隆抗体。在某些实施方案中，所述抗Siglec-7抗体是拮抗剂抗体。在某些实施方案中，所述抗Siglec-7抗体是激动剂抗体或惰性抗体。

[0238] 抗Siglec-7抗体结合亲和力

[0239] 抗Siglec-7抗体对人Siglec-7、哺乳动物Siglec-7或两者的解离常数(K_D)可以是小于100nM、小于90nM、小于80nM、小于70nM、小于60nM、小于50nM、小于40nM、小于30nM、小于20nM、小于10nM、小于9.5nM、小于9nM、小于8.5nM、小于8nM、小于7.5nM、小于7nM、小于6.5nM、小于6nM、小于5.5nM、小于5nM、小于4.5nM、小于4nM、小于3.5nM、小于3nM、小于2.5nM、小于2nM、小于1.5nM、小于1nM、小于0.5nM、小于0.4nM、小于0.3nM、小于0.2nM、小于0.1nM、小于0.05nM(即，50pM)、小于40pM、小于30pM、小于20pM、小于19pM、小于18pM、小于17pM、小于16pM、小于15pM、小于14pM、小于13pM、小于12pM、小于11pM、小于10pM或小于5pM。在一些实施方案中，所述抗体对人Siglec-7、哺乳动物Siglec-7或两者具有在约10nM至约10pM(即，0.01nM)或小于10pM范围内的解离常数(K_D)。在一些实施方案中，所述抗体对于人Siglec-7具有在约9.5nM至约17pM或小于17pM范围内的解离常数(K_D)。在一些实施方案中，所述抗体对于人Siglec-7具有在约2nM至约100pM范围内的解离常数(K_D)。解离常数可通过任何分析技术来测定，包括任何生物化学或生物物理学技术，如ELISA、表面等离子体共振(SPR)、生物层干涉测量法(参见例如ForteBio的Octet System)、等温滴定量热法(ITC)、差示扫描量热法(DSC)、圆二色性(CD)、停流分析以及比色或荧光蛋白解链分析。在一些实施方案中，Siglec-7的解离常数(K_D)在大约25℃的温度下测定。在一些实施方案中，使用单价抗体(例如，Fab)或全长抗体来测定K_D。在一些实施方案中，使用单价形式的全长抗体来测定K_D。在一些实施方案中，使用例如本文所述的表面等离子体共振测定(参见例如，实施例1)来测定K_D。

[0240] 可通过本领域中已知的各种测定来鉴定、筛选和/或表征另外的抗Siglec-7抗体，例如特异性地结合至本公开的Siglec-7蛋白的抗体的物理/化学性质和/或生物活性。

[0241] 能够结合Fcγ受体的抗Siglec-7抗体

[0242] 在一些实施方案中，本公开的抗Siglec-7抗体保留结合Fcγ受体的能力。在一些实施方案中，当此类抗体具有与受体活化相容的正确表位特异性时，此类抗体可具有使其能够聚簇并瞬时刺激例如Siglec-7受体的特征。在一些实施方案中，此类抗体随后可通过诱导Siglec-7降解、Siglec-7脱敏、Siglec-7裂解、Siglec-7内化、Siglec-7脱落、Siglec-7表达的下调和/或Siglec-7的溶酶体降解而充当Siglec-7表达的长期抑制剂和/或Siglec-7蛋白的一种或多种活性。

[0243] 在体内，本公开的抗Siglec-7抗体可簇集受体并通过多种潜在机制中的任何一种或多种瞬时活化Siglec-7。人抗体如IgG2的一些同种型由于其独特的结构而具有簇集受体或保留受体呈簇集构型、从而瞬时活化受体如Siglec-7而不结合至Fc受体的内在能力(例如，White等人，(2015)Cancer Cell 27,138-148)。

[0244] 在一些实施方案中，其它抗体可通过结合至邻近细胞上的Fcg受体来簇集受体(例如，Siglec-7)。在一些实施方案中，抗体的恒定IgG Fc区与Fcg受体的结合可导致抗体的聚集，并且抗体进而可聚集它们通过它们的可变区所结合的受体(Chu等人(2008)Mol Immunol，45:3926-3933；以及Wilson等人，(2011)Cancer Cell 19,101-113)。在一些实施方案中，结合至不引发细胞因子分泌、氧化爆发、增加的吞噬和增强的抗体依赖性细胞介导的细胞毒性(ADCC)的抑制性Fcg受体FcgR(FcgRIIB)是体内簇集抗体的优选方式，因为与FcgRIIB结合不与不利的免疫应答效应相关。

[0245] 存在本公开的抗Siglec-7抗体可簇集受体的其它机制。例如，如上所述，交联在一起的抗体片段(例如，Fab片段)可用于以与具有结合Fcg受体的Fc区的抗体相似的方式簇集受体(例如，Siglec-7)。在一些实施方案中，如果交联的抗体片段(例如，Fab片段)诱导细胞表面上的受体簇集并结合靶标上的适当表位(例如，Siglec-7)，则所述抗体片段可瞬时充当激动剂抗体。

[0246] 因此，在一些实施方案中，结合Siglec-7蛋白的本公开的抗体可包括激动剂抗体，所述激动剂抗体在它们例如降低Siglec-7的细胞水平、抑制一种或多种Siglec-7活性和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)之前由于其表位特异性而结合Siglec-7并瞬时活化一种或多种Siglec-7活性。在一些实施方案中，此类抗体可结合至Siglec-7上的配体结合位点并瞬时模拟天然配体的作用，或者通过结合至一个或多个不是配体结合位点的结构域来刺激靶抗原转导信号。在一些实施方案中，此类抗体不会干扰配体结合。在一些实施方案中，无论抗体是否结合至Siglec-7上的配体结合位点，所述抗体都可随后通过诱导Siglec-7降解、Siglec-7脱敏、Siglec-7裂解、Siglec-7内化、Siglec-7脱落、Siglec-7表达的下调和/或Siglec-7的溶酶体降解来充当Siglec-7表达和/或Siglec-7蛋白的一种或多种活性的长期抑制剂。

[0247] 在一些实施方案中，本公开的抗Siglec-7抗体是瞬时诱导Siglec-7蛋白的一种或多种活性的瞬时激动剂抗体。在一些实施方案中，所述抗体在与细胞中表达的Siglec-7蛋白结合后瞬时诱导一种或多种活性。在一些实施方案中，所述Siglec-7蛋白在细胞表面上表达。在一些实施方案中，Siglec-7蛋白的由本公开的瞬时激动剂抗Siglec-7抗体瞬时诱导的一种或多种活性可包括但不限于，通过Src家族酪氨酸激酶如Syk、LCK、FYM和/或ZAP70磷酸化Tyr-437和Tyr-460；募集并结合至酪氨酸特异性蛋白磷酸酶SHP1和SHP2；募集并结

合至PLC-γ1，其充当发动蛋白-1的鸟嘌呤核苷酸交换因子；募集并结合至含SH2结构域的蛋白质(例如Crk1)；募集并结合至脾酪氨酸激酶Syk；募集并结合至SH3-SH2-SH3生长因子受体结合蛋白2(Grb2)；募集并结合至多种含SH2的蛋白质；调节一种或多种促炎性细胞因子的表达，所述促炎性细胞因子如IFN-a4、IFN-β、IL-1â、IL-1α、TNF-á、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、CRP、MCP-1以及MIP-1-β；调节一种或多种细胞中的一种或多种促炎性细胞因子的表达，所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞；增加一种或多种抗炎细胞因子的表达，所述抗炎细胞因子如IL-4、IL-10、IL-13、IL-35、IL-16、TGF-β、IL-1Ra、G-CSF以及TNF、IFN-β1a、IFN-β1b或IL-6的可溶性受体；调节一种或多种细胞中的一种或多种抗炎细胞因子的表达，所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞；调节一种或多种选自以下的蛋白质的表达：C1qa、C1qB、C1qC、C1s、C1R、C4、C2、C3、ITGB2、HMOX1、LAT2、CASP1、CSTA、VSIG4、MS4A4A、C3AR1、GPX1、TyroBP、ALOX5AP、ITGAM、SLC7A7、CD4、ITGAX、以及PYCARD；抑制细胞外信号调控激酶(ERK)磷酸化；降低一种或多种细胞蛋白上的酪氨酸磷酸化，任选地，其中所述一种或多种细胞蛋白包含ZAP-70并且所述酪氨酸磷酸化发生在ZAP-70的Tyr-319上；调节C-C趋化因子受体7(CCR7)的表达；抑制针对表达CCL19的细胞和表达CCL21的细胞的小神经胶质细胞趋化性；减少由一种或多种细胞诱导的T细胞增殖，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞、M2小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞以及M2 NK细胞；抑制破骨细胞产生，降低破骨细胞生成速率或两者；降低一种或多种细胞的存活，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；降低一种或多种细胞的增殖，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；抑制一种或多种细胞的迁移，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；抑制一种或多种细胞的一种或多种功能，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK

细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;抑制一种或多种细胞的成熟,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;抑制一种或多种类型的清除,所述清除选自凋亡神经元清除、神经组织碎片清除、功能障碍性突触清除、非神经组织碎片清除、细菌清除、其它异物清除、致病蛋白清除、致病肽清除、致病核酸清除以及肿瘤细胞清除;任选地,其中所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽,并且所述肿瘤细胞来自癌症,所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌;抑制以下中的一种或多种的吞噬:凋亡神经元、神经组织碎片、功能障碍性突触、非神经组织碎片、细菌、其它异物、致病蛋白、致病肽、致病核酸或肿瘤细胞;任选地其中所述致病核酸是反义GGCCCC(G2C4)重复序列-扩增RNA,所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽,并且所述肿瘤细胞来自癌症,所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤或甲状腺癌;与肿瘤细胞上的Siglec-7配体结合;与细胞上的Siglec-7配体结合,所述细胞选自嗜中性粒细胞、树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞以及NK细胞;通过以下中的一种或多种抑制肿瘤细胞杀伤:小神经胶质细胞、巨噬细胞、嗜

中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；抑制以下中的一种或多种的抗肿瘤细胞增殖活性：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；抑制以下中的一种或多种的抗肿瘤细胞转移活性：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；抑制一种或多种含ITAM基序的受体，任选地其中所述一种或多种含ITAM基序的受体选自TREM1、TREM2、Sirpβ、FcgR、DAP10以及DAP12；通过一种或多种模式识别受体(PRR)抑制信号传导，任选地其中所述一种或多种PRR选自鉴定病原体相关分子模式(PAMP)的受体、鉴定损伤相关分子模式(DAMP)的受体以及其任何组合；抑制包含基序D/$Ex_{0-2}YxxL/IX_{6-8}YxxL/I$(SEQ ID NO:537)的一种或多种受体；通过一种或多种Toll样受体抑制信号传导；抑制JAK-STAT信号传导途径；抑制活化的B细胞的核因子κ-轻链增强子(NFêB)；含有ITAM基序的受体的去磷酸化；调节一种或多种炎性受体的表达，任选地其中所述一种或多种炎性受体包含CD86并且所述一种或多种炎性受体在以下中的一种或多种上表达：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突状细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；增加一种或多种Siglec-7依赖性基因的表达；破坏的Siglec-7依赖性基因表达的正常化；降低一种或多种ITAM依赖性基因的表达，任选地其中所述一种或多种ITAM依赖性基因通过活化T细胞(NFAT)转录因子的核因子活化；促进或挽救以下中的一种或多种的功能性：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；增加以下中的一种或多种浸润到肿瘤中：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量；增强骨髓源性抑制细胞的肿瘤促进活性；增加肿瘤或外周血液中肿瘤促进细胞因子的表达，任选地其中所述肿瘤促进细胞因子是TGF-β或IL-10；增加肿瘤促进FoxP3+调控性T淋巴细胞的肿瘤浸润；增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性；减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化；减少具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润；降低NK细胞的肿瘤杀伤潜力；减少具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润；减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润；增加肿瘤体积；增加肿瘤生长速率；增加转移；增加肿瘤复发率；降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效，任选地其中所述一种或多种免疫疗法是靶向一种或多种靶蛋白的免疫疗法，所述一种或多种靶蛋白选自PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、TREM1、TREM2、CSF-1受体以及其任何组合；抑制PLCã/PKC/钙动员；以及抑制PI3K/Akt、Ras/MAPK信号传导。可利用本领域中已知和本文公开的任何合适的技术或测定来测试本公开的抗Siglec-7抗体瞬时诱导Siglec-7蛋白的一种或多种活性的能力。不管此类抗体瞬时诱导的活性，此类抗体都可随后通过诱导Siglec-7降解、Siglec-7脱敏、Siglec-7裂解、Siglec-7内化、Siglec-7脱落、Siglec-7表达的下调和/或Siglec-7的溶酶体降解来充当Siglec-7表达和/或Siglec-7蛋白的一种或多种活性的长期抑制剂。在一些

实施方案中，所述Siglec-7抗体不依赖于与Fc受体的结合而瞬时诱导Siglec-7蛋白的一种或多种活性。

[0248] 以下表C中提供了示例性抗体Fc同种型和修饰。在一些实施方案中，能够结合Fcγ受体的本公开的抗Siglec-7抗体具有在以下表C中列出的Fc同种型。

[0249] 表C:能够结合Fcγ受体的示例性抗Siglec-7抗体Fc同种型

[0250]

Fc 同种型	突变(EU 编号方案)
IgG1	N297A
IgG1	D265A 和 N297A
IgG1	D270A
IgG1	L234A 和 L235A L234A 和 G237A L234A 和 L235A 和 G237A

[0251]

Fc 同种型	突变(EU 编号方案)
IgG1	D270A，和/或 P238D，和/或 L328E，和/或 S267E/L328F，和/或 E233，和/或 G237D，和/或 H268D，和/或 P271G，和/或 A330R
IgG1	P238D 和 L328E 和 E233D 和 G237D 和 H268D 和 P271G 和 A330R
IgG1	P238D 和 L328E 和 G237D 和 H268D 和 P271G 和 A330R
IgG1	P238D 和 S267E 和 L328F 和 E233D 和 G237D 和 H268D 和 P271G 和 A330R
IgG1	P238D 和 S267E 和 L328F 和 G237D 和 H268D 和 P271G 和 A330R
IgG2	V234A 和 G237A
IgG4	L235A 和 G237A 和 E318A
IgG4	S228P 和 L236E
IgG2/4 杂合体	IgG2 aa 118 至 260 和 IgG4 aa 261 至 447
	H268Q 和 V309L；以及 A330S 和 P331S
IgG1	C226S 和 C229S 和 E233P 和 L234V 和 L235A
IgG1	L234F 和 L235E 和 P331S
IgG2	C232S 或 C233S
IgG2	A330S 和 P331S
IgG1	S267E，和 L328F 单独 S267E
IgG2	S267E 和 L328F
IgG4	S267E 和 L328F
IgG2	具有 κ (轻链) LC 的 WT HC 具有 κ LC 的 HC C127S κ LC C214S κ LC C214S 和 HC C233S κ LC C214S 和 HC C232S 任何上述突变连同 P330S 和 P331S 突变 WT IgG1 的 F(ab')2 片段和任何上述突变
IgG1	用 IGg2 的 CH1 和铰链区取代 IgG1 的恒定重 1 (CH1)和铰链区 ASTKGPSVFPLAPCSRSTSESTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSNFGTQTYTCNVDHKPSNT KVDKTVER KCCVECPPCP (SEQ ID NO:475)

[0252]

Fc同种型	突变(EU编号方案)
	具有κLC
IgG1	以上列出的突变中的任一者连同A330L和/或L234F和/或L235E和/或P331S
IgG1、IgG2或IgG4	以上列出的突变中的任一者连同M252Y和/或S254T和/或T256E
小鼠IgG1	对于小鼠疾病模型
IgG4	WT

[0253] 除了表C中描述的同种型，并且不希望受理论束缚，认为结合人中的Fcg受体I、IIA、IIC、IIIA、IIIB和/或小鼠中的Fcg受体I、III和IV的具有人IgG1或IgG3同种型及其突变体的抗体(例如Strohl(2009)Current Opinion in Biotechnology 2009,20:685-691)也可充当瞬时激动剂抗体。

[0254] 在一些实施方案中，所述Fcγ受体结合抗体具有IgG类、IgM类或IgA类。在一些实施方案中，所述Fcγ受体结合抗体具有IgG1、IgG2、IgG3或IgG4同种型。

[0255] 在某些实施方案中，所述Fcγ受体结合抗体具有IgG2同种型。在一些实施方案中，所述Fcγ受体结合抗体含有人IgG2恒定区。在一些实施方案中，所述人IgG2恒定区包括Fc区。在一些实施方案中，所述Fcγ受体结合抗体结合抑制性Fc受体。在某些实施方案中，所述抑制性Fc受体是抑制性Fc-γ受体IIB(FcγIIB)。在一些实施方案中，所述Fc区含有一种或多种修饰。例如，在一些实施方案中，所述Fc区含有一种或多种氨基酸取代(例如，相对于同一同种型的野生型Fc区)。在一些实施方案中，所述一种或多种氨基酸取代选自V234A(Alegre等人，(1994)Transplantation 57:1537-1543.31;Xu等人，(2000)Cell Immunol，200:16-26)、G237A(Cole等人(1999)Transplantation,68:563-571)、H268Q、V309L、A330S、P331S(US 2007/0148167;Armour等人(1999)Eur J Immunol29:2613-2624;Armour等人(2000)The Haematology Journal 1(Suppl.1):27;Armour等人(2000)The Haematology Journal 1(Suppl.1):27)、C232S和/或C233S(White等人(2015)Cancer Cell 27,138-148)、S267E、L328F(Chu等人，(2008)Mol Immunol,45:3926-3933)、M252Y、S254T和/或T256E，其中该氨基酸位置根据EU或Kabat编号惯例。

[0256] 在一些实施方案中，Fcγ受体结合抗体具有IgG2同种型，其具有包含C127S氨基酸取代的重链恒定结构域，其中氨基酸位置根据EU或Kabat编号惯例(White等人，(2015)Cancer Cell 27,138-148;Lightle等人，(2010)PROTEIN SCIENCE 19:753-762;以及WO2008079246)。

[0257] 在一些实施方案中，Fcγ受体结合抗体具有IgG2同种型，其具有包含C214S氨基酸取代的κ轻链恒定结构域，其中氨基酸位置根据EU或Kabat编号惯例(White等人，(2015)Cancer Cell 27,138-148;Lightle等人，(2010)PROTEIN SCIENCE 19:753-762;以及WO2008079246)。

[0258] 在某些实施方案中，所述Fcγ受体结合抗体具有IgG1同种型。在一些实施方案中，所述Fcγ受体结合抗体含有小鼠IgG1恒定区。在一些实施方案中，所述Fcγ受体结合抗体

含有人IgG1恒定区。在一些实施方案中，所述人IgG1恒定区包括Fc区。在一些实施方案中，所述Fcγ受体结合抗体结合抑制性Fc受体。在某些实施方案中，所述抑制性Fc受体是抑制性Fc-γ受体IIB(FcγIIB)。在一些实施方案中，所述Fc区含有一种或多种修饰。例如，在一些实施方案中，所述Fc区含有一种或多种氨基酸取代(例如，相对于同一同种型的野生型Fc区)。在一些实施方案中，所述一种或多种氨基酸取代选自N297A(Bolt S等人(1993)Eur J Immunol23:403-411)、D265A(Shields等人(2001)R.J.Biol.Chem.276,6591-6604)、D270A、L234A、L235A(Hutchins等人(1995)Proc Natl Acad Sci USA,92:11980-11984;Alegre等人,(1994)Transplantation 57:1537-1543.31;Xu等人,(2000)Cell Immunol,200:16-26)、G237A(Alegre等人(1994)Transplantation 57:1537-1543.31;Xu等人(2000)Cell Immunol,200:16-26)、P238D、L328E、E233D、G237D、H268D、P271G、A330R、C226S、C229S、E233P、L234V、L234F、L235E(McEarchern等人,(2007)Blood,109:1185-1192)、P331S(Sazinsky等人,(2008)Proc Natl Acad Sci USA 2008,105:20167-20172)、S267E、L328F、A330L、M252Y、S254T、T256E、N297Q、P238S、P238A、A327Q、A327G、P329A、K322A和/或T394D，其中所述氨基酸位置根据EU或Kabat编号惯例。

[0259] 在一些实施方案中，所述抗体包含IgG2同种型重链恒定结构域1(CH1)和铰链区(White等人,(2015)Cancer Cell 27,138-148)。在某些实施方案中，所述IgG2同种型CH1和铰链区含有ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP(SEQ ID NO:475)的氨基酸序列。在一些实施方案中，所述抗体Fc区包含S267E氨基酸取代、L328F氨基酸取代或两者，和/或N297A或N297Q氨基酸取代，其中所述氨基酸位置根据EU或Kabat编号惯例。

[0260] 在某些实施方案中，所述Fcγ受体结合抗体具有IgG4同种型。在一些实施方案中，所述Fcγ受体结合抗体含有人IgG4恒定区。在一些实施方案中，所述人IgG4恒定区包括Fc区。在一些实施方案中，所述Fcγ受体结合抗体结合抑制性Fc受体。在某些实施方案中，所述抑制性Fc受体是抑制性Fc-γ受体IIB(FcγIIB)。在一些实施方案中，所述Fc区含有一种或多种修饰。例如，在一些实施方案中，所述Fc区含有一种或多种氨基酸取代(例如，相对于同一同种型的野生型Fc区)。在一些实施方案中，所述一种或多种氨基酸取代选自L235A、G237A、S228P、L236E(Reddy等人,(2000)J Immunol,164:1925-1933)、S267E、E318A、L328F、M252Y、S254T和/或T256E，其中该氨基酸位置根据EU或Kabat编号惯例。

[0261] 在某些实施方案中，所述Fcγ受体结合抗体具有杂合IgG2/4同种型。在一些实施方案中，所述Fcγ受体结合抗体包含含有人IgG2的根据EU或Kabat编号的氨基酸118至260以及人IgG4的根据EU或Kabat编号的氨基酸261-447的氨基酸序列(WO 1997/11971;WO 2007/106585)。

[0262] 在某些实施方案中，所述抗体含有小鼠IgG4恒定区(Bartholomaeus,等人(2014).J.Immunol.192,2091-2098)。

[0263] 在一些实施方案中，所述Fc区进一步含有一种或多种另外的氨基酸取代，所述氨基酸取代选自根据EU或Kabat编号的A330L、L234F、L235E或P331S以及其任何组合。

[0264] 惰性抗体

[0265] 本公开的抗Siglec-7抗体的另一类别包括惰性抗体。如本文所用，“惰性”抗体是指特异性地结合其靶抗原(例如Siglec-7)但不调节(例如降低/抑制或活化/诱导)抗原功

能的抗体。例如，在Siglec-7的情况下，惰性抗体不调节Siglec-7的细胞水平，不调节Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)，或不调节Siglec-7蛋白的一种或多种活性。在一些实施方案中，不具有在细胞表面上簇集Siglec-7的能力的抗体可以是惰性抗体，即使它们具有与受体活化相容的表位特异性。

[0266] 在一些实施方案中，结合Siglec-7蛋白的抗体可包括结合Siglec-7，但由于它们的表位特异性或特性不会降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)的抗体。在一些实施方案中，此类抗体可用作货物以例如将毒素(例如化学治疗剂)转运到肿瘤细胞中。此类抗体可优于目前商业上可获得的抗Siglec-7抗体，如抗体Mab1138(R&D Systems;目录号MAB 1138)。在一些实施方案中，本公开的惰性抗Siglec-7抗体可优于商业抗体，如抗体Mab1138，因为不降低Siglec-7的细胞水平的抗体将使Siglec-7完整地留在肿瘤细胞的表面上以用于通过另外的毒素缀合的抗体靶向。相比之下，降低Siglec-7的细胞水平的抗体将从细胞表面除去Siglec-7，并且将导致保护肿瘤细胞免受毒素缀合抗体的进一步靶向。因此，在一些实施方案中，本公开的抗体是结合Siglec-7但不能降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)或诱导Siglec-7蛋白的一种或多种活性的惰性抗体。

[0267] 降低或不降低细胞上Siglec-7的细胞水平的抗体可与展示与一种或多种Fcg受体降低的结合的惰性Fc区组合。以下表D中提供了此类Fc区和修饰的实例。在一些实施方案中，具有惰性Fc区的抗体具有以下表D中列出的Fc同种型。

[0268] 拮抗剂抗Siglec-7抗体

[0269] 本公开的抗Siglec-7抗体的第三类别包括拮抗剂抗体。在一些实施方案中，结合Siglec-7蛋白的抗体可包括拮抗剂抗体，所述拮抗剂抗体降低Siglec-7的细胞水平、抑制Siglec-7和/或一种或多种Siglec-7配体之间的相互作用(例如结合)并抑制Siglec-7蛋白的一种或多种活性。此类抗体通过在一种或多种Siglec-7配体存在下防止Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如结合)或通过防止信号转导从Siglec-7的细胞外结构域进入细胞质来抑制Siglec-7蛋白的一种或多种活性。拮抗剂抗体还可通过降低Siglec-7的细胞表面水平、诱导Siglec-7降解、Siglec-7脱敏、Siglec-7裂解、Siglec-7内化、Siglec-7脱落、Siglec-7表达的下调和/或Siglec-7的溶酶体降解来抑制Siglec-7蛋白的一种或多种活性。在一些实施方案中，此类拮抗性抗Siglec-7抗体可能不会瞬时活化Siglec-7。

[0270] 在一些实施方案中，本公开的拮抗剂抗Siglec-7抗体可具有本公开的瞬时激动剂抗Siglec-7抗体的表位特异性，但具有不能结合Fcg受体并因此不能例如瞬时簇集和活化Siglec-7的Fc结构域。

[0271] 在一些实施方案中，本公开的拮抗剂抗Siglec-7抗体具有但不限于一种或多种以下活性:降低Siglec-7蛋白与一种或多种Siglec-7配体(如含唾液酸的糖脂或含唾液酸的糖蛋白)结合的能力;降低细胞因子信号传导(SOCS)蛋白(例如，SOCS3蛋白)的抑制子与Siglec-7蛋白的结合的能力;增加Siglec-7蛋白的蛋白酶体降解的能力;降低循环树突细胞、巨噬细胞、单核细胞、T细胞和/或小神经胶质细胞表面上的Siglec-7的功能表达的能力;降低或抑制通过Src家族酪氨酸激酶如Syk、LCK、FYM和/或ZAP70磷酸化Tyr-437和Tyr-460的能力;抑制募集并结合至酪氨酸特异性蛋白磷酸酶SHP1和SHP2的能力;抑制募集并结

合至PLC-γ1的能力，所述PLC-γ1充当发动蛋白-1的鸟嘌呤核苷酸交换因子；抑制募集并结合至含SH2结构域的蛋白质(例如Crk1)的能力；抑制募集并结合至脾酪氨酸激酶Syk的能力；抑制募集并结合至SH3-SH2-SH3生长因子受体结合蛋白2(Grb2)的能力；抑制募集并结合至多种含SH2的蛋白质的能力；调节一种或多种促炎性细胞因子的表达的能力，任选地其中所述一种或多种抗炎细胞因子选自IFN-a4、IFN-β、IL-1β、IL-1α、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-33、MCP-1以及MIP-1-β；调节一种或多种细胞中的一种或多种促炎性细胞因子的表达的能力，所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞；调节一种或多种抗炎细胞因子的表达的能力，任选地其中所述一种或多种抗炎细胞因子选自IL-4、IL-10、IL-13、IL-35、IL-16、TGF-β、IL-1Ra、G-CSF以及TNF、IFN-β1a、IFN-β1b或IL-6的可溶性受体；调节一种或多种细胞中的一种或多种抗炎细胞因子的表达的能力，所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞；调节一种或多种选自以下的蛋白质的表达的能力：C1qa、C1qB、C1qC、C1s、C1R、C4、C2、C3、ITGB2、HMOX1、LAT2、CASP1、CSTA、VSIG4、MS4A4A、C3AR1、GPX1、TyroBP、ALOX5AP、ITGAM、SLC7A7、CD4、ITGAX以及PYCARD；抵消细胞外信号调控激酶(ERK)磷酸化的抑制；防止一种或多种细胞蛋白上的酪氨酸磷酸化降低，任选地，其中所述一种或多种细胞蛋白包含ZAP-70并且所述酪氨酸磷酸化发生在ZAP-70的Tyr-319上；调节C-C趋化因子受体7(CCR7)的表达的能力；防止抑制针对表达CCL19的细胞和表达CCL21的细胞的小神经胶质细胞趋化性的能力；防止减少由一种或多种细胞诱导的T细胞增殖的能力，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞、M2小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞以及M2 NK细胞；防止抑制破骨细胞产生的能力，防止降低破骨细胞生成速率的能力或两者；防止一种或多种细胞的存活降低的能力，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；防止降低一种或多种细胞的增殖，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞；增强一种或多种细胞的迁移的能力，所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细

胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;防止一种或多种细胞的一种或多种功能的降低的能力,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;增强一种或多种细胞的成熟的能力,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;增强一种或多种类型的清除的能力,所述清除选自凋亡神经元清除、神经组织碎片清除、功能障碍性突触清除、非神经组织碎片清除、细菌清除、其它异物清除、致病蛋白清除、致病肽清除以及肿瘤细胞清除;任选地,其中所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽,并且所述肿瘤细胞来自癌症,所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌;抑制以下中的一种或多种的吞噬:凋亡神经元、神经组织碎片、功能障碍性突触、非神经组织碎片、细菌、其它异物、致病蛋白、致病肽、致病核酸或肿瘤细胞;任选地其中所述致病核酸是反义GGCCCC(G2C4)重复序列-扩增RNA,所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽,并且所述肿瘤细胞来自癌症,所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤或甲状腺癌;

与肿瘤细胞上的Siglec-7配体结合;与细胞上的Siglec-7配体结合,所述细胞选自嗜中性粒细胞、树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞以及NK细胞;通过以下中的一种或多种抑制肿瘤细胞杀伤:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;活化以下中的一种或多种的抗肿瘤细胞增殖活性:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;增强以下中的一种或多种的抗肿瘤细胞转移活性的能力:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;增强一种或多种含ITAM基序的受体的活性的能力,任选地其中所述一种或多种含ITAM基序的受体选自TREM1、TREM2、Sirpβ、FcgR、DAP10以及DAP12;通过一种或多种模式识别受体(PRR)增强信号传导的能力,任选地其中所述一种或多种PRR选自鉴定病原体相关分子模式(PAMP)的受体、鉴定损伤相关分子模式(DAMP)的受体以及其任何组合;增强包含基序D/Ex_{0-2}YxxL/IX_{6-8}YxxL/I(SEQ ID NO:537)的一种或多种受体的活性的能力;增强通过一种或多种Toll样受体信号传导的能力;增强JAK-STAT信号传导途径的能力;增强活化的B细胞的核因子κ-轻链增强子(NFêB)的活性的能力;增加含有ITAM基序的受体的磷酸化的能力;增加一种或多种炎性受体的表达的能力,任选地其中所述一种或多种炎性受体包含CD86并且所述一种或多种炎性受体在以下中的一种或多种上表达:小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突状细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞;降低一种或多种Siglec-7依赖性基因的表达的能力;增强一种或多种ITAM依赖性基因的表达的能力,任选地其中所述一种或多种ITAM依赖性基因通过活化T细胞的核因子(NFAT)转录因子活化;降低或以其它方式抑制以下中的一种或多种的分化的能力:免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞;降低或以其它方式抑制以下中的一种或多种的功能性的能力:免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞;降低或以其它方式抑制以下中的一种或多种浸润到肿瘤中:免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞;降低或以其它方式抑制肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量的能力;降低或以其它方式抑制骨髓源性抑制细胞的肿瘤促进活性的能力;降低或以其它方式抑制肿瘤或外周血中肿瘤促进细胞因子如TGF-β或IL-10的表达的能力;降低或以其它方式抑制肿瘤促进FoxP3+调控性T淋巴细胞的肿瘤浸润的能力;降低或以其它方式抑制骨髓源性抑制细胞(MDSC)的肿瘤促进活性的能力;增加或以其它方式增强具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化;增加或以其它方式增强具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润的能力;增加或以其它方式增强NK细胞的肿瘤杀伤潜力的能力;增加或以其它方式增强具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润的能力;增加或以其它方式增强具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润的能力;降低肿瘤体积的能力;降低肿瘤生长速率的能力;降低或以其它方式抑制转移的能力;降低肿瘤复发率的能力;增加或以其它方式增强一

种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效的能力，任选地其中所述一种或多种免疫疗法是靶向一种或多种靶蛋白的免疫疗法，所述一种或多种靶蛋白选自PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、TREM1、TREM2、CSF-1受体以及其任何组合；增加或以其它方式增强PLCã/PKC/钙动员的能力；以及增加或以其它方式增强PI3K/Akt、Ras/MAPK信号传导的能力。

[0272] 在一些实施方案中，本公开的拮抗剂抗Siglec-7抗体具有展示与一种或多种Fcg受体降低的结合的Fc区。以下表D中提供了此类Fc区和修饰的实例。在一些实施方案中，所述抗体具有以下表D中列出的Fc同种型。

[0273] 具有降低的与Fcγ受体的结合的抗体Fc同种型

[0274] 在一些实施方案中，具有降低的与Fcγ受体的结合的抗Siglec-7抗体具有以下表D中列出的Fc同种型。

[0275] 表D:具有降低的与Fcγ受体的结合的示例性抗Siglec-7抗体Fc同种型

[0276]

Fc 同种型	突变(EU 编号方案)
IgG1	N297A 或 N297Q
IgG1	D265A、D270A 和 N297A
IgG1	L234A 和 L235A
IgG2	V234A 和 G237A
IgG4	F235A 和 G237A 和 E318A E233P 和/或 F234V N297A 或 N297Q
IgG4	S228P 和 L236E S241P S241P 和 L248E S228P 和 F234A 和 L235A
IgG2	H268Q 和 V309L 和 A330S 和 P331S
IgG1	C220S 和 C226S 和 C229S 和 P238S
IgG1	C226S 和 C229S 和 E233P 和 L234V，和 L235A
IgG1	E233P 和 L234V 和 L235A 和 G236-缺失

[0277]

Fc 同种型	突变(EU 编号方案)
	P238A D265A N297A A327Q 或 A327G P329A
IgG1	K322A 和 L234A 和 L235A
IgG1	L234F 和 L235E 和 P331S
IgG1 或 IgG4	T394D
IgG2	C232S 或 C233S N297A 或 N297Q
IgG2	V234A 和 G237A 和 P238S 和 H268A 和 V309L 和 A330S 和 P331S
IgG1 、 IgG2 或 IgG4	δa、b、c、ab、ac、g 修饰
IgG1	以上列出的突变中的任一者连同 A330L 或 L234F 和/或 L235E 和/或 P331S
IgG1 、 IgG2 或 IgG4	以上列出的突变中的任一者连同 M252Y 和/或 S254T 和/或 T256E

[0278] 在某些实施方案中,所述抗Siglec-7抗体具有IgG1同种型。在一些实施方案中,所述抗体含有小鼠IgG1恒定区。在一些实施方案中,所述抗体含有人IgG1恒定区。在一些实施方案中,所述人IgG1恒定区包括Fc区。在一些实施方案中,所述Fc区含有一种或多种修饰。例如,在一些实施方案中,所述Fc区含有一种或多种氨基酸取代(例如,相对于同一同种型的野生型Fc区)。

[0279] 在一些实施方案中,所述一种或多种氨基酸取代选自N297A、N297Q(Bolt S等人(1993)Eur J Immunol23:403-411)、D270A、D265A、L234A、L235A(McEarchern等人,(2007)Blood,109:1185-1192)、C226S、C229S(McEarchern等人,(2007)Blood,109:1185-1192)、P238S(Davis等人,(2007)J Rheumatol,34:2204-2210)、E233P、L234V(McEarchern等人,(2007)Blood,109:1185-1192)、P238A、A327Q、A327G、P329A(Shields RL.等人,(2001)J Biol Chem.276(9):6591-604)、K322A、L234F、L235E(Hezareh,等人,(2001)J Virol 75,12161-12168;Oganesyan等人,(2008).Acta Crystallographica 64,700-704)、P331S(Oganesyan等人,(2008)Acta Crystallographica 64,700-704)、T394D(Wilkinson等人(2013)MAbs 5(3):406-417)、A330L、M252Y、S254T和/或T256E,其中所述氨基酸位置根据EU或Kabat编号惯例。在某些实施方案中,所述Fc区在对应于根据EU或Kabat编号惯例的甘氨酸236的位置处进一步包含氨基酸缺失。

[0280] 在一些实施方案中,所述抗Siglec-7抗体具有IgG1同种型,所述同种型具有包含根据EU或Kabat编号惯例的C220S氨基酸取代的重链恒定区。在一些实施方案中,所述Fc区

进一步含有一种或多种另外的氨基酸取代,所述氨基酸取代选自根据EU或Kabat编号惯例的t A330L、L234F、L235E或P331S。在某些实施方案中,所述抗Siglec-7抗体具有IgG2同种型。在一些实施方案中,所述抗Siglec-7抗体含有人IgG2恒定区。在一些实施方案中,所述人IgG2恒定区包括Fc区。在一些实施方案中,所述Fc区含有一种或多种修饰。例如,在一些实施方案中,所述Fc区含有一种或多种氨基酸取代(例如,相对于同一同种型的野生型Fc区)。在一些实施方案中,所述一种或多种氨基酸取代选自P238S、V234A、G237A、H268A、H268Q、H268E、V309L、N297A、N297Q、V309L、A330S、P331S、C232S、C233S、M252Y、S254T和/或T256E,其中所述氨基酸位置根据EU或Kabat编号惯例(Vafa O.等人,(2014)Methods 65:114-126)。

[0281] 在某些实施方案中,所述抗Siglec-7抗体具有IgG4同种型。在一些实施方案中,所述抗Siglec-7抗体含有人IgG4恒定区。在一些实施方案中,所述人IgG4恒定区包括Fc区。在一些实施方案中,所述Fc区含有一种或多种修饰。例如,在一些实施方案中,所述Fc区含有一种或多种氨基酸取代(例如,相对于同一同种型的野生型Fc区)。在一些实施方案中,所述一种或多种氨基酸取代选自E233P、F234V、L235A、G237A、E318A(Hutchins等人(1995)Proc Natl Acad Sci USA,92:11980-11984)、S228P、L234A/F234A、L236E、S241P、L248E(Reddy等人,(2000)J Immunol,164:1925-1933;Angal等人,(1993)Mol Immunol.30(1):105-8;US 8614299 B2;Vafa O.等人,(2014)Methods 65:114-126)、T394D、M252Y、S254T、T256E、N297A、和/或N297Q,其中所述氨基酸位置根据EU或Kabat编号惯例。

[0282] 在一些实施方案中,所述Fc区进一步含有一种或多种选自M252Y、S254T和/或T256E的另外氨基酸取代,其中所述氨基酸位置根据EU或Kabat编号惯例。

[0283] 其它IgG突变

[0284] 在一些实施方案中,本文所述的一种或多种IgG1变体可与A330L突变(Lazar等人,(2006)Proc Natl Acad Sci USA,103:4005-4010)或L234F、L235E和/或P331S突变中的一种或多种(Sazinsky等人,(2008)Proc Natl Acad Sci USA,105:20167-20172)组合,其中所述氨基酸位置根据EU或Kabat编号惯例以消除补体活化。在一些实施方案中,本文所述的IgG变体可与一种或多种突变组合以增强人血清中的抗Siglec-7抗体半衰期(例如根据EU或Kabat编号惯例的M252Y、S254T、T256E突变)(Dall'Acqua等人,(2006)J Biol Chem,281:23514-23524;以及Strohl等人,(2009)Current Opinion in Biotechnology,20:685-691)。

[0285] 在一些实施方案中,本公开的IgG4变体可与根据EU或Kabat编号惯例的S228P突变(Angal等人,(1993)Mol Immunol,30:105-108)、F234A突变、L235A突变和/或与Peters等人,(2012)J Biol Chem.13;287(29):24525-33)中描述的一种或多种突变组合。

[0286] 在一些实施方案中,本公开的抗Siglec-7抗体具有IgG4同种型。在一些实施方案中,所述抗体Fc区含有根据EU编号,在残基位置228处的S228P氨基酸取代、在残基位置234处的F234A氨基酸取代以及在残基位置235处的L235A氨基酸取代。

[0287] 双特异性抗体

[0288] 本公开的某些方面涉及结合至本公开的Siglec-7蛋白上的一个或多个结构域和第二抗原的双特异性抗体。产生双特异性抗体的方法是本领域中熟知的和本文描述的。在一些实施方案中,本公开的双特异性抗体结合至本公开的Siglec-7蛋白的一个或多个氨基

酸残基，如人Siglec-7(SEQ ID NO:1)的一个或多个氨基酸残基，或Siglec-7蛋白上对应于SEQ ID NO:1的氨基酸残基的的氨基酸残基。在一些实施方案中，本公开的双特异性抗体识别第一抗原和第二抗原。在一些实施方案中，第一抗原是Siglec-7蛋白或其天然存在的变体。在一些实施方案中，第二抗原也是Siglec-7蛋白或其天然存在的变体。在一些实施方案中，第二抗原是促进跨血脑屏障的转运的抗原(参见例如，Gabathuler R.，Neurobiol.Dis.37(2010)48-57)。此类第二抗原包括但不限于转铁蛋白受体(TR)、胰岛素受体(HIR)、胰岛素样生长因子受体(IGFR)、低密度脂蛋白受体相关蛋白1和2(LPR-1和2)、白喉毒素受体、CRM197、美洲驼单结构域抗体、TMEM 30(A)、蛋白质转导结构域、TAT、Syn-B、穿膜素、聚精氨酸肽、血管肽肽如ANG1005(参见例如，Gabathuler，2010)和其它在血脑屏障内皮细胞上富集的细胞表面蛋白质(参见例如，Daneman等人，PLoS One.2010年10月29日；5(10)：e13741)。在一些实施方案中，第二抗原是致病蛋白，包括但不限于淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽。在一些实施方案中，第二抗原是在免疫细胞上表达的一种或多种配体和/或蛋白质，包括但不限于，CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、CD3以及磷脂酰丝氨酸。在一些实施方案中，第二抗原是在一种或多种肿瘤细胞上表达的蛋白质、脂质、多糖或糖脂。

[0289] 抗体片段

[0290] 本公开的某些方面涉及结合至本公开的Siglec-7蛋白、Siglec-7蛋白的天然存在的变体和Siglec-7蛋白的疾病变体中的一种或多种的抗体片段。在一些实施方案中，所述抗体片段是Fab、Fab′、Fab′-SH、F(ab′)2、Fv或scFv片段。

[0291] 在一些实施方案中，所述抗体片段与第二Siglec-7抗体和/或与一种或多种特异性地结合致病蛋白的抗体组合使用，所述致病蛋白选自：淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽以及其任何组合；或与一种或多

种结合免疫调节蛋白的抗体组合使用，所述免疫调节蛋白选自：CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、TREM1、TREM2、CSF-1受体、CD33、Siglec-5、Siglec-9、Siglec-11、磷脂酰丝氨酸以及其任何组合。

[0292] 在一些实施方案中，本公开的抗体片段可以是与本公开的任何抗Siglec-7抗体结合相同表位的功能片段。在一些实施方案中，所述抗体片段是本公开的抗Siglec-7抗体或抗体片段的微型化型式，其具有相应全长抗体的相同表位，但具有小得多的分子量。这种微型化抗Siglec-7抗体片段可具有更好的脑渗透能力和更短的半衰期，这对于成像和诊断应用是有利的(参见例如，Lütje S等人，Bioconjug Chem.20142月19日；25(2)：335-41；Tavaré R等人，Proc Natl Acad Sci USA.2014年1月21日；111(3)：1108-13；以及Wiehr S等人，Prostate.2014年5月；74(7)：743-55)。因此，在一些实施方案中，本公开的抗Siglec-7抗体片段具有与其相应的全长抗体相比更好的脑渗透和/或具有与其相应的全长抗体相比更短的半衰期。

[0293] 抗体框架

[0294] 本文所述的任何抗体还包含框架。在一些实施方案中，所述框架是人免疫球蛋白框架。例如，在一些实施方案中，抗体(例如，抗Siglec-7抗体)包含如任何以上实施方案中的HVR，并且还包含受体人框架，例如人免疫球蛋白框架或人共有框架。人免疫球蛋白框架可以是人抗体的一部分，或者可通过用人框架区置换一个或多个内源框架来将非人抗体人源化。可用于人源化的人框架区包括但不限于：使用“最佳拟合”方法选择的框架区(参见例如，Sims等人J.Immunol.151:2296(1993))；源于轻链或重链可变区的特定亚组的人抗体的共有序列的框架区(参见例如，Carter等人Proc.Natl.Acad.Sci.USA,89:4285(1992)；以及Presta等人，J.Immunol.,151:2623(1993))；人成熟(体细胞突变)框架区或人生殖系框架区(参见例如，Almagro和Fransson,Front.Biosci.13:1619-1633(2008))；以及由筛选FR文库获得的框架区(参见例如Baca等人，J.Biol.Chem.272:10678-10684(1997)以及Rosok等人，J.Biol.Chem.271:22611-22618(1996))。

[0295] 在一些实施方案中，抗体包含轻链可变区，所述轻链可变区包含本公开的HVR-L1、HVR-L2和HVR-L3以及如表3A中所示的轻链框架区中的一个、两个、三个或四个。在一些实施方案中，抗体包含重链可变区，所述重链可变区包含本公开的HVR-H1、HVR-H2和HVR-H3以及如表3B中所示的重链框架区中的一个、两个、三个或四个。在一些实施方案中，抗体包含轻链可变区，所述轻链可变区包含本公开的HVR-L1、HVR-L2和HVR-L3以及表3A中所示的轻链框架区中的一个、两个、三个或四个，并且还包含重链可变区，所述重链可变区包含本公开的HVR-H1、HVR-H2和HVR-H3以及表3B中所示的重链框架区中的一个、两个、三个或四个。

[0296] 抗体制备

[0297] 本公开的抗Siglec-7抗体可涵盖多克隆抗体、单克隆抗体、人源化和嵌合抗体、人抗体、抗体片段(例如Fab、Fab′-SH、Fv、scFv和$F(ab')_2$)、双特异性和多特异性抗体、多价抗体、异缀合物抗体、缀合抗体、文库衍生抗体、具有修饰效应子功能的抗体、含有抗体部分的融合蛋白以及包含抗原识别位点的免疫球蛋白分子的任何其它修饰构型，如具有本公开的Siglec-7蛋白的氨基酸残基的表位，包括抗体的糖基化变体、抗体的氨基酸序列变体和共价修饰的抗体。抗Siglec-7抗体可以是人、鼠、大鼠或任何其它来源(包括嵌合或人源化抗

体)。

[0298] (1)多克隆抗体

[0299] 通常在动物中通过多次皮下(sc)或腹膜内(ip)注射相关抗原和佐剂来产生多克隆抗体,如多克隆抗Siglec-7抗体。使用双功能或衍生剂将相关抗原(例如,本公开的纯化或重组Siglec-7蛋白)缀合至在待免疫物种中具有免疫原性的蛋白质可以是有用的,所述蛋白质例如钥孔血蓝蛋白(KLH)、血清白蛋白、牛甲状腺球蛋白或大豆胰蛋白酶抑制剂,所述双功能试剂或衍生剂例如马来酰亚胺苯甲酰磺基琥珀酰亚胺酯(通过半胱氨酸残基进行缀合)、N-羟基琥珀酰亚胺(通过赖氨酸残基)、戊二醛、琥珀酸酐、$SOCl_2$或$R^1N=C=NR$,其中R和R^1独立地是低级烷基基团。可使用的佐剂的实例包括弗氏完全佐剂(Freund′s complete adjuvant)和MPL-TDM佐剂(单磷酰基脂质A、合成海藻糖二霉菌酸酯(synthetic trehalose dicorynomycolate))。免疫方案可由本领域的技术人员选择而无需过多实验。

[0300] 通过将例如100μg(对于兔)或5μg(对于小鼠)的蛋白质或缀合物与3体积的弗氏完全佐剂组合并且将所述溶液皮内注射在多个部位来针对所需抗原、免疫原性缀合物或衍生物对动物进行免疫。一个月后,通过在多个部位皮下注射,用1/5至1/10的初始量的于弗氏完全佐剂中的肽或缀合物对动物加强免疫。七到十四天后,将动物放血并测定血清的抗体滴度。对动物加强免疫,直到效价稳定。缀合物也可在重组细胞培养物中制备为蛋白质融合体。此外,如明矾的聚集剂适用于增强免疫应答。

[0301] (2)单克隆抗体

[0302] 单克隆抗体如单克隆抗Siglec-7抗体从基本上同质抗体的群体获得,即构成所述群体的各个抗体是相同的,除了可能以微量存在的可能的天然存在的突变和/或翻译后修饰(例如,异构化,酰胺化)。因此,修饰语“单克隆”表明抗体的特征不是分立抗体的混合物。

[0303] 例如,单克隆抗体可使用最初由Kohler等人,Nature,256:495(1975)描述的杂交瘤方法制备,或可通过重组DNA方法(美国专利号4,816,567)来制备。

[0304] 在杂交瘤方法中,使小鼠或其它适当的宿主动物(诸如仓鼠)如上文所描述进行免疫以得到产生或能够产生将特异性结合至用于免疫的蛋白质(例如,本公开的纯化或重组Siglec-7蛋白)的抗体的淋巴细胞。可替代地,淋巴细胞可被体外免疫。然后,使用合适的融合剂(诸如聚乙二醇)使淋巴细胞与骨髓瘤细胞融合以形成杂交瘤细胞(Goding,Monoclonal Antibodies:Principles and Practice,第59-103页(Academic Press,1986))。

[0305] 免疫剂通常将包括抗原蛋白(例如,本公开的纯化或重组Siglec-7蛋白)或其融合变体。一般来说,如果需要人来源的细胞,则使用外周血淋巴细胞(“PBL”);而如果需要非人哺乳动物来源的细胞,则使用脾细胞或淋巴结细胞。然后使用合适的融合剂(如聚乙二醇)将淋巴细胞与永生化细胞系融合,以形成杂交瘤细胞。Goding,Monoclonal Antibodies:Principles and Practice,Academic Press(1986),第59-103页。

[0306] 永生化细胞系通常是转化的哺乳动物细胞,尤其是啮齿动物、牛或人来源的骨髓瘤细胞。通常,使用大鼠或小鼠骨髓瘤细胞系。接种所制备的杂交瘤细胞,并使其在优选含有一种或多种抑制未融合的亲本骨髓瘤细胞生长或存活的物质的合适的培养基中生长。例如,如果亲本骨髓瘤细胞缺乏酶次黄嘌呤鸟嘌呤磷酸核糖基转移酶(HGPRT或HPRT),那么用于杂交瘤的培养基通常将包括次黄嘌呤、氨基喋呤和胸苷(HAT培养基),其是防止缺乏

HGPRT的细胞的生长的物质。

[0307] 优选的永生化骨髓瘤细胞是那些有效融合、支持通过所选择的抗体产生细胞的稳定高水平抗体产生，且对培养基(诸如HAT培养基)敏感的骨髓瘤细胞。在这些之中，优选的是鼠类骨髓瘤系，诸如源自MOPC-21和MPC-11小鼠肿瘤(可从Salk Institute Cell Distribution Center,San Diego,California USA获得)的的细胞系以及SP-2细胞及其衍生物(例如,X63-Ag8-653)(可从American Type Culture Collection,Manassas,Virginia USA获得)。人骨髓瘤和小鼠-人异源骨髓瘤细胞系还被描述用于人单克隆抗体的产生(Kozbor,J.Immunol.,133:3001(1984);Brodeur等人,Monoclonal Antibody Production Techniques and Applications,第51-63页(Marcel Dekker,Inc.,New York,1987))。

[0308] 测定杂交瘤细胞生长所处的培养基中针对抗原的单克隆抗体(例如，本公开的Siglec-7蛋白)的产生。优选地，通过免疫沉淀法或通过体外结合测定(如放射免疫测定(RIA)或酶联免疫吸附测定(ELISA))来测定杂交瘤细胞产生的单克隆抗体的结合特异性。

[0309] 可测定其中培养杂交瘤细胞的培养基中针对所需抗原的单克隆抗体(例如本公开的Siglec-7蛋白)的存在。优选地，可通过免疫沉淀法或通过体外结合测定(如放射免疫测定(RIA)或酶联测定(ELISA))来测定单克隆抗体的结合亲和力和特异性。此类技术和测定是本领域中已知的。例如，结合亲和力可通过Munson等人,Anal.Biochem.,107:220(1980)的斯卡查德分析(Scatchard analysis)确定。

[0310] 在鉴定产生具有所需特异性、亲和力和/或活性的抗体的杂交瘤细胞后，就可通过有限稀释程序而将所述克隆进行亚克隆并且通过标准方法使其生长(Goding,同上)。用于这一目的的合适培养基包括例如D-MEM或RPMI-1640培养基。此外，杂交瘤细胞可作为哺乳动物体内的肿瘤在体内生长。

[0311] 由亚克隆分泌的单克隆抗体可通过常规免疫球蛋白纯化程序(例如像蛋白质A-琼脂糖色谱法、羟基磷灰石色谱法、凝胶电泳、透析、亲和色谱法以及如上所述的其它方法)从培养基、腹水或血清中适合地分离。

[0312] 抗Siglec-7单克隆抗体也可通过重组DNA方法来制备，如美国专利号4,816,567中公开和如上所述的那些方法。使用常规程序(例如，通过使用特异性地结合至编码鼠抗体的重链和轻链的基因的寡核苷酸探针)来容易地将编码单克隆抗体的DNA分离和/或测序。杂交瘤细胞充当这类DNA的优选来源。一旦分离，就可将DNA置于表达载体中，然后将其转染至宿主细胞，如大肠杆菌细胞、猴COS细胞、中国仓鼠卵巢(CHO)细胞、或不以另外的方式产生免疫球蛋白的骨髓瘤细胞中，以便在此类重组宿主细胞中合成单克隆抗体。关于在细菌中重组表达编码抗体的DNA的文献综述包括Skerra等人,Curr.Opin.Immunol.,5:256-262(1993)和Plückthun,Immunol.Rev.130:151-188(1992)。

[0313] 在某些实施方案中，抗Siglec-7抗体可从使用在McCafferty等人,Nature,348:552-554(1990)中描述的技术产生的抗体噬菌体文库分离。Clackson等人,Nature,352:624-628(1991)和Marks等人,J.Mol.Biol.,222:581-597(1991)描述了分别从噬菌体文库分离鼠抗体和人抗体。随后的公布描述通过链改组(Marks等人,Bio/Technology,10:779-783(1992))以及组合感染和体内重组作为构建非常大的噬菌体库的策略(Waterhouse等人,Nucl.Acids Res.,21:2265-2266(1993))来产生高亲和力(纳摩尔(“nM”)范围)的人抗体。因此，这些技术是用于分离具有所需特异性的单克隆抗体(例如，结合本公开的Siglec-

7蛋白的那些)的传统单克隆抗体杂交瘤技术的可行替代方案。

[0314] 还可例如通过取代人重链和轻链恒定结构域的编码序列代替同源鼠序列(美国专利号4,816,567;Morrison等人,Proc.Natl Acad.Sci.USA,81:6851(1984))或通过将非免疫球蛋白多肽的编码序列的全部或一部分共价连接至免疫球蛋白编码序列来修饰编码DNA的抗体或片段。通常,此类非免疫球蛋白多肽取代抗体的恒定结构域或它们取代抗体的一个抗原组合位点的可变结构域以产生嵌合二价抗体,所述抗体包含具有针对抗原的特异性的一个抗原组合位点和具有针对不同抗原的特异性的另一个抗原组合位点。

[0315] 本文所述的单克隆抗体(例如,本公开的抗Siglec-7抗体或其片段)可单价制备,其制备是本领域中熟知的。例如,一种方法涉及免疫球蛋白轻链和修饰的重链的重组表达。重链通常在Fc区中的任何点处截短以便防止重链交联。或者,相关的半胱氨酸残基可被另一个氨基酸残基取代或被缺失以防止交联。体外方法也适合于制备单价抗体。消化抗体以产生其片段,尤其是Fab片段可使用本领域中已知的常规技术来完成。

[0316] 可使用合成蛋白质化学中的已知方法(包括涉及交联剂的那些)在体外制备嵌合或杂合抗Siglec-7抗体。例如,可使用二硫化物交换反应或通过形成硫醚键来构建免疫毒素。用于此目的的适合试剂的实例包括亚氨基硫醇酯和甲基-4-巯基丁酰亚氨酸酯。

[0317] (3)人源化抗体

[0318] 本公开的抗Siglec-7抗体或其抗体片段可进一步包括人源化或人抗体。非人(例如鼠)抗体的人源化形式是嵌合免疫球蛋白、免疫球蛋白链或其片段(诸如Fab、Fab′-SH、Fv、scFv、$F(ab')_2$或抗体的其它抗原结合子序列),其含有源自非人免疫球蛋白的最小序列。人源化抗体包括人免疫球蛋白(接受者抗体),其中来自接受者的互补决定区(CDR)的残基被来自诸如小鼠、大鼠或兔的非人物种(供体抗体)的CDR的具有所需特异性、亲和力和能力的残基置换。在一些情况下,人免疫球蛋白的Fv框架残基被相应的非人残基置换。人源化抗体还可包含既不发现于接受者抗体中也不发现于输入CDR或框架序列中的残基。通常,所述人源化抗体将包含至少一个且通常两个可变结构域的基本全部,其中全部或基本全部的CDR区对应于非人免疫球蛋白的那些CDR区且全部或基本全部的FR区是人免疫球蛋白共有序列的那些FR区。所述人源化抗体优选地还将包含免疫球蛋白恒定区(Fc)的至少一部分,通常人免疫球蛋白的至少一部分。Jones等人,Nature 321:522-525(1986);Riechmann等人,Nature 332:323-329(1988)和Presta,Curr.Opin.Struct.Biol.2:593-596(1992)。

[0319] 用于人源化非人抗Siglec-7抗体的方法是本领域中熟知的。总体上,人源化抗体具有从非人来源引入其中的一个或多个氨基酸残基。这些非人氨基酸残基通常被称为“输入”残基,其通常取自“输入”可变结构域。人源化可基本上根据Winter和合作者,Jones等人,Nature 321:522-525(1986);Riechmann等人,Nature 332:323-327(1988);Verhoeyen等人,Science 239:1534-1536(1988)的方法,通过用啮齿动物CDR或CDR序列替换人抗体的相应序列来产生。因此,此类“人源化”抗体是嵌合抗体(美国专利号4,816,567),其中基本上小于完整人可变结构域已被来自非人物种的对应序列取代。实际上,人源化抗体通常是人抗体,其中一些CDR残基和可能一些FR残基被来自啮齿动物抗体中的类似部位的残基取代。

[0320] 用于制备人源化抗体的人可变结构域轻链与重链的选择对降低抗原性来说是非常重要的。根据所谓的“最佳拟合”方法,针对已知的人可变结构域序列的整个文库筛选啮

齿动物抗体的可变结构域的序列。与啮齿动物的序列最接近的人序列然后被接受作为人源化抗体的人框架(FR)。Sims等人,J.Immunol.,151:2296(1993);Chothia等人,J.Mol.Biol.,196:901(1987)。另一种方法使用源自轻链或重链的特定亚组的所有人抗体的共有序列的特定框架。相同的框架可用于若干不同的人源化抗体。Carter等人,Proc.Nat'l Acad.Sci.USA 89:4285(1992);Presta等人,J.Immunol.151:2623(1993)。

[0321] 此外,重要的是抗体保留对抗原的高亲和力和其它有利的生物性质而被人源化。为实现这一目标,根据优选的方法,利用亲本序列和人源化序列的三维模型通过分析亲本序列和各种概念上人源化的产物的方法制备人源化抗体。三维免疫球蛋白模型通常可用并且是本领域的技术人员熟悉的。计算机程序可用,所述程序说明并展示选择的候选免疫球蛋白序列的可能的三维构象结构。对这些展示的检查允许分析残基在候选免疫球蛋白序列的功能中的可能作用,即分析可影响候选免疫球蛋白结合其抗原的能力的残基。以这种方式,可从接受者和输入序列中选择FR残基并组合,以使得实现所需的抗体特征,如对一种或多种靶抗原(例如本公开的Siglec-7蛋白)的亲和力增加。通常,所述CDR残基直接并且最显著地牵涉于影响抗原结合。

[0322] 考虑了各种形式的人源化抗Siglec-7抗体。例如,人源化抗Siglec-7抗体可以是抗体片段如Fab,其任选地与一种或多种细胞毒性剂缀合以便产生免疫缀合物。或者,人源化抗Siglec-7抗体可以是完整抗体,如完整IgG1抗体。

[0323] (4)人抗体

[0324] 或者,可产生人抗Siglec-7抗体。例如,现在有可能产生在不存在内源性免疫球蛋白产生的情况下在免疫之后能够产生人抗体的全谱系的转基因动物(例如,小鼠)。嵌合和种系突变小鼠中抗体重链连接区(JH)基因的纯合缺失导致内源性抗体产生的完全抑制。人种系免疫球蛋白基因阵列在这种种系突变小鼠中的转移将导致在抗原激发后产生人抗体。参见例如,Jakobovits等人.,Proc.Nat'l Acad.Sci.USA,90:2551(1993);Jakobovits等人,Nature,362:255-258(1993);Bruggermann等人,Year in Immunol.,7:33(1993);美国专利号5,591,669以及WO 97/17852。

[0325] 或者,可使用噬菌体展示技术从来自未免疫供体的免疫球蛋白可变(V)结构域基因谱系体外产生人抗Siglec-7抗体和抗体片段。McCafferty等人,Nature 348:552-553(1990);Hoogenboom和Winter,J.Mol.Biol.227:381(1991)。根据这项技术,抗体V结构域基因是以框内方式克隆至丝状噬菌体(如M13或fd)的主要或次要外壳蛋白基因中,并且在噬菌体颗粒的表面上展示为功能性抗体片段。因为丝状颗粒含有噬菌体基因组的单链DNA拷贝,所以基于抗体的功能特性的选择还导致编码表现那些特性的抗体的基因的选择。因而,噬菌体模拟B细胞的一些特性。噬菌体展示可以例如综述于Johnson,Kevin S.和Chiswell,David J.,Curr.Opin Struct.Biol.3:564-571(1993)中的多种形式进行。若干V基因区段来源可以用于噬菌体展示。Clackson等人,Nature 352:624-628(1991)从源自免疫小鼠的脾脏的V基因的小随机组合文库分离了抗噁唑酮抗体的不同阵列。可构建来自未免疫人供体的V基因谱系,并且可按照由Marks等人,J.Mol.Biol.222:581-597(1991)或Griffith等人,EMBO J.12:725-734(1993)描述的技术而基本上分离针对抗原(包括自身抗原)的不同阵列的抗体。还参见美国专利号5,565,332和5,573,905。此外,酵母展示技术可用于在体外产生人抗Siglec-7抗体和抗体片段(例如,WO 2009/036379;WO 2010/105256;WO 2012/

009568;US 2009/0181855;US 2010/0056386;以及Feldhaus和Siegel(2004) J.Immunological Methods 290:69-80)。在其它实施方案中,核糖体展示技术可用于在体外产生人抗Siglec-7抗体和抗体片段(例如,Roberts和Szostak(1997)Proc Natl Acad Sci 94:12297-12302;Schaffitzel等人(1999)J.Immunolical Methods 231:119-135;Lipovsek和Plückthun(2004)J.Immunological Methods 290:51-67)。

[0326] Cole等人和Boerner等人的技术也可用于制备人抗Siglec-7单克隆抗体(Cole等人,Monoclonal Antibodies and Cancer Therapy,Alan R.Liss,第77页(1985)以及Boerner等人,J.Immunol.147(1):86-95(1991)。类似地,可通过将人免疫球蛋白基因座引入转基因动物,例如其中内源性免疫球蛋白基因已经部分或完全失活的小鼠来制备人抗Siglec-7抗体。在激发时,观察到人抗体产生,其与人中在所有方面中观察到的非常相似,包括基因重排、组装和抗体谱系。这种方法描述于例如美国专利号5,545,807;5,545,806、5,569,825、5,625,126、5,633,425、5,661,016以及以下科学出版物中:Marks等人,Bio/Technology 10:779-783(1992);Lonberg等人,Nature 368:856-859(1994);Morrison,Nature 368:812-13(1994);Fishwild等人,Nature Biotechnology 14:845-51(1996);Neuberger,Nature Biotechnology 14:826(1996)以及Lonberg和Huszar,Intern.Rev.Immunol.13:65-93(1995)中。

[0327] 最后,人抗Siglec-7抗体也可由活化的B细胞体外产生(参见美国专利号5,567,610和5,229,275)。

[0328] (5)抗体片段

[0329] 在某些实施方案中,使用抗Siglec-7抗体片段而不是完整的抗Siglec-7抗体是有利的。较小的片段大小允许实现快速清除和更好的脑渗透。

[0330] 已经开发了用于产生抗体片段的各种技术。传统上,这些片段是经由完整抗体的蛋白水解消化而衍生的(参见例如,Morimoto等人,J.Biochem.Biophys.Method.24:107-117(1992);以及Brennan等人,Science 229:81(1985))。然而,现在可通过重组宿主细胞,例如使用编码本公开的抗Siglec-7抗体的核酸直接产生这些片段。所有Fab、Fv和scFv抗体片段都可在大肠杆菌中表达并且从其分泌,因而允许大量这些片段的直接生产。抗Siglec-7抗体片段还可从以上所讨论的抗体噬菌体文库分离。或者,Fab′-SH片段可直接从大肠杆菌中回收并且化学偶联以便形成$F(ab')_2$片段(Carter等人,Bio/Technology 10:163-167(1992))。根据另一种方法,$F(ab')_2$片段可直接从重组宿主细胞培养物中分离。具有增加的体内半衰期的Fab和$F(ab')_2$抗体片段的产生描述于美国专利号5,869,046中。在其它实施方案中,所选择的抗体是单链Fv片段(scFv)。参见WO 93/16185;美国专利号5,571,894和美国专利号5,587,458。抗Siglec-7抗体片段也可以是“线性抗体”,例如,如美国专利5,641,870中所描述。此类线性抗体片段可以是单特异性的或双特异性的。

[0331] (6)双特异性和多特异性抗体

[0332] 双特异性抗体(BsAb)是对至少两种不同表位,包括相同或另一种蛋白质(例如本公开的一种或多种Siglec-7蛋白)上的那些表位具有结合特异性的抗体。或者,BsAb的一部分可配置为结合至靶Siglec-7抗原,并且另一部分可与结合至第二种蛋白质的臂组合。此类抗体可源自全长抗体或抗体片段(例如$F(ab')_2$双特异性抗体)。

[0333] 用于制备双特异性抗体的方法是本领域中已知的。全长双特异性抗体的传统产生

是基于两个免疫球蛋白重链/轻链对的共表达，其中两个链具有不同的特异性。Millstein等人，Nature，305:537-539(1983)。归因于免疫球蛋白重链和轻链的随机搭配，这些杂交瘤(四链瘤)产生10种不同抗体分子的一种潜在混合物，其中只有一个具有正确的双特异性结构。通常通过亲和色谱步骤进行的正确分子的纯化十分繁琐，并且产物产率是低的。类似的程序公开于WO 93/08829和Traunecker等人，EMBO J.，10:3655-3659(1991)中。

[0334] 根据一种不同的方法，具有所需结合特异性的抗体可变结构域(抗体-抗原组合位点)融合至免疫球蛋白恒定结构域序列。所述融合优选与免疫球蛋白重链恒定结构域一起，所述免疫球蛋白重链恒定结构域包含铰链、C_H2和C_H3区的至少一部分。优选具有存在于至少一个融合体中的包含轻链结合所需的位点的第一重链恒定区(C_H1)。将编码免疫球蛋白重链融合和(如果需要的话)免疫球蛋白轻链的DNA插入单独表达载体，并且共同转染至合适宿主生物体中。当在构建中使用的三条多肽链的不等比率提供最佳产率时，这在实施方案中为调节三种多肽片段的相互比率提供了极大的灵活性。然而，当相等比率的至少两条多肽链的表达产生高产率或当所述比率不具有特定显著性时，有可能将两个或所有三条多肽链的编码序列插入一个表达载体中。

[0335] 在这种方法的优选实施方案中，双特异性抗体由在一个臂中具有第一结合特异性的杂合免疫球蛋白重链和在另一个臂中的杂合免疫球蛋白重链-轻链对(从而提供第二结合特异性)组成。据发现这种不对称结构有助于将所需的双特异性化合物与不想要的免疫球蛋白链组合分开，因为在仅一半的双特异性分子中存在免疫球蛋白轻链提供了简单的分离方式。这一方法在WO 94/04690中公开。关于产生双特异性抗体的进一步细节，参见，例如，Suresh等人，Methods in Enzymology 121:210(1986)。

[0336] 根据在WO 96/27011或美国专利号5,731,168中描述的另一种方法，一对抗体分子之间的界面可被工程化以便将从重组细胞培养物回收的异源二聚体的百分比最大化。优选的界面包含抗体恒定结构域的C_H3区的至少一部分。在这种方法中，第一抗体分子的界面的一个或多个小氨基酸侧链用更大侧链(例如，酪氨酸或色氨酸)来置换。通过将大的氨基酸侧链置换为较小的侧链(例如，丙氨酸或苏氨酸)，在第二抗体分子的界面上生成与一条或多条大的侧链相同或相似大小的补偿“腔”。这提供了用于增加异源二聚体的产率超过其它不需要的最终产物如同源二聚体的机制。

[0337] 已经在文献中描述了从抗体片段产生双特异性抗体的技术。例如，双特异性抗体可使用化学键联来制备。Brennan等人，Science 229:81(1985)描述了一种程序，其中完整抗体被蛋白水解裂解以产生$F(ab')_2$片段。这些片段在存在二硫醇复合剂亚砷酸钠的情况下还原，以便稳定邻近的二硫醇并且防止分子间二硫化物形成。所产生的Fab′片段然后被转化为硫代硝基苯甲酸酯(TNB)衍生物。然后将Fab′-TNB衍生物之一再转化为Fab′-TNB衍生物以形成双特异性抗体。所产生的双特异性抗体可用作酶的选择性固定剂。

[0338] Fab′片段可直接从大肠杆菌中回收并化学偶联以形成双特异性抗体。Shalaby等人，J.Exp.Med.175:217-225(1992)描述了完全人源化的双特异性抗体$F(ab')_2$分子的产生。每个Fab′片段分别从大肠杆菌分泌并在体外进行定向化学偶联以形成双特异性抗体。由此形成的双特异性抗体能够结合至过度表达ErbB2受体的细胞和正常人T细胞，以及触发人细胞毒性淋巴细胞对人乳腺肿瘤靶标的溶解活性。

[0339] 还已经描述了直接自重组细胞培养物制备和分离二价抗体片段的各种技术。例

如,已使用亮氨酸拉链产生了二价抗体。Kostelny等人,J.Immunol.,148(5):1547-1553(1992)。来自Fos和Jun蛋白的亮氨酸拉链肽通过基因融合与两种不同抗体的Fab′部分连接。抗体同二聚体在铰链区处还原以形成单体,并且然后再次氧化以形成抗体异二聚体。由Hollinger等人,Proc.Nat'l Acad.Sci.USA,90:6444-6448(1993)描述的"双抗体"技术已经提供了用于制备双特异性/二价抗体片段的替代机制。所述片段包含通过接头与轻链可变结构域(V_L)连接的重链可变结构域(V_H),所述接头太短而不允许同一个链上的两个结构域之间的配对。因此,一个片段的V_H和V_L结构域被迫与另一个片段的互补V_L和V_H结构域配对,从而形成两个抗原结合位点。还已经报道了通过使用单链Fv(sFv)二聚体制备双特异性/二价抗体片段的另一种策略。参见Gruber等人,J.Immunol.,152:5368(1994)。

[0340] 还考虑了具有超过两个价态的抗体。例如,可以制备三特异性抗体。Tutt等人,J.Immunol.147:60(1991)。

[0341] 示例性双特异性抗体可结合至给定分子上的两个不同表位(例如,本公开的Siglec-7蛋白)。或者,靶向Siglec-7信号传导组分的臂可与结合至白细胞上的触发分子如T细胞受体分子(例如CD2、CD3、CD28或B7)或IgG的Fc受体(Fcγ R)(如FcγRI(CD64)、FcγRII(CD32)和FcγRIII(CD16)的臂组合,以便使细胞防御机制集中于表达特定蛋白质的细胞。双特异性抗体还可用于将细胞毒性剂定位至表达特定蛋白质的细胞。此类抗体拥有蛋白质结合臂和结合细胞毒性剂或放射性核素螯合剂(如EOTUBE、DPTA、DOTA或TETA)的臂。另一种目标双特异性抗体结合目标蛋白质并进一步结合组织因子(TF)。

[0342] (7)多价抗体

[0343] 与二价抗体相比,多价抗体可由表达抗体所结合的抗原的细胞来更快地内在化(和/或异化)。本公开的抗Siglec-7抗体或其抗体片段可以是具有三个或更多个抗原结合位点的多价抗体(它们是IgM类别以外的)(例如,四价抗体),所述抗体可通过编码抗体的多肽链的核酸的重组表达来容易地产生。多价抗体可包含二聚化结构域和三个或更多个抗原结合位点。优选的二聚化结构域包含Fc区或铰链区。在这种情形下,抗体将包含Fc区和Fc区的氨基末端的三个或更多个抗原结合位点。本文优选的多价抗体含有3个至约8个、但优选4个抗原结合位点。多价抗体含有至少一条多肽链(且优选两条多肽链),其中一条或多条多肽链包含两个或更多个可变结构域。例如,所述一条或多条多肽链可包含VD1-(X1)n-VD2-(X2)n-Fc,其中VD1是第一可变结构域,VD2是第二可变结构域,Fc是Fc区的一条多肽链,X1和X2表示氨基酸或多肽,并且n是0或1。类似地,一条或多条多肽链可包含V_H-C_H1-柔性接头-V_H-C_H1-Fc区链;或V_H-C_H1-V_H-C_H1-Fc区链。本文的多价抗体优选地进一步包含至少两个(且优选四个)轻链可变结构域多肽。本文的多价抗体可(例如)包含约两个至约八个轻链可变结构域多肽。在此考虑的轻链可变结构域多肽包含轻链可变结构域,并且任选地进一步包含CL结构域。多价抗体可识别Siglec-7抗原以及但不限于另外的抗原Aβ肽、抗原或α突触核蛋白(alpha synuclain)蛋白抗原或Tau蛋白抗原或TDP-43蛋白抗原或朊病毒蛋白抗原或亨廷顿蛋白或RAN、翻译产物抗原,包括由甘氨酸-丙氨酸(GA)、甘氨酸-脯氨酸(GP)、甘氨酸-精氨酸(GR)、脯氨酸-丙氨酸(PA)或脯氨酸-精氨酸(PR)构成的二肽重复序列(DPR肽),胰岛素受体、胰岛素样生长因子受体、转铁蛋白受体或促进跨血脑屏障的抗体转移的任何其它抗原。

[0344] (8)异缀合物抗体

[0345] 异缀合物抗体也在本公开的范围内。异缀合物抗体由两种共价连接的抗体(例如，本公开的抗Siglec-7抗体或其抗体片段)组成。举例来说，异缀合物中的一个抗体可偶联至抗生物素蛋白，另一个抗体可偶联至生物素。此类抗体已经(例如)被提出使免疫系统细胞靶向至非期望的细胞(美国专利号4,676,980)并且已经用于治疗HIV感染。国际公布号WO 91/00360、WO 92/200373和EP 0308936。考虑可使用合成蛋白质化学中的已知方法(包括涉及交联剂的那些)在体外制备所述抗体。例如，可使用二硫化物交换反应或通过形成硫醚键来构建免疫毒素。用于此目的的合适试剂的实例包括亚氨基硫醇酯和甲基-4-巯基丁酰亚胺酸酯以及例如在美国专利号4,676,980中公开的那些。异缀合物抗体可使用任何便利的交联方法来制成。合适交联剂在本领域中是熟知的，并且与许多交联技术一起在美国专利号4,676,980中公开。

[0346] (9)效应子功能工程化

[0347] 修饰本公开的抗Siglec-7抗体以改变效应子功能和/或增加抗体的血清半衰期也可以是合乎需要的。例如，恒定区上的Fc受体结合位点可被修饰或突变以除去或降低对某些Fc受体如FcγRI、FcγRII和/或FcγRIII的结合亲和力。在一些实施方案中，通过除去抗体的Fc区的N-糖基化(例如，在IgG的CH 2结构域中)，效应子功能受损。在一些实施方案中，通过修饰人IgG的诸如233-236、297和/或327-331的区域来使效应子功能受损，如PCT WO 99/58572和Armour等人，Molecular Immunology 40:585-593(2003)；Reddy等人，J.Immunology 164:1925-1933(2000)中所描述。

[0348] 为了增加抗体的血清半衰期，可例如将补救受体结合表位掺入到抗体(尤其是抗体片段)中，如在美国专利号5,739,277中所描述的。如本文所用，术语“补救受体结合表位”是指引起IgG分子的体内血清半衰期的增加的IgG分子(例如，IgG_1、IgG_2、IgG_3或IgG_4)的Fc区的表位。

[0349] (10)其它氨基酸序列修饰

[0350] 还考虑了本公开的抗Siglec-7抗体或其抗体片段的氨基酸序列修饰。例如，可能需要改善抗体或抗体片段的结合亲和力和/或其它生物性质。抗体或抗体片段的氨基酸序列变体可通过将适当核苷酸变化引入编码抗体或抗体片段的核酸中或通过肽合成来制备。此类修饰包括例如抗体的氨基酸序列内的残基的缺失和/或插入和/或取代。只要最终构建体具有所需特征(即与本公开的Siglec-7蛋白结合或物理相互作用的能力)，则进行缺失、插入和取代的任何组合以达到最终构建体。氨基酸变化也可改变抗体的翻译后过程，如改变糖基化位点的数目或位置。

[0351] 一种可用于鉴定抗Siglec-7抗体中为优选诱变位置的某些残基或区域的方法称作“丙氨酸扫描诱变”，如由Cunningham和Wells在Science，244:1081-1085(1989)中所描述。在此，鉴定残基或靶残基的组(例如，带电荷的残基诸如arg、asp、his、lys和glu)，并用中性或带负电荷的氨基酸(最优选丙氨酸或聚丙氨酸)置换以影响氨基酸与靶抗原的相互作用。然后，对于取代显示功能敏感度的那些氨基酸位置通过在(或针对)取代位点引入另外的或其它变体而被改善(refined)。因此，尽管用于引入氨基酸序列变异的位点被预先确定，但本身突变的性质不需要预先确定。例如，为了分析给定位点处突变的表现，在靶密码子或区域进行丙氨酸扫描或随机诱变，并筛选所表达的抗体变体的所需活性。

[0352] 氨基酸序列插入包括长度在一个残基至含有一百个或更多个残基的多肽的范围

内的氨基(“N”)和/或羧基(“C”)末端融合,以及具有单个或多个氨基酸残基的序列内插入。末端插入的实例包括具有N末端甲硫氨酰基残基的抗体或融合至细胞毒性多肽的抗体。抗体分子的其它插入变体包括抗体的N端或C端与增加抗体的血清半衰期的酶或多肽的融合。

[0353] 另一种类型的变体是氨基酸取代变体。这些变体在抗体分子中有至少一个氨基酸残基被不同的残基取代。取代诱变最感兴趣的位点包括高变区,但也考虑了FR改变。保守性取代展示于以下表E中的标题“优选取代”下。如果此类取代产生生物活性的改变,则可引入在表E中命名为“示例性取代”的、或如下进一步参考氨基酸类别所述的更多实质性改变,并且筛选产物。

[0354] 表E:氨基酸取代

[0355]

原始残基	示例性取代	优选的取代
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; asp, lys; arg	gln
Asp (D)	glu; asn	glu
Cys (C)	ser; ala	ser
Gln (Q)	asn; glu	asn
Glu (E)	asp; gln	asp
Gly (G)	ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; 正亮氨酸	leu
Leu (L)	正亮氨酸; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	tyr
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	Ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; 正亮氨酸	leu

[0356] 抗体的生物性质的实质性修饰通过选择取代来实现,所述取代对维持(a)取代区域中的多肽主链的结构,例如呈薄片或螺旋构象;(b)分子在靶位点处的电荷或疏水性;或(c)侧链体积的影响显著不同。基于共同的侧链性质将天然存在的残基分组:

[0357] (1)疏水性:正亮氨酸、met、ala、val、leu、ile;

[0358] (2)中性亲水性:cys、ser、thr;

[0359] (3)酸性:asp、glu;

[0360] (4)碱性:asn、gln、his、lys、arg;

[0361] (5)影响链取向的残基:gly、pro;以及

[0362] (6)芳族:trp、tyr、phe。

[0363] 非保守性取代需要将这些类别中的一类的成员更换成另一类别。

[0364] 不参与维持抗体的适当构象的任何半胱氨酸残基还可被(通常用丝氨酸)取代以便改进分子的氧化稳定性并且防止异常交联。相反,可将半胱氨酸键添加至抗体以改进它的稳定性(特别是在抗体是如Fv片段的抗体片段的情况下)。

[0365] 一种特别优选类型的取代变体涉及取代亲本抗体(例如,人源化或人抗Siglec-7抗体)的一个或多个高变区残基。一般而言,选择用于进一步发育的所得变体相对于产生它们的亲本抗体将具有改善的生物学性质。用于产生此类替代变体的便利方式涉及使用噬菌体展示的亲和力成熟。简言之,若干高变区位点(例如,6-7个位点)被突变以在每个位点产生所有可能的氨基酸取代。如此产生的抗体变体以单价方式从丝状噬菌体颗粒展示,作为与每个颗粒内包装的M13的基因III产物的融合物。然后,如本文所公开,针对噬菌体展示变体的生物活性(例如,结合亲和力)来筛选它们。为了鉴定用于修饰的候选高变区位点,可进行丙氨酸扫描诱变以鉴定对抗原结合有显著贡献的高变区残基。或者或另外,分析抗原-抗体复合物的晶体结构以鉴定抗体与抗原(例如,本公开的Siglec-7蛋白)之间的接触点可能是有益的。根据本文阐述的技术,此类接触残基和相邻残基是用于取代的候选物。一旦产生了此类变体,就如本文所述对一组变体进行筛选,并且可选择在一种或多种相关测定中具有优异性质的抗体用于进一步发育。

[0366] 抗体的另一种类型的氨基酸变体改变抗体的原始糖基化模式。改变是指缺失抗体中发现的一个或多个碳水化合物部分,和/或添加不存在于抗体中的一个或多个糖基化位点。

[0367] 抗体的糖基化通常是N-连接的或O-连接的。N-连接是指碳水化合物部分连接于天冬酰胺残基的侧链。其中X是除脯氨酸之外的任何氨基酸的三肽序列天冬酰胺-X-丝氨酸和天冬酰胺-X-苏氨酸是碳水化合物部分酶促连接于天冬酰胺侧链的识别序列。因此,在多肽中的这些三肽序列中的任何一个的存在产生潜在糖基化位点。O-连接的糖基化是指糖N-乙酰半乳糖胺、半乳糖或木糖之一与羟氨基酸连接,最常见的是丝氨酸或苏氨酸,不过也可以使用5-羟基脯氨酸或5-羟基赖氨酸。

[0368] 糖化位点至抗体的添加宜通过改变氨基酸序列以使得其含有上述三肽序列中的一个或多个来实现(对于经N连接的糖化位点)。改变也可通过对原始蛋白的序列的一个或多个丝氨酸或苏氨酸残基的添加或取代来造成(对于O-连接的糖基化位点)。

[0369] 编码抗IgE抗体的氨基酸序列变体的核酸分子通过本领域中已知的多种方法来制备。这些方法包括但不限于从天然来源分离(在天然存在的氨基酸序列变体的情况下)或通过抗体(例如本公开的抗Siglec-7抗体)或抗体片段的先前制备的变体或非变体型式的寡核苷酸介导(或定点)诱变、PCR诱变和盒式诱变制备。

[0370] (11)抗体缀合物

[0371] 本公开的抗Siglec-7抗体或其抗体片段可与可检测标记、毒素或治疗剂缀合。可使用本领域中已知用于将分子如可检测标记、毒素或治疗剂缀合至抗体的任何合适的方

法。

[0372] 例如,药物缀合涉及将生物活性细胞毒性(抗癌剂)有效负载或药物偶联至特异性地靶向某种肿瘤标志物(例如,理想地,仅在肿瘤细胞之中或之上发现的蛋白质)的抗体。抗体在体内追踪这些蛋白质并将其自身附接到癌细胞表面。抗体与靶蛋白(抗原)之间的生物化学反应在肿瘤细胞中触发信号,其然后与细胞毒素一起吸收或内化抗体。在ADC被内化后,细胞毒性药物被释放并杀死癌症。由于这种靶向作用,理想情况下所述药物具有较低的副作用,并且比其它化学治疗药物给出更宽的治疗窗口。所公开的用于缀合抗体的技术是本领域中已知的(参见例如,Jane de Lartigue,OncLive2012年7月5日;ADC Review on antibody-drug conjugates;和Ducry等人,(2010).Bioconjugate Chemistry21(1):5-13)。

[0373] 在一些实施方案中,本公开的抗Siglec-7抗体可缀合至选自以下的毒素:蓖麻毒素、蓖麻毒素A链、多柔比星、道诺霉素、类美登素、紫杉醇、溴化乙锭、丝裂霉素、依托泊苷、替尼泊苷、长春新碱、长春花碱、秋水仙碱、二羟基炭疽菌素二酮、放线菌素、白喉毒素、假单胞菌外毒素(PE)A、PE40、相思豆毒素、相思豆毒素A链、蒴莲根毒素A链、α-八叠球菌素、白树毒素、丝林霉素(mitogellin)、局限曲菌素(retstrictocin)、酚霉素、伊诺霉素、麻疯树逆境蛋白、巴豆毒素、加利车霉素、肥皂草抑制剂、糖皮质激素、奥瑞斯他汀、金霉素(auromycin)、钇、铋、康普瑞汀(combrestatin)、倍癌霉素(duocarmycins)、多拉司他汀、cc1065以及顺铂。

[0374] (12)其它抗体修饰

[0375] 本公开的抗Siglec-7抗体或其抗体片段可进一步修饰以含有本领域中已知且容易获得的另外的非蛋白质部分。优选地,适合衍生化抗体的部分是水溶性聚合物。水溶性聚合物的非限制性实例包括但不限于聚乙二醇(PEG)、乙二醇/丙二醇共聚物、羧甲基纤维素、右旋糖酐、聚乙烯醇、聚乙烯吡咯烷酮、聚-1,3-二氧戊环、聚-1,3,6-三噁烷、乙烯/马来酸酐共聚物、聚氨基酸(均聚物或无规共聚物)、和右旋糖酐或聚(n-乙烯吡咯烷酮)聚乙二醇、聚丙二醇均聚物、聚环氧丙烷/环氧乙烷共聚物、聚氧乙烯化多元醇(例如甘油)、聚乙烯醇及其混合物。聚乙二醇丙醛由于其在水中的稳定性可具有制造优势。所述聚合物可具有任何分子量,并且可为分支或未分支的。连接到抗体的聚合物的数目可变化,并且如果连接多于一个聚合物,那么其可为相同或不同分子。一般来说,用于衍生化的聚合物的数目和/或类型可基于包括但不限于有待改善的抗体的特定性质或功能、抗体衍生物是否将在限定定条件下用于疗法中等考虑因素加以确定。此类技术和其它合适的制剂公开于Remington:The Science and Practice of Pharmacy,第20版,Alfonso Gennaro,编,Philadelphia College of Pharmacy and Science(2000)。

[0376] 结合测定和其它测定

[0377] 可例如通过已知的方法如ELISA、表面等离子体共振(SPR)、蛋白质印迹等来测试本公开的抗Siglec-7抗体的抗原结合活性。

[0378] 在一些实施方案中,竞争测定可用于鉴定与表2A、2B、3A、3B、6A和6B中列出或选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体中的任一种竞争的抗体。在某些实施方案中,这种竞争抗体结合至由表2A、2B、3A、3B、6A和6B中列出或选自1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、

4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8的抗体中的任一种结合的相同表位(例如,线性或构象表位)。用于作图抗体所结合的表位的详细示例性方法提供于Morris(1996)“Epitope Mapping Protocols,”于Methods in Molecular Biology第66卷(Humana Press,Totowa,NJ)中。

[0379] 在示例性竞争测定中,将固定的Siglec-7或细胞表面上表达Siglec-7的细胞在包含结合至Siglec-7的第一标记抗体(例如人或非人灵长类动物)和第二未标记抗体的溶液中孵育,所述第二未标记抗体正在针对其与所述第一抗体竞争结合至Siglec-7的能力进行测试。第二抗体可存在于杂交瘤上清液中。作为对照,将固定的Siglec-7或表达Siglec-7的细胞在包含第一标记抗体而不含第二未标记抗体的溶液中孵育。在容许第一抗体与Siglec-7结合的条件下孵育之后,移除过量未结合的抗体,并且测量与固定的Siglec-7或表达Siglec-7的细胞缔合的标记的量。如果相对于对照样品,与固定的Siglec-7或表达Siglec-7的细胞缔合的标记的量在测试样品中基本上降低,则然后指示第二抗体与第一抗体竞争结合至Siglec-7。参见Harlow和Lane(1988)Antibodies:A Laboratory Manual第14章(Cold Spring Harbor Laboratory,Cold Spring Harbor,NY)。

[0380] 核酸、载体和宿主细胞

[0381] 可使用例如如美国专利号4,816,567中所描述的重组方法和组合物来产生本公开的抗Siglec-7抗体。在一些实施方案中,提供了具有编码本公开的任何抗Siglec-7抗体的核苷酸序列的分离的核酸。此类核酸可编码含有抗Siglec-7抗体的VL的氨基酸序列和/或含有抗Siglec-7抗体的VH的氨基酸序列(例如所述抗体的轻链和/或重链)。在一些实施方案中,提供一种或多种含有此类核酸的载体(例如表达载体)。在一些实施方案中,还提供一种含有这种核酸的宿主细胞。在一些实施方案中,宿主细胞含有(例如已用以下转导):(1)含有编码含有抗体的VL的氨基酸序列和含有抗体的VH的氨基酸序列的核酸的载体,或(2)含有编码含有抗体的VL的氨基酸序列的核酸的第一载体和含有编码含有抗体的VH的氨基酸序列的核酸的第二载体。在一些实施方案中,宿主细胞是真核的,例如中国仓鼠卵巢(CHO)细胞或淋巴样细胞(例如,Y0、NS0、Sp20细胞)。

[0382] 提供了制备本公开的抗Siglec-7抗体的方法。在一些实施方案中,所述方法包括在适合表达抗体的条件下培养含有编码抗Siglec-7抗体的核酸的本公开的宿主细胞。在一些实施方案中,随后从宿主细胞(或宿主细胞培养基)回收抗体。

[0383] 为了重组产生本公开的抗Siglec-7抗体,分离编码抗Siglec-7抗体的核酸并将所述核酸插入到一个或多个载体中以进一步在宿主细胞中克隆和/或表达。此类核酸可易于使用常规程序(例如通过使用能够特异性结合至编码抗体的重链和轻链的基因的寡核苷酸探针)进行分离和测序。

[0384] 本文所述的含有编码本公开的任何抗Siglec-7抗体的核酸序列或其片段多肽(包括抗体)的合适载体包括但不限于克隆载体和表达载体。合适的克隆载体可根据标准技术构建,或者可选自本领域中可用的大量克隆载体。尽管选择的克隆载体可根据预期使用的宿主细胞而变化,但有用的克隆载体通常具有自我复制的能力,可具有针对特定限制性内切核酸酶的单一靶标,和/或可携带可用于选择含有载体的克隆的标记的基因。合适的实例包括质粒和细菌病毒,例如,pUC18、pUC19、Bluescript(例如,pBS SK+)及其衍生物、mp18、mp19、pBR322、pMB9、ColE1、pCR1、RP4、噬菌体DNA以及穿梭载体如pSA3和pAT28。这些和许多

其它克隆载体可从商业供应商如BioRad、Strategene和Invitrogen获得。

[0385] 表达载体通常是含有本公开的核酸的可复制多核苷酸构建体。所述表达载体通常可在宿主细胞中作为游离基因或染色体DNA的整体部分复制。合适的表达载体包括但不限于PCT公布号WO 87/04462中公开的质粒、病毒载体，包括腺病毒、腺相关病毒、逆转录病毒、粘粒和表达载体。载体组分通常可包括但不限于以下中的一种或多种：信号序列；复制起点；一种或多种标记基因；合适的转录控制元件(如启动子、增强子和终止子)。为了表达(即翻译)，通常还需要一种或多种翻译控制元件，如核糖体结合位点、翻译起始位点和终止密码子。

[0386] 含有目标核酸的载体可通过多种适当方式中的任一种引入宿主细胞，所述方式包括电穿孔；使用氯化钙、氯化铷、磷酸钙、DEAE-葡聚糖或其它物质转染；微粒轰击；脂质体转染；以及感染(例如，在载体是传染因子如牛痘病毒的情况下)。引入载体或多核苷酸的选择通常将取决于宿主细胞的特征。在一些实施方案中，所述载体含有核酸，所述核酸含有编码本公开的抗Siglec-7抗体的一条或多条氨基酸序列。

[0387] 用于克隆或表达抗体编码载体的合适宿主细胞包括原核或真核细胞。例如，本公开的抗Siglec-7抗体可在细菌中产生，特别是当不需要糖基化和Fc效应子功能时。关于在细菌中表达抗体片段和多肽(例如，美国专利号5,648,237、5,789,199和5,840,523；以及Charlton，Methods in Molecular Biology，第248卷(B.K.C.Lo，编，Humana Press，Totowa，NJ，2003)，第245-254页，其描述在大肠杆菌中表达抗体片段)。在表达之后，抗体可从细菌细胞糊状物分离于可溶性部分中并且可进一步纯化。

[0388] 除原核生物之外，诸如丝状真菌或酵母的真核微生物也为适于抗体编码性载体的克隆或表达宿主，包括糖基化路径已被“人源化”，从而产生具有部分或完全人糖基化型态的抗体的真菌和酵母菌株(例如，Gerngross，Nat.Biotech.22:1409-1414(2004)；以及Li等人，Nat.Biotech.24:210-215(2006))。

[0389] 用于表达糖基化抗体的合适宿主细胞还可来源于多细胞生物体(无脊椎动物和脊椎动物)。无脊椎动物细胞的实例包括植物和昆虫细胞。已鉴别众多可连同昆虫细胞一起使用的杆状病毒株，尤其是用于转染草地夜蛾(Spodoptera frugiperda)细胞。植物细胞培养物也可用作宿主(例如，美国专利号5,959,177、6,040,498、6,420,548、7,125,978和6,417,429，其描述用于在转基因植物中产生抗体的PLANTIBODIES™技术)。

[0390] 脊椎动物细胞也可用作宿主。例如，可使用适于悬浮生长的哺乳动物细胞系。有用的哺乳动物宿主细胞系的其它实例是由SV40转化的猴肾CV1细胞系(COS-7)；人胚肾系(如例如Graham等人，J.Gen Virol.36:59(1977)中所述的293或293细胞)；幼仓鼠肾细胞(BHK)；小鼠塞尔托利细胞(sertoli cells)(如例如Mather，Biol.Reprod.23:243-251(1980)中所述的TM4细胞)；猴肾细胞(CV1)；非洲绿猴肾细胞(VERO-76)；人宫颈癌细胞(HELA)；犬肾细胞(MDCK；水牛大鼠肝细胞(BRL 3A)；人肺细胞(W138)；人肝细胞(Hep G2)；小鼠乳腺肿瘤(MMT 060562)；如例如Mather等人，Annals N.Y.Acad.Sci.383:44-68(1982)中所述的TRI细胞；MRC 5细胞；以及FS4细胞。其它有用的哺乳动物宿主细胞系包括中国仓鼠卵巢(CHO)细胞，包括DHFR-CHO细胞(Urlaub等人，Proc.Natl.Acad.Sci.USA 77:4216(1980))；以及骨髓瘤细胞系，如Y0、NS0及Sp2/0。对于适于抗体产生的某些哺乳动物宿主细胞系的综述，参见例如Yazaki和Wu，Methods in Molecular Biology，第248卷(B.K.C.Lo

编,Humana Press,Totowa,NJ),第255-268页(2003)。

[0391] Siglec-7活性

[0392] PI3K活化

[0393] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在与细胞中表达的Siglec-7蛋白结合后诱导PI3K活化。

[0394] PI3K是能够磷酸化磷脂酰肌醇(PtdIns)的肌醇环的3位羟基的相关细胞内信号转导激酶家族。基于一级结构、调控和体外脂质底物特异性,PI3K家族被分为三种不同的类别(I类、II类和III类)。

[0395] 活化的PI3K产生各种3-磷酸化磷酸肌醇,包括但不限于PtdIns3P、PtdIns(3,4)P2、PtdIns(3,5)P2以及PtdIns(3,4,5)P3。这些3-磷酸化磷酸肌醇的以将信号传导蛋白募集到各种细胞膜上的机制起作用。这些信号传导蛋白含有磷酸肌醇结合结构域,包括但不限于PX结构域、普列克底物蛋白(pleckstrin)同源结构域(PH结构域)和FYVE结构域。可使用本领域中已知用于确定PI3K活化的任何方法。

[0396] 在一些实施方案中,本公开的Siglec-7药剂,如本公开的抗Siglec-7抗体有益于预防与PI3K活性的水平降低相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病,所述病况和/或疾病包括但不限于:痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0397] 调节的细胞因子表达

[0398] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在结合至细胞表面上表达的Siglec-7蛋白之后调节(例如增加或减少)脑中的促炎性介质。在某些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)在结合至细胞中表达的Siglec-7蛋白后调节细胞因子(例如促炎性介质)的表达和/或减少抗炎介质的表达。

[0399] 炎症是血管组织对诸如病原体、受损细胞或刺激物的有害刺激的复杂生物反应的一部分。急性炎症的典型症状是疼痛、发热、发红和肿胀。炎症是通过限制损伤部位或通过募集和活化免疫系统的细胞清除感染来保护生物体的免疫应答。炎症应答受到严密调控并

在其持续时间和严重程度方面限制以避免对生物体造成损害。炎症可分为急性或慢性炎症。急性炎症是由先天性免疫应答驱动的，所述先天性免疫应答最初识别有害刺激物并将来自血液的白细胞募集到损伤组织中。一连串生物化学事件(包括细胞因子和趋化因子释放)传送炎性应答，涉及局部血管系统、免疫系统和损伤组织内的各种细胞。慢性炎症延长并持续，其导致参与炎症应答的免疫细胞类型逐渐改变。作为炎症过程的结果，慢性炎症的特征在于组织的进行性破坏和纤维化。

[0400] 如本文所用，抗炎介质是直接或间接(例如通过抗炎信号传导途径)参与降低、抑制或灭活炎症应答的机制的蛋白质。可使用本领域中已知用于鉴定和表征抗炎介质的任何方法。抗炎介质的实例包括但不限于细胞因子，如IL-4、IL-10、IL-13、IL-35、IL-16、IFN-α、TGF-β、IL-1Ra、G-CSF以及TNF、IFN-β1a、IFN-β1b或IL-6的可溶性受体。促炎性介质的实例包括但不限于细胞因子，如IFN-a4、IFN-β、IL-1β、IL-1α、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-23、CXCL10、IL-33、MCP-1以及MIP-1-β。

[0401] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可调节(例如增加或减少)细胞因子如IL-1b、IL-8和TNF-a的表达。在某些实施方案中，调节的细胞因子表达发生在巨噬细胞、嗜中性粒细胞、天然杀伤(NK)细胞、树突细胞、单核细胞、破骨细胞、皮肤朗格汉斯细胞(Langerhans cells of skin)、库普弗细胞(Kupffer cells)、T细胞和/或小神经胶质细胞中。调节的表达可包括但不限于基因表达的增加、转录表达的增加或蛋白质表达的增加。可使用本领域中已知用于确定基因、转录物(例如，mRNA)和/或蛋白质表达的任何方法。例如，RNA印迹分析可用于确定细胞因子基因表达水平，RT-PCR可用于测定细胞因子转录的水平，并且蛋白质印迹分析可用于确定细胞因子蛋白水平。

[0402] 如本文所用，如果细胞因子在用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)治疗的受试者的一种或多种细胞中的表达与未用Siglec-7药剂治疗的相应受试者的一种或多种细胞中表达的相同细胞因子的表达相比得到调节，则所述细胞因子可具有调节的表达。在一些实施方案中，例如与未用Siglec-7药剂治疗的相应受试者的一种或多种细胞中的细胞因子表达相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可将受试者的一种或多种细胞中的细胞因子表达调节至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与未用Siglec-7药剂治疗的相应受试者的一种或多种细胞中的细胞因子表达相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)将受试者的一种或多种细胞中的细胞因子表达调节至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0403] 在一些实施方案中，本公开的Siglec-7药剂，如本公开的抗Siglec-7抗体适用于

预防与一种或多种促炎性介质的异常水平相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0404] 调节的促炎性介质表达

[0405] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在结合至细胞中表达的Siglec-7蛋白后调节(例如增加或减少)促炎性介质的表达。

[0406] 如本文所用，促炎性介质是直接或间接(例如通过促炎信号传导途径)参与诱导、活化、促进或以其它方式增加炎症应答的机制的蛋白质。可使用本领域中已知用于鉴定和表征促炎性介质的任何方法。

[0407] 促炎性介质的实例包括但不限于细胞因子，如I和II型干扰素、IFN-a4、IFN-β、IL-1β、IL-1α、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、IL-33、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、CRP、MCP-1以及MIP-1-β。

[0408] 在一些实施方案中，本公开的抗Siglec-7抗体可调节促炎性介质的功能性表达和/或分泌，所述促炎性介质如I型和II型干扰素、IFN-a、IFN-b、IL-1β、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、IL-33、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-23、CXCL10、CRP、MCP-1以及MIP-1-β。在某些实施方案中，调节的促炎性介质表达发生在巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、单核细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞、T细胞和/或小神经胶质细胞中。调节的表达可包括但不限于调节的基因表达、调节的转录表达或调节的蛋白质表达。可使用本领域中已知用于确定基因、转录物(例如，mRNA)和/或蛋白质表达的任何方法。例如，RNA印迹分析可用于确定促炎性介质基因表达水平，RT-PCR可用于测定促炎性介质转录的水平，并且蛋白质印迹分析可用于确定促炎性介质蛋白质水平。

[0409] 在某些实施方案中，促炎性介质包括炎性细胞因子。因此，在某些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可调节一种或多种炎性细胞因子的分泌。可通过本公开的抗Siglec-7抗体调节分泌的炎性细胞因子的实例包括但不限于如I型

和II型干扰素、IFN-a4、IFN-b、IL-1β、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、IL-33、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-23，CXCL10、MCP-1以及MIP-1-β。

[0410] 在某些实施方案中，促炎性介质包括炎性受体。因此，在某些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可调节一种或多种炎性受体的表达。表达可通过本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)调节的炎性受体的实例包括但不限于CD86、CD80、CD83。

[0411] 如本文所用，如果促炎性介质在用本公开的Siglec-7药剂(如本公开的激动剂抗Siglec-7抗体)治疗的受试者的一种或多种细胞中的表达与未用所述激动剂抗Siglec-7抗体处理的相应受试者的一种或多种细胞中表达的相同促炎性介质的表达相比得到调节(增加或减少)，则所述促炎性介质可具有调节的表达。在一些实施方案中，例如与未用抗Siglec-7抗体处理的相应受试者的一种或多种细胞中的促炎性介质表达相比，本公开的抗Siglec-7抗体可将受试者的一种或多种细胞中的促炎性介质表达调节至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与未用抗Siglec-7抗体处理的相应受试者的一种或多种细胞中的促炎性介质表达相比，所述抗Siglec-7抗体可将受试者的一种或多种细胞中的促炎性介质表达调节至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0412] 在一些实施方案中，本公开的一些Siglec-7药剂，如本公开的抗Siglec-7抗体可适用于预防与一种或多种促炎性介质的异常水平相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、

感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0413] ERK磷酸化

[0414] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在与细胞中表达的Siglec-7蛋白结合后诱导细胞外信号调控激酶(ERK)磷酸化。

[0415] 细胞外信号调控激酶(ERK)是广泛表达的蛋白激酶细胞内信号传导激酶，所述激酶参与例如分化细胞中的减数分裂、有丝分裂和有丝分裂期后功能。各种刺激物(如生长因子、细胞因子、病毒感染、异三聚体G蛋白偶联受体的配体、转化剂和致癌物质)活化ERK途径。ERK的磷酸化导致其激酶活性的活化。

[0416] 在一些实施方案中，本公开的Siglec-7药剂，如本公开的抗Siglec-7抗体有益于预防与ERK磷酸化的水平降低相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0417] Syk磷酸化

[0418] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在与细胞中表达的Siglec-7蛋白结合后诱导脾酪氨酸激酶(Syk)磷酸化。

[0419] 脾酪氨酸激酶(Syk)是细胞内信号传导分子，其通过磷酸化若干底物而在Siglec-7下游起作用，由此促进形成导致细胞活化和炎症过程的信号传导复合物。

[0420] 在一些实施方案中，本公开的Siglec-7药剂，如本公开的抗Siglec-7抗体有益于预防与Syk磷酸化的水平降低相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏

伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0421] Siglec-7磷酸化

[0422] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在于细胞中表达的Siglec-7蛋白结合后通过Src家族酪氨酸激酶(如Src、Syk、Fyn、Fgr、Lck、Hck、Blk、Lyn和Frk)瞬时诱导Tyr-437和Tyr-460的Siglec-7磷酸化。

[0423] 在一些实施方案中,本公开的Siglec-7药剂,如本公开的抗Siglec-7抗体有益于预防与Siglec-7磷酸化的水平降低相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病,所述病况和/或疾病包括但不限于:痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0424] 含有ITAM基序的受体的磷酸化

[0425] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在与细胞中表达的Siglec-7蛋白结合后诱导磷酸化含ITAM基序的受体,如TREM1、TREM2、Sirpβ、FcgR、DAP10和DAP12。

[0426] 在一些实施方案中,本公开的Siglec-7药剂,如本公开的抗Siglec-7抗体有益于预防与含ITAM基序的受体的磷酸化的水平降低相关的病况和/或疾病、降低所述病况和/或

疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0427] 调节的C-C趋化因子受体7表达

[0428] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在与细胞中表达的Siglec-7蛋白结合后调节C-C趋化因子受体7(CCR7)的表达。调节(例如增加或减少)表达可包括但不限于基因表达的调节、转录表达的调节或蛋白质表达的调节。可使用本领域中已知用于确定基因、转录物(例如，mRNA)和/或蛋白质表达的任何方法。例如，RNA印迹分析可用于确定抗炎介质基因表达水平，RT-PCR可用于测定抗炎介质转录的水平，并且蛋白质印迹分析可用于确定抗炎介质蛋白质水平。

[0429] C-C趋化因子受体7(CCR7)是G蛋白偶联受体家族的成员。CCR7在各种淋巴组织中表达并可活化B细胞和T细胞。在一些实施方案中，CCR7可调节记忆T细胞向次级淋巴器官如淋巴结的迁移。在其它实施方案中，CCR7可刺激树突细胞成熟。CCR7是可结合趋化因子(C-C基序)配体CCL19/ELC和CCL21的受体蛋白。

[0430] 如本文所用，如果CCR7在用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)治疗的受试者的一种或多种细胞中的表达与未用Siglec-7药剂治疗的相应受试者的一种或多种细胞中表达的CCR7的表达相比得到调节(例如，增加或减少)，则CCR7可具有调节的表达。在一些实施方案中，例如与未用Siglec-7药剂治疗的相应受试者的一种或多种细胞中的CCR7表达相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可将受试者的一种或多种细胞中的CCR7表达调节至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与未用Siglec-7药剂治疗的相应受试者的一种或多种细胞中的CCR7表达相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)将受试者的一种或多种细胞中的CCR7表达调节至少1.5倍、至少1.6

倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0431] 在一些实施方案中，CCR7的表达增加在巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞和/或小神经胶质细胞中发生。CCR7的表达增加可诱导朝向表达趋化因子CCL19和CCL21的细胞的小神经胶质细胞趋化性。因此，在某些实施方案中，本公开的抗Siglec-7抗体可诱导朝向表达CCL19和CCL21的细胞的小神经胶质细胞趋化性。

[0432] 在一些实施方案中，本公开的Siglec-7药剂，如本公开的抗Siglec-7抗体适用于预防与CCR7的异常水平相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0433] 调节的免疫相关蛋白表达

[0434] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec7抗体)可在与细胞中表达的Siglec-7蛋白结合后调节PD-L1、PD-L2、B7-H3、CD11b、CD200R、CD163和/或CD206的表达。调节(例如增加或减少)表达可包括但不限于基因表达的调节、转录表达的调节或蛋白质表达的调节。可使用本领域中已知用于确定基因、转录物(例如，mRNA)和/或蛋白质表达的任何方法。例如，RNA印迹分析可用于确定抗炎介质基因表达水平，RT-PCR可用于测定抗炎介质转录的水平，并且蛋白质印迹分析可用于确定抗炎介质蛋白质水平。

[0435] 如本文所用，如果PD-L1、PD-L2、B7-H3、CD11b、CD200R、CD163和/或CD206在用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)治疗的受试者的一种或多种细胞中的表达与未用Siglec-7药剂治疗的相应受试者的一种或多种细胞中表达的PD-L1、PD-L2、B7-H3、CD11b、CD200R、CD163和/或CD206的表达相比得到调节(例如，增加或减少)，则PD-L1、PD-L2、B7-H3、CD11b、CD200R、CD163和/或CD206可具有调节的表达。在一些实施方案中，例如与未用Siglec-7药剂治疗的相应受试者的一种或多种细胞中的PD-L1、PD-L2、B7-H3、

CD11b、CD200R、CD163和/或CD206表达相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可将受试者的一种或多种细胞中的PD-L1、PD-L2、B7-H3、CD11b、CD200R、CD163和/或CD206表达调节至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与未用Siglec-7药剂治疗的相应受试者的一种或多种细胞中的PD-L1、PD-L2、B7-H3、CD11b、CD200R、CD163和/或CD206表达相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)将受试者的一种或多种细胞中的PD-L1、PD-L2、B7-H3、CD11b、CD200R、CD163和/或CD206表达调节至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0436] 在一些实施方案中，本公开的Siglec-7药剂，如本公开的抗Siglec-7抗体适用于预防与PD-L1、PD-L2、B7-H2、B7-H3、CD11b、CD200R、CD163和/或CD206的异常水平相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0437] 骨髓源性树突细胞诱导抗原特异性T细胞增殖的能力的增强或正常化

[0438] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在与细胞中表达的Siglec-7蛋白结合后增强和/或正常化骨髓源性树突细胞诱导抗原特异性T细胞增殖的能力。

[0439] 在一些实施方案中，例如与未用Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)处理的相应受试者的一种或多种骨髓源性树突细胞中骨髓源性树突细胞诱导抗原特异

性T细胞增殖的能力相比，所述药剂可使骨髓源性树突细胞诱导抗原特异性T细胞增殖的能力增强和/或正常化至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与未用Siglec-7药剂治疗的相应受试者的一种或多种骨髓源性树突细胞中骨髓源性树突细胞诱导抗原特异性T细胞增殖的能力相比，所述Siglec-7药剂(如拮抗剂抗Siglec-7抗体)可使受试者的一种或多种骨髓源性树突细胞中骨髓源性树突细胞诱导抗原特异性T细胞增殖的能力增强和/或正常化至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0440] 在一些实施方案中，本公开的Siglec-7药剂，如本公开的抗Siglec-7抗体有益于预防与骨髓源性树突细胞诱导抗原特异性T细胞增殖的能力降低或失调相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0441] 破骨细胞产生

[0442] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在结合至细胞中表达的Siglec-7蛋白后诱导破骨细胞产生和/或增加破骨细胞生成速率。

[0443] 如本文所用，破骨细胞是一种类型的骨细胞，所述骨细胞可通过移除其矿化基质并破坏有机骨(例如骨吸收)来移除骨组织。破骨细胞可通过骨髓系的细胞的融合而形成。在一些实施方案中，破骨细胞的特征可在于抗酒石酸酸性磷酸酶(TRAP)和组织蛋白酶K的

高表达。

[0444] 如本文所用,如果用本公开的Siglec-7药剂(如拮抗剂抗Siglec-7抗体)处理的受试者中破骨细胞生成的速率大于未用Siglec-7药剂治疗的相应受试者的破骨细胞生成速率,则破骨细胞生成速率可被提高。在一些实施方案中,例如与未用Siglec-7药剂治疗的相应受试者中的破骨细胞生成速率相比,本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)可使受试者中的破骨细胞生成速率提高至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少55%、至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少100%、至少110%、至少115%、至少120%、至少125%、至少130%、至少135%、至少140%、至少145%、至少150%、至少160%、至少170%、至少180%、至少190%或至少200%。在其它实施方案中,例如与未用Siglec-7药剂治疗的相应受试者中的破骨细胞生成速率相比,本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)可使受试者中的破骨细胞生成速率提高至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0445] 如本文所用,如果用本公开的Siglec-7药剂(如激动剂抗Siglec-7抗体)处理的受试者中的破骨细胞生成速率小于在未用Siglec-7药剂治疗的相应受试者中的破骨细胞生成速率,则破骨细胞生成速率可被降低。在一些实施方案中,例如与未用Siglec-7药剂治疗的相应受试者中的破骨细胞生成速率相比,本公开的Siglec-7药剂(如本公开的激动剂抗Siglec-7抗体)可使受试者中的破骨细胞生成速率降低至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少55%、至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少100%、至少110%、至少115%、至少120%、至少125%、至少130%、至少135%、至少140%、至少145%、至少150%、至少160%、至少170%、至少180%、至少190%或至少200%。在其它实施方案中,例如与未用Siglec-7药剂治疗的相应受试者中的破骨细胞生成速率相比,本公开的Siglec-7药剂(如本公开的激动剂抗Siglec-7抗体)可使受试者中的破骨细胞生成速率降低至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0446] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)有益于预防与异常骨形成和维持相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病,所述病况或疾病包括与骨密度的病理性降低相关的骨质疏松症和与骨密度的病理性增加相关的骨质疏松性疾病。

[0447] Siglec-7表达细胞的增殖和存活

[0448] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在与

细胞上表达的Siglec-7蛋白结合后增加树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞、T细胞和/或小神经胶质细胞的增殖、存活和/或功能。

[0449] 如本文所用，本公开的巨噬细胞包括但不限于M1巨噬细胞、活化的M1巨噬细胞和M2巨噬细胞。如本文所用，本公开的嗜中性粒细胞包括但不限于M1嗜中性粒细胞、活化的M1嗜中性粒细胞和M2嗜中性粒细胞。如本文所用，本公开的天然杀伤(NK)细胞包括但不限于M1 NK细胞、活化的M1 NK细胞和M2 NK细胞。如本文所用，本公开的小神经胶质细胞包括但不限于M1小神经胶质细胞、活化的M1小神经胶质细胞和M2小神经胶质细胞。

[0450] 小神经胶质细胞是一种类型的神经胶质细胞，其是脑和脊髓的驻留巨噬细胞并因此充当中枢神经系统(CNS)中主动免疫防御的第一和主要形式。小神经胶质细胞构成脑内总胶质细胞群体的20％。小神经胶质细胞不断清除CNS的斑块、受损神经元和传染因子。脑和脊髓被认为是“免疫赦免”器官，因为它们通过一系列被称为血脑屏障的内皮细胞与身体其它部位分开，所述血脑屏障阻止大多数病原体到达易感神经组织。在传染因子直接引入脑或跨过血脑屏障的情况下，小神经胶质细胞必须迅速反应以限制炎症并在传染因子损伤敏感神经组织之前破坏传染因子。由于体内其它部位没有抗体(少数抗体足够小至跨过血脑屏障)，小神经胶质细胞必须能够识别异物、吞咽它们并充当活化T细胞的抗原呈递细胞。由于此过程必须迅速完成以防止潜在的致命损伤，所以小神经胶质细胞对CNS中的甚至小的病理变化也极其敏感。它们实现这种敏感性的部分原因是具有独特的钾通道，所述钾通道对细胞外钾的即使较小变化也做出反应。

[0451] 在一些实施方案中，本公开的抗Siglec-7抗体可增加树突细胞、单核细胞、巨噬细胞、嗜中性粒细胞、NK细胞和/或小神经胶质细胞上的CD80、CD83和/或CD86的表达。

[0452] 如本文所用，如果用Siglec-7药剂(如本公开的抗Siglec-7抗体)治疗的受试者中树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、单核细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖率、存活率和/或功能大于未用Siglec-7药剂治疗的相应受试者中树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、单核细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞、T细胞和/或小神经胶质细胞的增殖率、存活率和/或功能，则巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、单核细胞、T细胞和/或小神经胶质细胞的增殖率、存活率和/或功能可包括增加的表达。在一些实施方案中，例如与未用Siglec-7药剂治疗的相应受试者中树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、单核细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞、T细胞和/或小神经胶质细胞的增殖率、存活率和/或功能相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使受试者中的树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、单核细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞、T细胞和/或小神经胶质细胞的增殖率、存活率和/或功能提高至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与未用Siglec-7药剂治疗的相应受试者中树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、单核细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞、T细胞和/或小神经胶质细胞的增殖率、存活

率和/或功能相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使受试者中的树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、单核细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞、T细胞和/或小神经胶质细胞的增殖率、存活率和/或功能提高至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0453] 在一些实施方案中，本公开的Siglec-7药剂，如本公开的抗Siglec-7抗体有益于预防与树突细胞、嗜中性粒细胞、巨噬细胞、嗜中性粒细胞、NK细胞、单核细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞、T细胞和/或小神经胶质细胞的增殖、存活、凋亡增加和/或功能的降低相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0454] 清除和吞噬

[0455] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在与以下中的一种或多种的细胞中表达的Siglec-7蛋白质结合后诱导清除和/或吞噬：凋亡神经元、神经系统的神经组织碎片、功能障碍性突触、神经系统的非神经组织碎片、细菌、其它异物、致病蛋白、致病肽、致病核酸或肿瘤细胞。在某些实施方案中，致病蛋白包括但不限于淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列

(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽。在某些实施方案中,致病核酸包括但不限于反义GGCCCC(G2C4)重复序列-扩增RNA。

[0456] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可诱导一种或多种类型的清除,包括但不限于凋亡神经元清除、神经组织碎片清除、功能障碍性突触清除、非神经组织碎片清除、细菌或其它异物清除、致病蛋白清除、致病肽清除、致病核酸清除以及肿瘤细胞清除。

[0457] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可诱导以下中的一种或多种的吞噬:凋亡神经元、神经组织碎片、功能障碍性突触、非神经组织碎片、细菌、其它异物、致病蛋白、致病肽、致病核酸和/或肿瘤细胞。

[0458] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可在巨噬细胞集落刺激因子(M-CSF)水平降低的条件下增加嗜中性粒细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、单核细胞和/或小神经胶质细胞的吞噬。

[0459] 在一些实施方案中,本公开的Siglec-7药剂,如本公开的抗Siglec-7抗体有益于预防与凋亡神经元、神经系统的神经组织碎片、神经系统的非神经组织碎片、细菌、其它异物、致病蛋白相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病,所述病况和/或疾病包括但不限于:痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0460] Siglec-7依赖性基因表达

[0461] 在一些实施方案中,本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)可降低Siglec-7依赖性基因的活性和/或表达,并且通过其增加与活化免疫系统的信号级联相关的基因表达,如与含有ITAM的受体、模式识别受体、Toll样受体、损伤相关分子模式(DAMP)受体如转录因子的活化T细胞核因子(NFAT)家族的一种或多种转录因子的相关的基因表达。

[0462] 在一些实施方案中,本公开的Siglec-7药剂,如本公开的拮抗剂抗Siglec-7抗体

有益于预防与Siglec-7依赖性基因的高水平相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述病况和/或疾病包括但不限于：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和流感嗜血杆菌。

[0463] T细胞的Siglec-7依赖性活化

[0464] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)可增加细胞毒性T细胞、辅助T细胞或两者的活性。在一些实施方案中，本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)有益于预防与细胞毒性T细胞、辅助T细胞或两者的活性降低相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述疾病和/或病况包括但不限于肿瘤，包括实体肿瘤如膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌。

[0465] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)可诱导以下各项的增殖、存活、活性和/或数量的增加：T细胞、细胞毒性T细胞、$CD3^+$ T细胞(例如肿瘤浸润$CD3^+$ T细胞等)、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞。在一些实施方案中，本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)在骨髓源性抑制细胞(MDSC)的存在诱导以下各项的增殖、存活、活性和/或数目的增加：T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞。

[0466] 如本文所用，如果在用Siglec-7药剂(如本公开的抗Siglec-7抗体)治疗的受试者中T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖率、存活率、活性和/或数目大于未用Siglec-7药剂治疗的相应受试者中T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖率、存活率、活性和/或数目，则T细胞、细

胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖率、存活率、活性和/或数目可包括增加的比率。在一些实施方案中，例如与未用Siglec-7药剂治疗的相应受试者中T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖、存活、活性和/或数目的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使受试者中T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖、存活、活性和/或数目提高至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与未用Siglec-7药剂治疗的相应受试者中T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖、存活、活性和/或数目的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使受试者中T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖、存活、活性和/或数目提高至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0467] 在一些实施方案中，例如与在骨髓源性抑制细胞(MDSC)存在下未用Siglec-7药剂处理的T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖、存活、活性和/或数目的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使在骨髓源性抑制细胞(MDSC)存在下T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖、存活、活性和/或数目提高至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与在骨髓源性抑制细胞(MDSC)存在下未用Siglec-7药剂处理的T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖、存活、活性和/或数目的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使在骨髓源性抑制细胞(MDSC)存在下T细胞、细胞毒性T细胞、$CD3^+$ T细胞、辅助T细胞、树突细胞、巨噬细胞、单核细胞、嗜中性粒细

胞、破骨细胞、皮肤朗格汉斯细胞、库普弗细胞和/或小神经胶质细胞的增殖、存活、活性和/或数目提高至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0468] 嗜中性粒细胞的Siglec-7依赖性抑制

[0469] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的激动剂抗Siglec-7抗体)可降低嗜中性粒细胞的活性。在一些实施方案中，本公开的Siglec-7药剂(如本公开的激动剂抗Siglec-7抗体)有益于预防与天然杀伤细胞、嗜中性粒细胞或两者的活性的活性降低相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述疾病和/或病况包括但不限于肿瘤，包括实体肿瘤如膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌。

[0470] 天然杀伤(NK)细胞的Siglec-7依赖性增强的细胞杀伤

[0471] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)可提高NK细胞的杀伤活性。在一些实施方案中，本公开的Siglec-7药剂(如本公开的节抗性抗Siglec-7抗体)有益于预防与天然杀伤细胞、嗜中性粒细胞或两者的活性的活性降低相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况和/或疾病，所述疾病和/或病况包括但不限于肿瘤，包括实体肿瘤如膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌。

[0472] 肿瘤相关免疫细胞的Siglec-7依赖性抑制

[0473] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的激动剂抗Siglec-7抗体)可降低T调控性细胞或抑制性肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞或骨髓源性抑制细胞的活性、增殖、存活率、功能性，降低所述细胞至肿瘤或淋巴器官(例如脾和淋巴结)的浸润和/或促进所述细胞的细胞凋亡。在一些实施方案中，本公开的Siglec-7药剂(如本公开的激动剂抗Siglec-7抗体)有益于预防与一种或多种类型的免疫抑制细胞的活性相关的病况和/或疾病、降低所述病况和/或疾病的风险或治疗所述病况或疾病，包括但不限于肿瘤，包括不表达Siglec-7的实体肿瘤，如膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、甲状腺癌以及表达Siglec-7的血液肿瘤，如白血病细胞。

[0474] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)可减少$CD14^+$骨髓细胞的数目(例如，肿瘤浸润$CD14^+$骨髓细胞的数目、外周血$CD14^+$骨髓细胞的数目等)、降低肿瘤生长速率、减小肿瘤体积或减少或抑制骨髓源性抑制细胞(MDSC)的分化、存活和/或一种或多种功能。

[0475] 在一些实施方案中，例如与未用Siglec-7药剂治疗的相应受试者中$CD14^+$骨髓细胞的数目、肿瘤生长速率、肿瘤体积、骨髓源性抑制细胞(MDSC)的分化、存活和/或一种或多

种功能的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使受试者中$CD14^+$骨髓细胞的数目(例如，肿瘤浸润$CD14^+$骨髓细胞的数目、外周血$CD14^+$骨髓细胞的数目等)降低、肿瘤生长速率降低、肿瘤体积减小或骨髓源性抑制细胞(MDSC)的分化、存活和/或一种或多种功能降低或抑制至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与未用Siglec-7药剂治疗的相应受试者中$CD14^+$骨髓细胞的数目、肿瘤生长速率、肿瘤体积、骨髓源性抑制细胞(MDSC)的分化、存活和/或一种或多种功能的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使受试者中$CD14^+$骨髓细胞的数目(例如，肿瘤浸润$CD14^+$骨髓细胞的数目、外周血$CD14^+$骨髓细胞的数目等)降低、肿瘤生长速率降低、肿瘤体积减小或骨髓源性抑制细胞(MDSC)的分化、存活和/或一种或多种功能降低或抑制至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0476] 检查点抑制剂疗法的功效增加

[0477] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)可提高一种或多种检查点抑制剂疗法和/或免疫调节疗法的功效，所述疗法如靶向CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3和/或LAG3中的一种或多种的PD-1抑制剂或疗法。

[0478] 在一些实施方案中，例如与未用Siglec-7药剂治疗的接受一种或多种检查点抑制剂疗法和/或免疫调节疗法，如靶向CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3和/或LAG3中的一种或多种的PD-1抑制剂或疗法的相应受试者中此类一种或多种疗法的有效性的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使接受一种或多种检查点抑制剂疗法和/或免疫调节疗法，如靶向CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3和/或LAG3中的一种或多种的PD-1抑制剂或疗法的受试者中此类一种或多种疗法的功效提高至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在其它实施方案中，例如与未用Siglec-7药剂治疗的接受一种或多种检查点抑制剂疗法和/或免疫调节疗法，如靶向CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3和/或LAG3中的一种或多种的PD-1抑制剂或疗法的相应受试者中此类一种或多种疗法的有效性的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使接受一种或多种检查点抑制剂疗法和/或免疫调节疗法，如靶向CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3和/或LAG3中的一种或多种的PD-1抑制剂或疗法的受试者中此类一种或多种疗法的功效提高至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少

2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0479] 化疗药物的功效增加

[0480] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)可增加一种或多种化学治疗剂的功效，所述化学治疗剂如吉西他滨、卡培他滨、蒽环类药物、多柔比星(Adriamycin®)、表柔比星(Ellence®)、紫杉烷、紫杉醇(Taxol®)、多西他赛(Taxotere®)、5-氟尿嘧啶(5-FU)、环磷酰胺(Cytoxan®)和/或卡铂(Paraplatin®)。

[0481] 在一些实施方案中，例如与未用Siglec-7药剂治疗的接受此类一种或多种疗法的相应受试者中一种或多种化学治疗剂的有效性的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使接受此类一种或多种疗法的受试者中一种或多种化学治疗剂的功效提高至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少160％、至少170％、至少180％、至少190％或至少200％。在一些实施方案中，例如与未用Siglec-7药剂治疗的接受此类一种或多种疗法的相应受试者中一种或多种化学治疗剂的有效性的水平相比，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可使接受此类一种或多种疗法的受试者中一种或多种化学治疗剂的功效提高至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍。

[0482] 药物组合物

[0483] 本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可通过将诸如抗Siglec-7抗体的药剂与适当药学上可接受的载体或稀释剂组合而并入用于治疗性施用的各种制剂中，并且可被配制成固体、半固体、液体或气体形式的制剂。此类制剂的实例包括但不限于片剂、胶囊剂、粉剂、颗粒剂、软膏剂、溶液、栓剂、注射剂、吸入剂、凝胶剂、微球以及气雾剂。药物组合物可包括(取决于所需的制剂)药学上可接受的、非毒性稀释剂载体，所述稀释剂载体是常见用来配制用于动物或人施用的药物组合物的媒介物。选择所述稀释剂以免影响组合的生物活性。此类稀释剂的实例包括但不限于蒸馏水、缓冲水、生理盐水、PBS、林格氏溶液(Ringer's solution)、右旋糖溶液和汉克氏溶液(Hank's solution)。本公开的药物组合物或制剂还可包含其它载体、佐剂或非毒性非治疗性非免疫原性稳定剂、赋形剂等。所述组合物还可包含接近生理条件的另外物质，例如pH调节和缓冲剂、毒性调节剂、润湿剂和洗涤剂。

[0484] 本公开的药物组合物还可例如包含诸如氧化剂的多种稳定剂中的任一种。当所述药物组合物包含多肽时，所述多肽可与多种熟知的化合物复合，所述化合物增强多肽的体内稳定性或另外增强其药理学性质(例如，增加多肽的半衰期、降低其毒性并增强溶解或吸

收)。此类修饰或复合剂的实例包括但不限于硫酸盐、葡糖酸盐、柠檬酸盐和磷酸盐。组合物的多肽也可与增强其体内属性的分子复合。此类分子包括但不限于碳水化合物、多元胺、氨基酸、其它肽、离子(例如,钠、钾、钙、镁、锰)和脂质。

[0485] 适用于多种施用类型的制剂的另外实例可见于Remington's Pharmaceutical Sciences,Mace Publishing Company,Philadelphia,PA,第17版(1985)中。对于药物递送方法的简评,参见Langer,Science 249:1527-1533(1990)。

[0486] 对于口服施用,所述活性成分可以固体剂型(如胶囊剂、片剂和粉剂)施用或液体剂型(酏剂、糖浆剂和混悬剂)施用。可将活性组分与非活性成分和粉状载体一起封装在明胶胶囊中,所述粉状载体如葡萄糖、乳糖、蔗糖、甘露糖醇、淀粉、纤维素或纤维素衍生物、硬脂酸镁、硬脂酸、糖精钠、滑石、碳酸镁。可添加以提供所需的颜色、味道、稳定性、缓冲能力、分散或其它已知所需的特征的另外非活性成分的实例是氧化铁红、硅胶、月桂基硫酸钠、二氧化钛以及可食用白色墨水。类似的稀释剂可用于制造压缩片剂。片剂和胶囊剂都可制成持续释放产品,以在数小时内提供药物的连续释放。压缩片剂可以是糖衣或薄膜包衣以掩蔽任何令人不愉快的味道并保护片剂不受大气的影响,或肠溶包衣以在胃肠道中选择性崩解。用于口服施用的液体剂型可含有着色剂和调味剂以增加患者的接受性。

[0487] 用于胃肠外施用的制剂包括水性和非水性等张无菌注射溶液,其可含有抗氧化剂、缓冲剂、抑菌剂和致使制剂与预定接受者的血液等张的溶质;及水性和非水性无菌混悬液,其可包括悬浮剂、增溶剂、增稠剂、稳定剂以及防腐剂。

[0488] 用来配制药物组合物的组分优选地具有高纯度并且基本上不含潜在有害的污染物(例如,至少国家食品(NF)级、通常至少分析级并且更通常至少药物级)。此外,意图用于体内使用的组合物通常为无菌的。为了达到在使用之前必须合成给定的化合物的程度,所得到的产物通常基本上不含任何潜在的毒性剂、具体为任何内毒素,所述毒性剂可在合成或纯化过程期间存在。用于胃肠外施用的组合物也为无菌的,基本上等渗的并且在GMP条件下制得。

[0489] 为了在脑或中枢神经系统中保留和稳定化,可优化制剂。当药剂被施用到颅隔室中时,希望药剂保留在隔室中,并且不扩散或以其它方式跨过血脑屏障。稳定技术包括交联、多聚化或连接至诸如聚乙二醇、聚丙烯酰胺、中性蛋白质载体等的基团以便实现分子量的增加。

[0490] 用于增加保留的其它策略包括在生物可降解或生物可侵蚀植入物中包埋本公开的药剂,如本公开的抗Siglec-7抗体。治疗活性剂的释放速率由穿过聚合物基质的运输速率和植入物的生物降解来控制。药物通过聚合物屏障的运输还将受到化合物溶解度、聚合物亲水性、聚合物交联程度、聚合物在吸水时的膨胀以便使聚合物屏障更易透过药物、植入物的几何形状等影响。所述植入物具有与被选作植入部位的区域的大小和形状相称的尺寸。植入物可以是颗粒、片、贴片、斑块、纤维、微胶囊等,并且可具有与所选择的插入部位相容的任何大小或形状。

[0491] 所述植入物可为整体的,即活性剂均匀地分布于整个聚合物基质中或包封,其中活性剂的储库由聚合物基质包封。待使用的聚合物组合物的选择将随施用部位、所需的治疗时间段、患者耐受性、待治疗的疾病的性质等而变化。聚合物的特性将包括在植入部位的生物降解性、与目标药剂的相容性、易于包封、在生理环境中的半衰期。

[0492] 可使用的生物可降解聚合物组合物可以是有机酯或醚,其在降解时产生生理上可接受的降解产物,包括单体。酸酐、酰胺、原酸酯等本身或与其它单体组合可使用。聚合物将是缩聚物。聚合物可以是交联的或非交联的。另外特别关注羟基脂肪族羧酸聚合物(呈均聚物或共聚物)及多糖。关注的聚酯包括D-乳酸、L-乳酸、外消旋乳酸、乙醇酸、聚己内酯及其组合的聚合物。通过使用L-乳酸酯或D-乳酸酯获得缓慢生物降解的聚合物,而使用外消旋物时降解基本上增强。特别关注乙醇酸和乳酸的共聚物,其中通过乙醇酸与乳酸的比率控制生物降解速率。最快降解的共聚物具有大致相等量的乙醇酸和乳酸,其中均聚物更耐降解。乙醇酸与乳酸的比率也将影响植入物的脆弱性,其中对于较大的几何形状,更柔性的植入物是合乎需要的。目标多糖是海藻酸钙和官能化纤维素,尤其是特征为不溶于水、分子量为约5kD至500kD的羧甲基纤维素酯等。生物可降解水凝胶也可用于本公开的植入物中。水凝胶通常是一种共聚物材料,其特征在于吸收液体的能力。可使用的示例性生物可降解水凝胶在以下文献中进行了描述:Heller in:Hydrogels in Medicine and Pharmacy,N.A.Peppes编,第III卷,CRC Press,Boca Raton,Fla.,1987,第137-149页。

[0493] 药物剂量

[0494] 含有本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)的本公开的药物组合物可根据已知的方法如作为团注静脉内施用或通过在一段时间内连续输注、通过肌内、腹膜内、脑脊髓内、颅内、脊柱内、皮下、关节内、滑膜内、鞘内、口服、局部或吸入途径施用至需要用Siglec-7药剂治疗的个体(优选人)。

[0495] 本公开的药物组合物的剂量和所需药物浓度可根据预期的特定用途而变化。确定合适的施用剂量或途径完全在普通技术人员的技能范围内。动物实验为确定人疗法的有效剂量提供了可靠的指导。有效剂量的物种间缩放可按照以下文献中描述的原则进行:Mordenti,J.和Chappell,W.“The Use of Interspecies Scaling in Toxicokinetics,”In Toxicokinetics and New Drug Development,Yacobi等人,编,Pergamon Press,New York 1989,第42-46页。

[0496] 为了体内施用本公开的任何Siglec-7药剂(如本公开的任何抗Siglec-7抗体),正常剂量的量可取决于施用途径,从每天约10ng/kg至约100mg/kg的个体体重或更多、优选约1mg/kg/天至10mg/kg/天变化。为在若干天或更长时间内重复施用,根据待治疗的疾病、病症或病况的严重程度,可持续治疗直至实现所需症状抑制。

[0497] 示例性给药方案可包括施用约2mg/kg的本公开的Siglec-7药剂(如抗Siglec-7抗体)的初始剂量,随后每隔一周施用约1mg/kg的每周维持剂量。取决于医师所希望达到的药物动力学衰减的型态而定,其它剂量方案也可能适用。例如,本文预期一周向个体给予一次至二十一次。在某些实施方案中,可使用约3μg/kg至约2mg/kg(如约3μg/kg、约10μg/kg、约30μg/kg、约100μg/kg、约300μg/kg、约1mg/kg以及约2/mg/kg)范围内的给药。在某些实施方案中,给药频率是每天三次、每天两次、每天一次、每隔一天一次、每周一次、每两周一次、每四周一次、每五周一次、每六周一次、每七周一次、每八周一次、每九周一次、每十周一次或每月一次、每两个月一次、每三个月或更长一次。所述疗法的进展易于通过常规技术和测定进行监测。包括Siglec-7药剂(如所施用的抗Siglec-7抗体)的给药方案可独立于所使用的剂量随时间而变化。

[0498] 用于特定Siglec-7药剂(如特定抗Siglec-7抗体)的剂量可在已经给予一次或多

次施用Siglec-7药剂(如抗Siglec-7抗体)的个体中凭经验确定。向个体给予递增剂量的Siglec-7药剂,如抗Siglec-7抗体。为了评估Siglec-7药剂(如抗Siglec-7抗体)的功效,可监测本公开的任何疾病、病症或病况(例如,额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、癫痫发作、视网膜营养不良、创伤性脑损伤、脊髓损伤、长期抑郁症、动脉粥样硬化性血管疾病和正常老化的不良症状)的临床症状。

[0499] 根据例如接受者的生理状况、施用目的是治疗性的还是预防性的和熟练从业人员已知的其它因素,本公开的Siglec-7药剂(如抗Siglec-7抗体)的施用可以是连续的或间断的。Siglec-7药剂(如抗Siglec-7抗体)的施用可在预先选择的时间段内基本上连续或可以是一系列间隔的剂量。

[0500] 在文献中提供了关于特定剂量和递送方法的指导;参见例如美国专利号4,657,760;5,206,344;或5,225,212。在本公开的范围内的是不同的制剂对于不同的治疗和不同的病症将是有效的,并且意图治疗特定器官或组织的施用可能需要以不同于另一器官或组织的方式递送。而且,剂量可通过一次或多次分开的施用或通过连续输注施用。对于历经若干天或更长时间的重复施用,取决于情况,治疗持续直到出现所需疾病症状抑制。然而,可使用其它剂量方案。此疗法的进展易于通过常规技术和测定进行监测。

[0501] 治疗用途

[0502] 本公开的其它方面提供调节(例如,活化或抑制)有需要的个体中的一种或多种Siglec-7活性的方法,所述活性包括但不限于调节(例如,活化或抑制)本公开的Siglec-7蛋白;抵消Src家族酪氨酸激酶如Syk、LCK、FYM和/或ZAP70对Tyr-437和Tyr-460的一种或多种磷酸化;募集并结合至酪氨酸特异性蛋白磷酸酶SHP1和SHP2;募集并结合至PLC-γ1,其充当发动蛋白-1的鸟嘌呤核苷酸交换因子;募集并结合至含SH2结构域的蛋白质(例如Crk1);募集并结合至脾酪氨酸激酶Syk;募集并结合至SH3-SH2-SH3生长因子受体结合蛋白2(Grb2);募集并结合至多种含SH2的蛋白质;调节(例如,活化或抑制)一种或多种促炎性细胞因子的表达,任选地其中所述一种或多种抗炎细胞因子选自IFN-a4、IFN-β、IL-1β、IL-1α、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-33、MCP-1以及MIP-1-β;调节(例如,活化或抑制)一种或多种细胞中的一种或多种促炎性细胞因子的表达,所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞;调节(例如,活化或抑制)一种或多种抗炎细胞因子的表达,任选地其中所述一种或多种抗炎细胞因子选自IL-4、IL-10、IL-13、IL-35、IL-16、TGF-β、IL-1Ra、G-CSF以及TNF、IFN-β1a、IFN-β1b或IL-6的可溶性受体;调节(例如,活化或抑制)一种或多种细胞中的一种或多种抗炎细胞因子的表达,所述一种或多种细胞选自巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞以及小神经胶质细胞;调节(例如,活化或抑制)一种或多种选自以下的蛋白质的表达:C1qa、C1qB、C1qC、C1s、C1R、C4、C2、C3、ITGB2、HMOX1、LAT2、CASP1、CSTA、VSIG4、MS4A4A、C3AR1、GPX1、TyroBP、ALOX5AP、ITGAM、SLC7A7、CD4、ITGAX、以及PYCARD;活化细胞外信号调控激酶(ERK)磷酸化;调节(例如,活化或抑制)一种或多种细胞蛋白上的酪氨酸磷酸化,任选地,其中所述一种或多种细胞蛋白包含ZAP-70并且所述酪氨酸磷酸化发生在ZAP-70的Tyr-319上;调节(例如,活化或抑制)C-C趋化因子受体7(CCR7)的

表达;活化针对表达CCL19的细胞和表达CCL21的细胞的小神经胶质细胞趋化性;调节(例如,活化或抑制)由一种或多种细胞诱导的T细胞增殖,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞、M2小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞以及M2 NK细胞;调节(例如,活化或抑制)破骨细胞产生,调节(例如,活化或抑制)破骨细胞生成速率或两者;调节(例如,活化或抑制)一种或多种细胞的存活,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;调节(例如,活化或抑制)一种或多种细胞的增殖,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;调节(例如,活化或抑制)一种或多种细胞的迁移,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;调节(例如,活化或抑制)一种或多种细胞的一种或多种功能,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;调节(例如,活化或抑制)一种或多种细胞的成熟,所述一种或多种细胞选自树突细胞、骨髓源性树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、M1巨噬细胞、M1嗜中性粒细胞、M1 NK细胞、活化的M1巨噬细胞、活化的M1嗜中性粒细胞、活化的M1 NK细胞、M2巨噬细胞、M2嗜中性粒细胞、M2 NK细胞、单核细胞、破骨细胞、T细胞、T辅助细胞、细胞毒性T细胞、粒细胞、嗜中性粒细胞、小神经胶质细胞、M1小神经胶质细胞、活化的M1小神经胶质细胞以及M2小神经胶质细胞;活化一种或多种类型的清除,所述清除选自凋亡神经元清除、神经组织碎片清除、功能障碍性突触清除、非神经组织碎片清除、细菌清除、其它异物清除、致病蛋白清除、致病肽清除、致病核酸清除以及肿瘤细胞清除;任选地,其中所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、

胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽，并且所述肿瘤细胞来自癌症，所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌；活化以下中的一种或多种的吞噬：凋亡神经元、神经组织碎片、功能障碍性突触、非神经组织碎片、细菌、其它异物、致病蛋白、致病肽、致病核酸或肿瘤细胞；任选地其中所述致病核酸是反义GGCCCC(G2C4)重复序列-扩增RNA，所述致病蛋白选自淀粉样蛋白β、寡聚淀粉样蛋白β、淀粉样蛋白β斑块、淀粉样蛋白前体蛋白或其片段、Tau、IAPP、α-突触核蛋白、TDP-43、FUS蛋白、C9orf72(染色体9开放阅读框72)、c9RAN蛋白、朊病毒蛋白、PrPSc、亨廷顿蛋白、降钙素、超氧化物歧化酶、共济失调蛋白、共济失调蛋白1、共济失调蛋白2、共济失调蛋白3、共济失调蛋白7、共济失调蛋白8、共济失调蛋白10、路易体、心房利钠因子、胰岛淀粉样蛋白多肽、胰岛素、载脂蛋白AI、血清淀粉样蛋白A、中介素、催乳素、甲状腺素运载蛋白、溶菌酶、β2微球蛋白、凝溶胶蛋白、角膜上皮蛋白、半胱氨酸蛋白酶抑制剂、免疫球蛋白轻链AL、S-IBM蛋白、重复序列相关非ATG(RAN)翻译产物、二肽重复序列(DPR)肽、甘氨酸-丙氨酸(GA)重复序列肽、甘氨酸-脯氨酸(GP)重复序列肽、甘氨酸-精氨酸(GR)重复序列肽、脯氨酸-丙氨酸(PA)重复序列肽、泛素以及脯氨酸-精氨酸(PR)重复序列肽，并且所述肿瘤细胞来自癌症，所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤或甲状腺癌；抑制与肿瘤细胞上的Siglec-7配体结合；调节(例如，活化或抑制)与细胞上的Siglec-7配体结合，所述细胞选自嗜中性粒细胞、树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞、巨噬细胞以及NK细胞；通过以下中的一种或多种活化肿瘤细胞杀伤：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；活化以下中的一种或多种的抗肿瘤细胞增殖活性：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；活化以下中的一种或多种的抗肿瘤细胞转移活性：小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；调节(例如，活化或抑制)一种或多种含ITAM基序的受体，任选地其中所述一种或多种含ITAM基序的受体选自TREM1、TREM2、Sirpβ、FcgR、DAP10以及DAP12；调节(例如，活化或抑制)一种或多种模式识别受体(PRR)的信号传导，任选地其中所述一种或多种PRR选自鉴定病原体相关分子模式(PAMP)的受体、鉴定损伤相关分子模式(DAMP)的受体以及其任何组合；调节(例如，活化或抑制)包含基序D/Ex_{0-2}YxxL/IX_{6-8}YxxL/I(SEQ ID NO:537)的一种或多种受体；调节(例如，活化或抑制)一种或多种Toll样受体的信号传导；调节(例如，活化或抑制)JAK-STAT信号传导途径；调节(例如，活化或抑制)活化的B细胞的核因子κ-轻链增强子(NFκB)；含有ITAM基序的受体的磷酸化；调节(例如，活化或抑制)一种或多种炎性受体的表达，任选地其中所述一种或多种炎性受体包含CD86并且所述一种或多种炎性受体在以下中的一种或多种上表达：小神经胶质细

胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、骨髓源性树突状细胞、嗜中性粒细胞、T细胞、T辅助细胞或细胞毒性T细胞；调节(例如，活化或抑制)一种或多种Siglec-7依赖性基因的表达；破坏的Siglec-7依赖性基因表达的正常化；调节(例如，活化或抑制)一种或多种ITAM依赖性基因的表达，任选地其中所述一种或多种ITAM依赖性基因通过活化T细胞(NFAT)转录因子的核因子活化；挽救以下中的一种或多种的功能性：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；和/或减少以下中的一种或多种浸润到肿瘤中：免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞以及调控性T细胞；增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量；增强骨髓源性抑制细胞的肿瘤促进活性；增加肿瘤或外周血液中肿瘤促进细胞因子的表达，任选地其中所述肿瘤促进细胞因子是TGF-β或IL-10；增加肿瘤促进FoxP3+调控性T淋巴细胞的肿瘤浸润；增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性；减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化；减少具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润；降低NK细胞的肿瘤杀伤潜力；减少具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润；减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润；增加肿瘤体积；增加肿瘤生长速率；增加转移；增加肿瘤复发率；降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或一种或多种癌症疫苗的功效，任选地其中所述一种或多种免疫疗法是靶向一种或多种靶蛋白的免疫疗法，所述一种或多种靶蛋白选自PD1/PDL1、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5、TREM1、TREM2、CSF-1受体以及其任何组合；抑制PLCã/PKC/钙动员；和/或抑制PI3K/Akt、Ras/MAPK信号传导，所述方法通过向所述个体施用治疗有效量的本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)来调节(例如，活化或抑制)所述个体中的一种或多种Siglec-7活性。

[0503] 如本文所公开，本公开的降低Siglec-7的细胞水平和/或抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的Siglec-7药剂(如本公开的抗Siglec-7抗体)可用于预防以下疾病、降低所述疾病的风险或治疗所述疾病：痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特

发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和/或流感嗜血杆菌。在一些实施方案中,所述药剂选自抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、结合一种或多种Siglec-7配体的可溶性Siglec受体、Siglec-Fc融合蛋白、Siglec免疫粘附素、反义分子、siRNA、小分子抑制剂、蛋白质以及肽。在一些实施方案中,所述Siglec-7药剂是激动剂抗体。在一些实施方案中,所述Siglec-7药剂是惰性抗体。在一些实施方案中,所述Siglec-7药剂是拮抗剂抗体。

[0504] 在一些实施方案中,本公开提供预防以下疾病、降低所述疾病的风险或治疗所述疾病的方法:痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病和癌症、膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和/或流感嗜血杆菌,所述方法通过向有需要的个体施用治疗有效量的本公开的药剂,所述药剂降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者。在一些实施方案中,所述药剂选自抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、结合一种或多种Siglec-7配体的可溶性Siglec受体、Siglec-Fc融合蛋白、Siglec免疫粘附素、反义分子、siRNA、小分子抑制剂、蛋白质以及肽。在一些实施方案中,所述药剂是本公开的抗Siglec-7抗体。

[0505] 在一些实施方案中,本公开提供通过向有需要的个体施用治疗有效量的本公开的降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者的药剂来预防癌症、降低癌症的风险或治疗癌症。在一些实施方案中,所述药剂选自抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、结合一种或多种Siglec-7配体的可溶性Siglec受体、Siglec-Fc融合蛋白、Siglec免疫粘附素、反义分子、siRNA、小分子抑制剂、蛋白质以及肽。在一些实施方案中,所述药剂是本公开的抗Siglec-7抗体。在一些实施方案中,所述癌症表达Siglec-7或一种或多种Siglec-7配体。在一些实施方案中,所述癌症是膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急

性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)和/或多发性骨髓瘤。在一些实施方案中,所述抗Siglec-7抗体抑制一种或多种选自以下的Siglec-7活性:(a)促进以下中的一种或多种的增殖、成熟、迁移、分化和/或功能性:免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关抑制嗜中性粒细胞、肿瘤相关抑制NK细胞以及调控性T细胞;(b)增强以下中的一种或多种浸润到肿瘤中:免疫抑制树突细胞、免疫抑制巨噬细胞、免疫抑制嗜中性粒细胞、免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关抑制嗜中性粒细胞、肿瘤相关抑制NK细胞以及调控性T细胞;(c)增加肿瘤、外周血或其它淋巴器官中肿瘤促进骨髓细胞/粒细胞免疫抑制细胞的数量;(d)增强骨髓源性抑制细胞(MDSC)的肿瘤促进活性;(e)增加肿瘤或外周血液中肿瘤促进细胞因子的表达,任选地其中所述肿瘤促进细胞因子是TGF-β或IL-10;(f)增加肿瘤促进FoxP3+调控性T淋巴细胞的肿瘤浸润;(g)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的活化;(h)减少具有肿瘤杀伤潜力的肿瘤特异性T淋巴细胞的浸润;(i)减少具有肿瘤杀伤潜力的肿瘤特异性NK细胞的浸润;(j)降低NK细胞的肿瘤杀伤潜力;(k)减少具有增强免疫应答的潜力的肿瘤特异性B淋巴细胞的浸润;(l)增加肿瘤体积;(m)增加肿瘤生长速率;(n)增加转移;(o)增加肿瘤复发率;(p)降低一种或多种调节抗肿瘤T细胞应答的免疫疗法或癌症疫苗的功效,如一种或多种免疫疗法是靶向一种或多种靶蛋白的免疫疗法,所述一种或多种靶蛋白选自PD1/PDL1、CTLA4、CD40、OX40、ICOS、CD28、CD137/4-1BB、CD27、GITR、PD-L1、CTLA4、PD-L2、PD-1、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG、DR-5以及其任何组合;(q)抑制PLCγ/PKC/钙动员;以及(r)抑制PI3K/Akt、Ras/MAPK信号传导。在一些实施方案中,所述药剂展示一种或多种选自以下的活性:(a)增加肿瘤浸润$CD3^+$ T细胞的数量;(b)抑制Siglec-7与一种或多种Siglec-7配体的结合;(c)降低外周免疫细胞中Siglec-7的细胞水平;(d)减少非致瘤性$CD14^+$骨髓细胞的数量,任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞,或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于血液中;(e)减少非致瘤性$CD14^+$骨髓细胞的数量,任选地其中所述非致瘤性$CD14^+$骨髓细胞是肿瘤浸润细胞,或任选地其中所述非致瘤性$CD14^+$骨髓细胞存在于肿瘤中;(f)降低一种或多种细胞中的PD-L1水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);(g)降低一种或多种细胞中的PD-L2水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);(h)降低一种或多种细胞中的CD11b水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);(i)降低一种或多种细胞中的B7-H3水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);(j)降低一种或多种细胞中的CD200R水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);(k)降低一种或多种细胞中的CD163水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);(l)降低一种或多种细胞中的CD206水平,任选地其中所述一种或多种细胞是非致瘤性骨髓源性抑制细胞(MDSC);(m)降低实体肿瘤的肿瘤生长速率;(n)减小肿瘤体积;(o)提高一种或多种PD-1抑制剂的功效;(p)提高一种或多种检查点抑制剂疗法和/或免疫调节疗法的功效,任选地其中所述一种或多种检查点抑制剂疗法和/或免疫调节疗法靶向以下中的一种或多种:CTL4、腺苷途径、PD-L1、PD-L2、OX40、TIM3、LAG3或其任何组合;(q)抑制非致瘤性骨髓源性抑制细胞的(MDSC)分化、存活和/或一种或多种功能;(r)诱导一

种或多种骨髓源性抑制细胞(MDSC)的细胞死亡;以及(s)在非致瘤性骨髓源性抑制细胞(MDSC)存在下增加T细胞的增殖。

[0506] 如本文所公开,本公开的药剂(如本公开的抗Siglec-7抗体)也可用于诱导和/或促进一种或多种免疫细胞(例如先天性免疫细胞或适应性免疫细胞)的存活成熟、功能性、迁移或增殖。在一些实施方案中,本公开提供诱导或促进有需要的个体中一种或多种免疫细胞的存活、成熟、功能性、迁移或增殖的方法,所述方法通过向所述个体施用治疗有效量的本公开的降低Siglec-7的细胞水平、抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用或两者的药剂。在一些实施方案中,所述药剂选自抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、结合一种或多种Siglec-7配体的可溶性Siglec受体、Siglec-Fc融合蛋白、Siglec免疫粘附素、反义分子、siRNA、小分子抑制剂、蛋白质以及肽。在一些实施方案中,所述药剂是本公开的分离的抗Siglec-7抗体。在一些实施方案中,所述一种或多种免疫细胞选自树突细胞、巨噬细胞、嗜中性粒细胞、NK细胞、小神经胶质细胞、T细胞、T辅助细胞、细胞毒性T细胞以及其任何组合。

[0507] 在一些实施方案中,所述药剂是激动剂抗Siglec-7抗体。在一些实施方案中,所述药剂是本公开的瞬时激动剂抗Siglec-7抗体,所述抗体最初充当激动剂且然后充当长期拮抗剂抗体。在一些实施方案中,所述药剂是惰性抗Siglec-7抗体。在一些实施方案中,所述药剂是拮抗剂抗Siglec-7抗体。在一些实施方案中,所述抗Siglec-7抗体降低Siglec-7的细胞(例如,细胞表面、细胞内或总)水平。在一些实施方案中,所述抗Siglec-7抗体诱导Siglec-7的降解。在一些实施方案中,所述抗Siglec-7抗体诱导Siglec-7的裂解。在一些实施方案中,所述抗Siglec-7抗体诱导Siglec-7的内化。在一些实施方案中,所述抗Siglec-7抗体诱导Siglec-7的脱落。在一些实施方案中,所述抗Siglec-7抗体诱导Siglec-7表达的下调。在一些实施方案中,所述抗Siglec-7抗体抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(例如,结合)。在一些实施方案中,所述抗Siglec-7抗体瞬时活化并然后诱导Siglec-7的降解。在一些实施方案中,所述抗Siglec-7抗体瞬时活化并然后诱导Siglec-7的裂解。在一些实施方案中,所述抗Siglec-7抗体瞬时活化并然后诱导Siglec-7的内化。在一些实施方案中,所述抗Siglec-7抗体瞬时活化并然后诱导Siglec-7的脱落。在一些实施方案中,所述抗Siglec-7抗体瞬时活化并然后诱导Siglec-7表达的下调。在一些实施方案中,所述抗Siglec-7抗体瞬时活化并然后诱导Siglec-7的表达降低。在某些实施方案中,个体具有Siglec-7变体等位基因。

[0508] 如本文所公开,本公开的与Siglec-7结合或相互作用的药剂(如本公开的抗Siglec-7抗体)可进一步用于降低以下各项的活性、功能性或存活:调控性T细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、肿瘤包埋的免疫抑制嗜中性粒细胞、肿瘤包埋的免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞、急性骨髓性白血病AML)细胞、慢性淋巴细胞性白血病(CLL)细胞和/或慢性骨髓性白血病(CML)细胞。在一些实施方案中,本公开提供通过向有需要的个体施用治疗有效量的与Siglec-7结合或相互作用的药剂来降低所述个体中以下各项的活性、功能性或存活的方法:调控性T细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、肿瘤包埋的免疫抑制嗜中性粒细胞、肿瘤包埋的免疫抑制NK细胞、骨髓源性抑制细胞、肿瘤相关巨噬细胞、肿瘤相关嗜中性粒细胞、肿瘤相关NK细胞、急性骨髓性白血病(AML)细

胞、慢性淋巴细胞性白血病(CLL)细胞或慢性骨髓性白血病(CML)细胞。在一些实施方案中，所述药剂选自抗体、拮抗剂抗体、惰性抗体、激动剂抗体、Siglec-7配体、Siglec-7配体激动剂片段、Siglec-7免疫粘附素、Siglec-7配体模拟物、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、结合一种或多种Siglec-7配体的可溶性Siglec受体、结合一种或多种Siglec-7配体的Siglec-Fc融合蛋白以及小分子化合物。在一些实施方案中，所述药剂是本公开的分离的抗Siglec-7抗体或抗Siglec-7抗体缀合物。在一些实施方案中，所述抗Siglec-7抗体缀合物包含缀合至可检测标记物、毒素或治疗剂的抗Siglec-7抗体。

[0509] 如本文所公开，本公开的与Siglec-7结合或相互作用的药剂(如本公开的抗Siglec-7抗体)可用于在体外或体内降低一种或多种细胞上Siglec-7的细胞水平，所述细胞包括但不限于红细胞、细菌细胞、凋亡细胞、神经细胞、神经胶质细胞、小神经胶质细胞、星形胶质细胞、肿瘤细胞、病毒、树突细胞、与β淀粉状蛋白斑块结合的Siglec-7配体、与Tau缠结结合的Siglec-7配体、致病蛋白上的Siglec-7配体、致病肽上的Siglec-7配体、巨噬细胞、嗜中性粒细胞、天然杀伤细胞、单核细胞、T细胞、T辅助细胞、细胞毒性T细胞、B细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、骨髓源性抑制细胞和/或调控性T细胞。在一些实施方案中，本公开提供通过向有需要的个体施用治疗有效量的与Siglec-7结合或相互作用的药剂来降低所述个体的一种或多种细胞上Siglec-7的细胞水平的方法。在一些实施方案中，所述药剂选自抗体、拮抗剂抗体、惰性抗体、激动剂抗体、Siglec-7配体、Siglec-7配体激动剂片段、Siglec-7免疫粘附素、Siglec-7配体模拟物、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、结合一种或多种Siglec-7配体的可溶性Siglec受体、结合一种或多种Siglec-7配体的Siglec-Fc融合蛋白以及小分子化合物。在一些实施方案中，所述药剂是本公开的分离的抗Siglec-7抗体或抗Siglec-7抗体缀合物。在一些实施方案中，所述抗Siglec-7抗体缀合物包含缀合至可检测标记物、毒素或治疗剂的抗Siglec-7抗体。在一些实施方案中，所述一种或多种细胞选自红细胞、细菌细胞、凋亡细胞、神经细胞、神经胶质细胞、小神经胶质细胞、星形胶质细胞、肿瘤细胞、病毒、树突细胞、与β淀粉状蛋白斑块结合的Siglec-7配体、与Tau缠结结合的Siglec-7配体、致病蛋白上的Siglec-7配体、致病肽上的Siglec-7配体、巨噬细胞、嗜中性粒细胞、天然杀伤细胞、单核细胞、T细胞、T辅助细胞、细胞毒性T细胞、B细胞、肿瘤包埋的免疫抑制树突细胞、肿瘤包埋的免疫抑制巨噬细胞、骨髓源性抑制细胞、调控性T细胞以及其任何组合。

[0510] Siglec-7的细胞水平可指但不限于Siglec-7的细胞表面水平、Siglec-7的细胞内水平和Siglec-7的总水平。在一些实施方案中，Siglec-7的细胞水平的降低包括Siglec-7的细胞表面水平的降低。如本文所用，如果抗Siglec-7抗体诱导Siglec-7的细胞表面水平降低21％或更多，如通过本文所述或本领域中已知的任何体外基于细胞的测定或合适的体内模型所测量，则所述抗Siglec-7抗体降低Siglec-7的细胞表面水平。在一些实施方案中，Siglec-7的细胞水平的降低包括Siglec-7的细胞内水平的降低。如本文所用，如果抗Siglec-7抗体诱导Siglec-7的细胞内水平降低21％或更多，如通过本文所述或本领域中已知的任何体外基于细胞的测定或合适的体内模型所测量，则所述抗Siglec-7抗体降低Siglec-7的细胞内水平。在一些实施方案中，Siglec-7的细胞水平的降低包括Siglec-7的总水平的降低。如本文所用，如果抗Siglec-7抗体诱导Siglec-7的总水平降低21％或更多，如通过本文所述或本领域中已知的任何体外基于细胞的测定或合适的体内模型所测量，则

所述抗Siglec-7抗体降低Siglec-7的总水平。在一些实施方案中，所述抗Siglec-7抗体诱导Siglec-7降解、Siglec-7裂解、Siglec-7内化、Siglec-7脱落和/或Siglec-7表达的下调。在一些实施方案中，利用体外细胞测定在原代细胞(例如树突细胞、骨髓源性树突细胞、单核细胞、小神经胶质细胞和巨噬细胞)上或细胞系上测量Siglec-7的细胞水平。在一些实施方案中，所述抗Siglec-7抗体以在500pM至18pM范围内的EC_{50}降低Siglec-7的细胞水平。在一些实施方案中，所述抗Siglec-7抗体以在350pM至33pM范围内的EC_{50}降低Siglec-7的细胞水平。在一些实施方案中，EC_{50}在大约37℃的温度下测定。在一些实施方案中，所述抗Siglec-7抗体对于人Siglec-7具有在约10nM至10pM或小于10pM范围内的解离常数(K_D)。在可与前述实施方案中的任一项组合的一些实施方案中，所述抗Siglec-7抗体对于人Siglec-7具有在约9.5nM至约17pM或小于17pM范围内的解离常数(K_D)。在一些实施方案中，解离常数(K_D)在大约25℃的温度下测定。在一些实施方案中，所述抗Siglec-7抗体以在2nM至100pM范围内的EC_{50}结合至人树突细胞。在一些实施方案中，所述抗Siglec-7抗体以在1.4nM至300pM范围内的EC_{50}结合至人树突细胞。在一些实施方案中，结合至人树突细胞的EC_{50}在大约4℃的温度下测定。

[0511] 在一些实施方案中，所述个体具有Siglec-7的杂合变体。

[0512] 在一些实施方案中，本公开的方法可进一步涉及Siglec-7药剂(如抗Siglec-7抗体或双特异性抗Siglec-7抗体)与结合模式识别受体的抗体、结合Toll样受体的抗体、与损伤相关分子模式(DAMP)受体结合的抗体和/或与细胞因子结合的抗体或针对白细胞介素的抗体)的共同施用。

[0513] 在一些实施方案中，本公开的方法还可包括向所述个体施用至少一种特异性地结合至抑制性检查点分子的抗体，和/或一种或多种标准或研究性抗癌疗法。在一些实施方案中，所述至少一种特异性地结合至抑制性检查点分子的抗体与所述抗Siglec-7抗体组合施用。在一些实施方案中，所述至少一种特异性地结合至抑制性检查点分子的抗体选自抗PD-L1抗体、抗CTLA4抗体、抗PD-L2抗体、抗PD-1抗体、抗B7-H3抗体、抗B7-H4抗体和抗HVEM抗体、抗B-和T-淋巴细胞衰减子(BTLA)抗体、抗杀伤抑制性受体(KIR)抗体、抗GAL9抗体、抗TIM3抗体、抗A2AR抗体、抗LAG-3抗体、抗磷脂酰丝氨酸抗体、抗CD27抗体、抗TNFa抗体、抗CD33抗体、抗Siglec-5抗体、抗Siglec-9抗体、抗Siglec-11抗体、拮抗性抗TREM1抗体、拮抗性抗TREM2抗体以及其任何组合。在一些实施方案中，所述一种或多种标准或研究性抗癌疗法选自放射疗法、细胞毒性化学疗法、靶向疗法、伊马替尼疗法、曲妥珠单抗疗法、依那西普疗法、过继细胞转移(ACT)疗法、嵌合抗原受体T细胞转移(CAR-T)疗法、疫苗疗法以及细胞因子疗法。

[0514] 在一些实施方案中，本公开的方法还可包括向所述个体施用至少一种特异性地结合至抑制性细胞因子的抗体。在一些实施方案中，所述至少一种特异性地结合至抑制性细胞因子的抗体与所述Siglec-7药剂，如抗Siglec-7抗体组合施用。在一些实施方案中，所述至少一种特异性地结合至抑制性细胞因子的抗体选自抗CCL2抗体、抗CSF-1抗体、抗IL-2抗体以及其任何组合。

[0515] 在一些实施方案中，本公开的方法还可包括向所述个体施用至少一种特异性地结合至刺激性检查点蛋白的激动性抗体。在一些实施方案中，所述至少一种特异性地结合至刺激性检查点蛋白的激动性抗体与所述Siglec-7药剂如抗Siglec-7抗体组合施用。在一些

实施方案中，所述至少一种特异性地结合至刺激性检查点蛋白的激动性抗体选自激动剂抗CD40抗体、激动剂抗OX40抗体、激动剂抗ICOS抗体、激动剂抗CD28抗体、激动性抗TREM1抗体、激动性抗TREM2抗体、激动剂抗CD137/4-1BB抗体、激动剂抗CD27抗体、激动剂抗糖皮质激素诱导的TNFR相关蛋白GITR抗体以及其任何组合。

[0516] 在一些实施方案中，本公开的方法还可包括向所述个体施用至少一种刺激性细胞因子。在一些实施方案中，所述至少一种刺激性细胞因子与所述Siglec-7药剂，如抗Siglec-7抗体组合施用。在一些实施方案中，所述至少一种刺激性细胞因子选自IFN-a4、IFN-b、IL-1β、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-23、CXCL10、IL-33、MCP-1、MIP-1-β以及其任何组合。

[0517] 痴呆

[0518] 痴呆是一种非特异性综合征(即一组体征和症状)，其表现为先前未受损害的人严重丧失全局认知能力，超出正常衰老所可能预期的。由于独特的全脑损伤，痴呆可能是静息的。或者，痴呆可能是渐进的，由于身体的损伤或疾病导致长期下降。虽然痴呆症在老年人群中较为常见，但也可发生在65岁以前。受痴呆影响的认知领域包括但不限于记忆、注意广度、语言和问题解决。一般来说，在个体被诊断为患有痴呆之前，症状必须存在至少六个月。

[0519] 痴呆的示例性形式包括但不限于额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、词义性痴呆和路易体痴呆。

[0520] 在一些实施方案中，施用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可预防痴呆、降低痴呆的风险和/或治疗痴呆。在一些实施方案中，施用Siglec-7药剂(如抗Siglec-7抗体)可调节患有痴呆的个体中的一种或多种Siglec-7活性。

[0521] 额颞叶痴呆

[0522] 额颞叶痴呆(FTD)是由大脑额叶的进行性恶化引起的病况。随时间推移，退化可能进展至颞叶。患病率仅次于阿尔茨海默氏病(AD)，FTD占早老性痴呆症病例的20％。FTD的临床特征包括记忆缺失、行为异常、人格改变以及语言障碍(Cruts,M.&Van Broeckhoven,C.,Trends Genet.24:186-194(2008);Neary,D.,等人,Neurology 51:1546-1554(1998);Ratnavalli,E.,Brayne,C.,Dawson,K.&Hodges,J.R.,Neurology 58:1615-1621(2002))。

[0523] 大部分FTD病例以常染色体显性方式遗传，但即使在一个家族中，症状也可跨越伴随行为障碍的FTD，至原发性进行性失语、皮质基底神经节变性。与大多数神经退行性疾病一样，FTD的特征可在于患病脑中特定蛋白质聚集体的病理性存在。历史上，FTD的第一次描述认识到神经原纤维缠结或皮克体内存在过度磷酸化Tau蛋白的神经元内累积。微管相关蛋白Tau的因果作用得到了若干家族中编码Tau蛋白的基因突变的鉴定的支持(Hutton,M.,等人,Nature 393:702-705(1998)。然而，大多数FTD大脑显示没有过度磷酸化Tau的累积，但对泛素(Ub)和TAR DNA结合蛋白(TDP43)缺失表现出免疫应答性(Neumann,M.,等人,Arch.Neurol.64:1388-1394(2007))。大多数带有Ub包涵体的那些FTD病例(FTD-U)显示在颗粒蛋白前体基因中携带突变。

[0524] 在一些实施方案中，施用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可预防FTD、降低FTD的风险和/或治疗FTD。在一些实施方案中，施用Siglec-7药剂(如抗Siglec-7抗体)可调节患有FTD的个体中的一种或多种Siglec-7活性。

[0525] 阿尔茨海默氏病

[0526] 阿尔茨海默氏病(AD)是痴呆的最常见形式。该疾病无法治愈,其随着疾病的进展恶化,且最终导致死亡。大多数情况下,AD在65岁以上的人群中得到诊断。然而,不太普遍的早发型阿尔茨海默氏病可早得多地发生。

[0527] 阿尔茨海默氏病的常见症状包括行为症状,如难以记住最近的事件;认知症状、困惑、易怒和攻击、情绪波动、语言障碍以及长期记忆丧失。随着疾病进展,身体机能丧失,最终导致死亡。阿尔茨海默氏病在变得完全明显之前发展未知和可变的时间量,并且可在未确诊的情况下进展多年。

[0528] 在一些实施方案中,施用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可预防阿尔茨海默氏病、降低阿尔茨海默氏病的风险和/或治疗阿尔茨海默氏病。在一些实施方案中,施用Siglec-7药剂(如抗Siglec-7抗体)可调节患有阿尔茨海默氏病的个体中的一种或多种Siglec-7活性。

[0529] 帕金森氏病

[0530] 可被称为特发性或原发性帕金森综合征、运动功能减退的刚性综合症(HRS)或震颤性麻痹的帕金森氏病是影响运动系统控制的神经退行性脑病症。脑中多巴胺产生细胞的进行性死亡导致帕金森氏病的主要症状。大多数情况下,帕金森氏病在50岁以上的人群中得到诊断。帕金森氏病在大多数人中是特发性的(没有已知原因)。然而,遗传因素也在所述疾病中起作用。

[0531] 帕金森氏病的症状包括但不限于手、手臂、腿、下巴和面部的颤抖、肢体和躯干的肌肉强直、运动缓慢(运动迟缓)、姿势不稳定、行走困难、神经精神问题、言语或行为改变、抑郁、焦虑、疼痛、精神病、痴呆、幻觉、以及睡眠问题。

[0532] 在一些实施方案中,施用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可预防帕金森氏病、降低帕金森氏病的风险和/或治疗帕金森氏病。在一些实施方案中,施用Siglec-7药剂(如抗Siglec-7抗体)可调节患有帕金森氏病的个体中的一种或多种Siglec-7活性。

[0533] 肌萎缩性侧索硬化(ALS)

[0534] 如本文所用,肌萎缩性侧索硬化(ALS)或运动神经元疾病或卢伽雷氏病(Lou Gehrig's disease)可互换使用,并且是指具有不同病因学的衰竭性疾病,其特征在于快速进行性无力、肌肉萎缩和束缚、肌肉痉挛、说话困难(构音障碍)、吞咽困难(difficulty swallowing)(吞咽困难(dysphagia))和呼吸困难(difficulty breathing)(呼吸困难(dyspnea))。

[0535] 已经显示,颗粒蛋白前体在ALS中发挥作用(Schymick,JC等人,(2007)J Neurol Neurosurg Psychiatry.;78:754-6)并再次保护由引起ALS的蛋白质(如TDP-43)引起的损伤(Laird,AS等人,(2010).PLoS ONE 5:e13368)。还证明了pro-NGF在脊髓损伤后诱导p75介导的少突胶质细胞和皮质脊髓神经元的死亡(Beatty等人,Neuron(2002),36,第375-386页;Giehl等人,Proc.Natl.Acad.Sci USA(2004),101,第6226-30页)。

[0536] 在一些实施方案中,施用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可预防ALS、降低ALS的风险和/或治疗ALS。在一些实施方案中,施用Siglec-7药剂(如抗Siglec-7抗体)可调节患有肌萎缩性侧索硬化的个体中的一种或多种Siglec-7活性。

[0537] 亨廷顿氏病

[0538] 亨廷顿氏病(HD)是由亨廷顿基因(HTT)中的常染色体显性突变引起的遗传性神经退行性疾病。亨廷顿基因内的细胞因子-腺嘌呤-鸟嘌呤(CAG)三联体重复序列的扩增导致由所述基因编码的亨廷顿蛋白(Htt)的突变形式的产生。这种突变体亨廷顿蛋白(mHtt)是有毒的并且促成神经元死亡。亨廷顿氏病的症状最常出现在35岁与44岁之间,胆识它们可在任何年龄段出现。

[0539] 亨廷顿氏病的症状包括但不限于运动控制问题、急躁、随机运动(舞蹈病)、异常眼运动、平衡受损、癫痫发作、咀嚼困难、吞咽困难、认知问题、言语改变、记忆缺陷、思维困难、失眠、疲劳、痴呆、人格变化、抑郁、焦虑以及强迫行为。

[0540] 在一些实施方案中,施用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可预防亨廷顿氏病、降低亨廷顿氏病的风险和/或治疗亨廷顿氏病(HD)。在一些实施方案中,施用Siglec-7药剂(如抗Siglec-7抗体)可调节患有亨廷顿氏病的个体中的一种或多种Siglec-7活性。

[0541] Tau蛋白病

[0542] Tau蛋白病(Taupathy diseases)或Tau蛋白病(Tauopathies)是由脑内微管相关蛋白tau的聚集引起的一类神经退行性疾病。阿尔茨海默氏病(AD)是最熟知的Tau蛋白病,并且以不溶性神经原纤维缠结(NFT)的形式在神经元中累积tau蛋白。其它Tau蛋白疾病和病症包括进行性核上性麻痹、拳击员痴呆症、与染色体17有关的额颞叶痴呆和帕金森综合征、利替可-波帝格病(Lytico-Bodig disease)(关岛帕金森氏痴呆综合征(Parkinson-dementia complex of Guam))、缠结主导型痴呆、神经节神经胶质瘤和神经节细胞瘤、脑膜血管瘤病、亚急性硬化性全脑炎、铅中毒脑病、结节性硬化症、哈-斯二氏病(Hallervorden-Spatz disease)、脂褐质沉积症、皮克氏病(Pick's disease)、皮质基底变性、嗜银颗粒性病(AGD)、亨廷顿氏病以及额颞叶变性。

[0543] 在一些实施方案中,施用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可预防Tau蛋白病、降低Tau蛋白病的风险和/或治疗Tau蛋白病。在一些实施方案中,施用Siglec-7药剂(如抗Siglec-7抗体)可调节患有Tau蛋白病的个体中的一种或多种Siglec-7活性。

[0544] 多发性硬化症

[0545] 多发性硬化症(MS)也可被称为播散性硬化症或播散性脑脊髓炎。MS是一种炎性疾病,其中大脑和脊髓轴突周围的脂肪髓鞘受损,从而导致脱髓鞘和瘢痕形成以及广泛的体征和症状。MS影响大脑和脊髓中的神经细胞彼此有效通信的能力。神经细胞通过将称为动作电位的电信号向下传递给称为轴突的长纤维来进行通信,所述长纤维包含在称为髓磷脂的绝缘物质内。在MS中,身体自身的免疫系统攻击并损伤髓磷脂。当髓磷脂丢失时,轴突不再能有效地传导信号。MS发病通常在年轻人中发生,并且在女性中更常见。

[0546] MS的症状包括但不限于感觉的变化,如敏感性丧失或麻刺感;刺痛或麻木,如感觉减退和感觉异常;肌无力;阵挛;肌肉痉挛;移动困难;协调和平衡困难,如共济失调;言语困难,如构音障碍或吞咽困难,如吞咽困难;视觉问题,如眼球震颤,包括光幻视的视神经炎以及复视;疲劳;急性或慢性疼痛;以及膀胱和肠道困难;不同程度的认知障碍;抑郁或情绪不稳定的情感症状;乌特霍夫现象(Uhthoff's phenomenon),其是由于暴露于高于平常环境温度而导致的现存症状恶化;和莱尔米体征(Lhermitte's sign),其是在弯曲脖子时向下

和向后流动的电感觉。

[0547] 在一些实施方案中，施用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可预防多发性硬化症、降低多发性硬化症的风险和/或治疗多发性硬化症。在一些实施方案中，施用Siglec-7药剂(如抗Siglec-7抗体)可调节患有多发性硬化症的个体中的一种或多种Siglec-7活性。

[0548] 癌症

[0549] 本公开的其它方面提供了通过向有需要的个体施用治疗有效量的本公开的Siglec-7药剂(如本公开的分离的抗Siglec-7抗体)来预防癌症、降低癌症的风险或治疗癌症的方法。公开的任何分离的抗体都可用于这些方法中。在一些实施方案中，分离的抗体是本公开的激动剂抗体。在其它实施方案中，分离的抗体是本公开的拮抗剂抗体。在其它实施方案中，分离的抗体是本公开的惰性抗体。在其它实施方案中，分离的抗体是本公开的抗体缀合物。

[0550] 如本文所公开，已知肿瘤微环境含有异质免疫浸润物，其包括T淋巴细胞、巨噬细胞、嗜中性粒细胞、NK细胞以及骨髓/粒细胞谱系的细胞。T调控性细胞、肿瘤包埋的免疫抑制骨髓细胞和/或M2巨噬细胞、M2嗜中性粒细胞和/或M2-NK细胞在肿瘤中的存在和活性与不良预后相关。相比之下，细胞毒性T细胞的存在和活性有利于癌症治疗。预期直接或间接增强细胞毒性T细胞的活性并降低各种免疫抑制细胞的数目和活性的疗法提供显著治疗益处。开创性的临床前研究已经显示靶向免疫抑制细胞的药物(例如CSF1/CSF1R阻断抗体)与活化细胞毒性T细胞的免疫检查点阻断抗体之间的协同作用，从而表明操纵两种细胞类型在肿瘤模型中显示效力，其中个体疗法作用不佳(Zhu Y;Cancer Res.2014年9月15日;74(18):5057-69)。因此，在一些实施方案中，阻断在骨髓细胞、T细胞子集和肿瘤相关免疫细胞上表达的Siglec-7可刺激有益的抗肿瘤免疫应答，从而产生治疗性抗肿瘤免疫应答。

[0551] 在一些实施方案中，用于预防癌症、降低癌症的风险或治疗患有癌症的个体的方法还包括向所述个体施用特异性地结合至抑制性检查点分子的至少一种抗体。与抑制性检查点分子特异性结合的抗体的实例包括但不限于抗PD-L1抗体、抗CTLA4抗体、抗PD-L2抗体、抗PD-1抗体、抗B7-H3抗体、抗B7-H4抗体、抗HVEM抗体、抗BTLA抗体、抗GAL9抗体、抗TIM3抗体、抗A2AR抗体、抗LAG-3抗体、抗磷脂酰丝氨酸抗体以及其任何组合。在一些实施方案中，特异性地结合至抑制性检查点分子的至少一种抗体与本公开的Siglec-7药剂(如本公开的拮抗剂抗Siglec-7抗体)组合施用。

[0552] 在一些实施方案中，待通过本公开的方法预防或治疗的癌症包括但不限于鳞状细胞癌(例如上皮鳞状细胞癌)、肺癌(包括小细胞肺癌、非小细胞癌肺癌、肺腺癌以及肺鳞状癌)、腹膜癌、肝细胞癌、胃癌或胃脏癌(gastric or stomach cancer)(包括胃肠癌和胃肠道间质癌)、胰腺癌、成胶质细胞瘤、宫颈癌、卵巢癌、肝癌、膀胱癌、泌尿道癌、肝癌、乳腺癌、结肠癌、直肠癌、结肠直肠癌、子宫内膜癌或子宫癌、唾液腺癌、肾癌或肾脏癌(kidney or renal cancer)、前列腺癌、外阴癌、甲状腺癌、肝癌、肛管癌、阴茎癌、黑色素瘤、浅表扩散性黑色素瘤、恶性雀斑样痣黑色素瘤、肢端雀斑样痣黑色素瘤、结节性黑色素瘤、多发性骨髓瘤和B细胞淋巴瘤、慢性淋巴细胞性白血病(CLL)、急性成淋巴细胞性白血病(ALL)、毛细胞白血病、慢性成髓细胞性白血病和移植后淋巴增殖性病症(PTLD)以及与瘢痣病相关的异常血管增生、水肿(如与脑肿瘤相关的水肿)、麦格氏综合征(Meigs' syndrome)、脑癌以及头颈

癌和相关转移。在一些实施方案中，癌症是结肠直肠癌。在一些实施方案中，所述癌症选自膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)以及多发性骨髓瘤。在一些实施方案中，癌症选自非小细胞肺癌、成胶质细胞瘤、成神经细胞瘤、肾细胞癌、膀胱癌、卵巢癌、黑色素瘤、乳腺癌、胃癌以及肝细胞癌。

[0553] 在一些实施方案中，癌症是三阴性乳腺癌。在一些实施方案中，癌症可以是早期癌症或晚期癌症。在一些实施方案中，癌症可以是原发性肿瘤。在一些实施方案中，癌症可以是在第二部位处源自任何上述类型的癌症的转移性肿瘤。

[0554] 在一些实施方案中，本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)可用于预防癌症、降低癌症的风险或治疗癌症，所述癌症包括但不限于膀胱癌、乳腺癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤以及甲状腺癌。

[0555] 在一些实施方案中，本公开提供了通过向患有癌症的个体施用治疗有效量的本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)来预防癌症、降低癌症的风险或治疗所述个体的方法。

[0556] 在一些实施方案中，所述方法还包括向所述个体施用至少一种特异性地结合至抑制性免疫检查点分子的抗体和/或另一种标准或研究性抗癌疗法。在一些实施方案中，所述至少一种特异性地结合至抑制性检查点分子的抗体与Siglec-7药剂(如本公开的抗Siglec-7抗体)组合施用。在一些实施方案中，特异性地结合至抑制性检查点分子的至少一种抗体选自抗PD-L1抗体、抗CTLA4抗体、抗PD-L2抗体、抗PD-1抗体、抗B7-H3抗体、抗B7-H4抗体和抗HVEM抗体、抗B和T淋巴细胞衰减因子(BTLA)抗体、抗杀伤抑制性受体(KIR)抗体、抗GAL9抗体、抗TIM3抗体、抗A2AR抗体、抗LAG-3抗体、抗磷脂酰丝氨酸抗体、抗CD27抗体以及其任何组合。在一些实施方案中，所述标准或研究性抗癌疗法是选自以下各项的一种或多种疗法：放射疗法、细胞毒性化学疗法、靶向疗法、伊马替尼(Gleevec®)、曲妥珠单抗(Herceptin®)、过继细胞转移(ACT)、嵌合抗原受体T细胞转移(CAR-T)、疫苗疗法以及细胞因子疗法。

[0557] 在一些实施方案中，所述方法还包括向所述个体施用至少一种特异性地结合至抑制性细胞因子的抗体。在一些实施方案中，所述至少一种特异性地结合至抑制性细胞因子的抗体与Siglec-7药剂(如本公开的抗Siglec-7抗体)组合施用。在一些实施方案中，所述至少一种特异性地结合至抑制性细胞因子的抗体选自抗CCL2抗体、抗CSF-1抗体、抗IL-2抗体以及其任何组合。

[0558] 在一些实施方案中，所述方法还包括向所述个体施用至少一种特异性地结合至刺激性免疫检查点蛋白的激动性抗体。在一些实施方案中，所述至少一种特异性地结合至刺激性检查点蛋白的激动性抗体与Siglec-7药剂(如本公开抗Siglec-7抗体)组合施用。在一些实施方案中，所述至少一种特异性地结合至刺激性检查点蛋白的激动性抗体选自激动剂抗CD40抗体、激动剂抗OX40抗体、激动剂抗ICOS抗体、激动剂抗CD28抗体、激动剂抗CD137/4-1BB抗体、激动剂抗CD27抗体、激动剂抗糖皮质激素诱导的TNFR相关蛋白GITR抗体以及其任何组合。

[0559] 在一些实施方案中，所述方法还包括向所述个体施用至少一种刺激性细胞因子。在一些实施方案中，所述至少一种刺激性细胞因子与所述Siglec-7药剂(如本公开的抗Siglec-7抗体)组合施用。在一些实施方案中，所述至少一种刺激性细胞因子选自IFN-a4、IFN-b、IL-1β、TNF-α、IL-6、IL-8、CRP、IL-20家族成员、LIF、IFN-γ、OSM、CNTF、GM-CSF、IL-11、IL-12、IL-17、IL-18、IL-23、CXCL10、IL-33、MCP-1、MIP-1-β以及其任何组合。

[0560] 评估方法

[0561] 本公开还提供评估个体对与Siglec-7结合或相互作用的药剂的应答性的方法。在一些实施方案中，所述方法包括：测量在向所述个体施用与Siglec-7结合或相互作用的药剂之前从所述个体获得的血液样品中非致瘤性骨髓细胞上一种或多种标志物的表达水平；向所述个体施用治疗有效量的所述药剂；以及测量在施用所述药剂后从所述个体获得的血液样品中非致瘤性骨髓细胞上所述一种或多种标志物的表达水平。在一些实施方案中，在施用与Siglec-7结合或相互作用的药剂后，非致瘤性骨髓细胞上所述一种或多种标志物的水平降低表明所述个体对所述药剂应答。在一些实施方案中，所述一种或多种标志物是CD45和CD14中的一种或多种。在一些实施方案中，所述方法还包括施用一种或多种另外的治疗有效量的所述药剂。在一些实施方案中，所述药剂是本文公开的任何Siglec-7药剂。在一些实施方案中，所述药剂选自由以下各项组成的组：抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、反义分子、siRNA、小分子抑制剂、蛋白质以及肽。在一些实施方案中，所述药剂是分离的抗Siglec-7抗体或抗Siglec-7抗体-缀合物。在一些实施方案中，所述抗Siglec-7抗体是本文公开的抗Siglec-7抗体中的任一种。

[0562] 本公开还提供评估个体对与Siglec-7结合或相互作用的药剂的应答性的方法。在一些实施方案中，所述方法包括：测量在向所述个体施用与Siglec-7结合或相互作用的药剂之前从所述个体获得的血液样品中非致瘤性骨髓细胞上CD45和CD14的表达水平；向所述个体施用治疗有效量的所述药剂；以及测量在施用所述药剂后从所述个体获得的血液样品中非致瘤性骨髓细胞上CD45和CD14的表达水平。在一些实施方案中，在施用与Siglec-7结合或相互作用的药剂后，非致瘤性骨髓细胞上CD45和CD14的水平降低表明所述个体对所述药剂应答。在一些实施方案中，所述方法还包括施用一种或多种另外的治疗有效量的所述药剂。在一些实施方案中，所述药剂是本文公开的任何Siglec-7药剂。在一些实施方案中，所述药剂选自由以下各项组成的组：抗体、可溶性Siglec-7受体、Siglec-7-Fc融合蛋白、Siglec-7免疫粘附素、反义分子、siRNA、小分子抑制剂、蛋白质以及肽。在一些实施方案中，所述药剂是分离的抗Siglec-7抗体或抗Siglec-7抗体-缀合物。在一些实施方案中，所述抗Siglec-7抗体是本文公开的抗Siglec-7抗体中的任一种。

[0563] 在一些实施方案中，在施用与Siglec-7结合或相互作用的药剂后，非致瘤性骨髓细胞上CD45和CD14水平的至少5％、至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少55％、至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％、至少100％，105％、至少110％、至少115％、至少120％、至少125％、至少130％、至少135％、至少140％、至少145％、至少150％、至少155％、至少160％、至少165％、至少170％、至少175％、至少180％、至少185％、至少190％、至少195％、至少200％、至少250％或至少500％降低表明所述个体对所述药剂应答。在一些实施方案中，在施用与Siglec-7结合或相互作用的药剂后，非致瘤性骨髓细胞上CD45和

CD14水平的至少1.5倍、至少1.6倍、至少1.7倍、至少1.8倍、至少1.9倍、至少2.0倍、至少2.1倍、至少2.15倍、至少2.2倍、至少2.25倍、至少2.3倍、至少2.35倍、至少2.4倍、至少2.45倍、至少2.5倍、至少2.55倍、至少3.0倍、至少3.5倍、至少4.0倍、至少4.5倍、至少5.0倍、至少5.5倍、至少6.0倍、至少6.5倍、至少7.0倍、至少7.5倍、至少8.0倍、至少8.5倍、至少9.0倍、至少9.5倍或至少10倍降低表明所述个体对所述药剂应答。

[0564] 试剂盒/制品

[0565] 本公开还提供包括本公开的Siglec-7药剂(例如,本文所述的抗Siglec-7抗体)或其功能片段的试剂盒和/或制品。本公开的试剂盒和/或制品可包括一个或多个含有本公开的纯化抗体的容器。在一些实施方案中,所述试剂盒和/或制品还包括根据本公开的方法的使用说明书。在一些实施方案中,这些说明书包括施用本公开的Siglec-7药剂(如本公开的抗Siglec-7抗体)以根据本公开的任何方法预防选自以下各项的疾病、病症或损伤、降低所述疾病、病症或损伤的风险或治疗患有所述疾病、病症或损伤的个体的说明:痴呆、额颞叶痴呆、阿尔茨海默氏病、血管性痴呆、混合性痴呆、克罗伊茨费尔特-雅格布病、正常压力脑积水、肌萎缩性侧索硬化、亨廷顿氏病、Tau蛋白病、那须哈科拉病、中风、急性创伤、慢性创伤、狼疮、急性和慢性结肠炎、类风湿性关节炎、伤口愈合、克罗恩氏病、炎性肠病、溃疡性结肠炎、肥胖症、疟疾、特发性震颤、中枢神经系统狼疮、白塞氏病、帕金森氏病、路易体痴呆、多系统萎缩症、夏伊-德拉戈综合征、进行性核上性麻痹、皮质基底节变性、急性播散性脑脊髓炎、肉芽肿性病症、类肉瘤病、老化疾病、癫痫、脊髓损伤、创伤性脑损伤、年龄相关性黄斑变性、青光眼、色素性视网膜炎、视网膜变性、呼吸道感染、败血症、眼部感染、全身感染、狼疮、关节炎、多发性硬化症、低骨密度、骨质疏松症、骨生成、骨硬化病、骨佩吉特氏病、以及癌症(包括膀胱癌、脑癌、乳腺癌、结肠癌、直肠癌、子宫内膜癌、肾癌、肾细胞癌、肾盂癌、白血病、肺癌、黑色素瘤、非霍奇金氏淋巴瘤、胰腺癌、前列腺癌、卵巢癌、纤维肉瘤、急性成淋巴细胞性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性骨髓性白血病(CML)、多发性骨髓瘤、真性红细胞增多症、特发性血小板增多症、原发性或特发性骨髓纤维化、原发性或特发性骨髓硬化、骨髓源性肿瘤、表达Siglec-7的肿瘤、甲状腺癌)、感染、CNS疱疹、寄生虫感染、锥虫感染、克氏感染、铜绿假单胞菌感染、杜氏利什曼原虫感染、B族链球菌感染、空肠弯曲杆菌感染、脑膜炎奈瑟氏菌感染、I型HIV和/或流感嗜血杆菌。

[0566] 在一些实施方案中,所述说明书包括如何检测例如个体中、组织样品中或细胞中的Siglec-7蛋白质的描述。所述试剂盒和/或制品可进一步包括基于鉴定个体是否患有疾病和疾病阶段来选择适合于治疗的个体的描述。

[0567] 在一些实施方案中,所述试剂盒和/或制品还可包括本公开的另一种抗体(例如,至少一种特异性地结合至抑制性检查点分子的抗体,至少一种特异性地结合至抑制性细胞因子的抗体和/或至少一种特异性地结合至刺激性检查点蛋白的激动性抗体)和/或至少一种刺激性细胞因子。在一些实施方案中,所述试剂盒和/或制品可进一步包括根据本公开的任何方法,与本公开的Siglec-7药剂(例如,本文所述的抗Siglec-7抗体)组合使用所述抗体和/或刺激细胞因子的说明书,与抗体和/或刺激性细胞因子组合使用本公开的Siglec-7药剂(例如,本文所述的抗Siglec-7抗体)的说明书,或使用本公开的Siglec-7药剂(例如,本文描述的抗Siglec-7抗体)和抗体和/或刺激性细胞因子的说明书。

[0568] 所述说明书通常包括关于预期治疗的剂量、给药方案和施用途径的信息。所述容

器可为单位剂量、散装(bulk)包装(例如,多剂量包装)或亚单位剂量。在本公开的试剂盒和/或制品中提供的说明书通常是在标签或包装插页(例如包括在试剂盒中的纸张)上的书面说明,但机器可读指令(例如,在磁性或光存储盘上携带的指令)也是可以接受的。

[0569] 标签或包装插页指示所述组合物用于治疗例如本公开的疾病。可提供说明书以实践本文所述的任何方法。

[0570] 本公开的试剂盒和/或制品处于合适的包装中。合适的包装包括但不限于小瓶、瓶、罐、软包装(例如,密封的聚脂薄膜或塑料袋)等。还考虑与特定装置(如吸入器)、经鼻施用装置(例如雾化器))或输注装置(如微型泵)组合使用的包装。试剂盒和/或制品可具有无菌入口(例如,所述容器可以是具有皮下注射针头可刺穿的塞子的静脉内注射溶液袋或小瓶)。所述容器装还可具有无菌入口(例如,所述容器可以是具有皮下注射针头可刺穿的塞子的静脉注射溶液袋或小瓶)。所述组合物中的至少一种活性剂是本公开的Siglec-7药剂(例如本文所述的抗Siglec-7抗体)。所述容器可进一步包括第二药物活性剂。

[0571] 试剂盒和/或制品可任选地提供附加组成部分,如缓冲剂和解释性信息。通常,所述试剂盒包括容器和在容器上或与容器相关的标签或一张或多张包装插页。

[0572] 诊断用途

[0573] 本公开的Siglec-7药剂,如本公开的分离的抗体(例如,本文所述的抗Siglec-7抗体)还具有诊断效用。因此,本公开提供使用本公开的抗体或其功能片段用于诊断目的,诸如检测个体中或来源于个体的组织样品中的Siglec-7蛋白的方法。

[0574] 在一些实施方案中,个体是人。在一些实施方案中,个体是患有本公开的疾病、病症或损伤或处于发展所述疾病、病症或损伤风险中的人患者。在一些实施方案中,所述诊断方法涉及检测生物样品如生物活检标本、组织或细胞中的Siglec-7蛋白。使本公开的Siglec-7药剂(例如本文所述的抗Siglec-7抗体)与生物样品接触并检测抗原结合的抗体。例如,活检标本可用本文所述的抗Siglec-7抗体染色以便检测和/或定量疾病相关细胞。所述检测方法可涉及定量抗原结合抗体。生物样品中的抗体检测可用本领域中已知的任何方法进行,包括免疫荧光显微术、免疫细胞化学、免疫组织化学、ELISA、FACS分析、免疫沉淀或微正电子发射断层摄影术。在某些实施方案中,例如用^{18}F放射性标记所述抗体,且随后利用微正电子发射断层摄影术分析进行检测。还可通过诸如正电子发射断层摄影术(PET)、X射线计算机断层摄影术、单光子发射计算机断层摄影术(SPECT)、计算机断层摄影术(CT)以及计算机轴向断层摄影术(CAT)的非侵入性技术在患者中定量抗体结合。

[0575] 在其它实施方案中,本公开的分离的抗体(例如,本文所述的抗Siglec-7抗体)可用于检测和/或定量例如取自临床前疾病模型(例如,非人疾病模型)的脑标本中的小神经胶质细胞。如此,本公开的分离的抗体(例如,本文所述的抗Siglec-7抗体)可适用于评价与对照相比,在神经系统疾病或损伤(如额颞叶痴呆、阿尔茨海默氏病、血管性痴、癫痫发作、视网膜营养不良、动脉粥样硬化性血管疾病、那须哈科拉病或多发性硬化症)的模型中在治疗后的治疗应答。

[0576] 通过参考以下实施例将更完全地理解本公开。然而,所述实施例并不应当被解释为对本公开的范围进行限制。贯穿本公开的所有引用据此以引用的方式明确并入本文中。

实施例

[0577] 实施例1:抗Siglec-7抗体的产生、鉴定和表征

[0578] 引言

[0579] 人Siglec-7的氨基酸序列在下文在SEQ ID NO:1中列出。人Siglec-7含有位于SEQ ID NO:1的氨基酸残基1-18处的信号序列,位于SEQ ID NO:1的氨基酸残基39-122处的细胞外免疫球蛋白样可变型(IgV)结构域,位于SEQ ID NO:1的氨基酸残基150-233和240-336的两个Ig-样C2-型结构域,位于SEQ ID NO:1的氨基酸残基354-376处的跨膜结构域,位于SEQ ID NO:1的氨基酸残基435-440处的ITIM基序1以及位于SEQ ID NO:1的氨基酸残基459-463处的ITIM基序2。人Siglec-7与Siglec-7同系物的比对在图1A中示出,并且人Siglec-7的三维表示在图1B中示出。

[0580] Siglec-7氨基酸序列(SEQ ID NO:1):

[0581]
```
10         20         30         40         50
MLLLLLLPLL WGRERVEGQK SNRKDYSLTM QSSVTVQEGM CVHVRCSFSY
        60         70         80         90        100
PVDSQTDSDP VHGYWFRAGN DISWKAPVAT NNPAWAVQEE TRDRFHLLGD
       110        120        130        140        150
PQTKNCTLSI RDARMSDAGR YFFRMEKGNI KWNYKYDQLS VNVTALTHRP
       160        170        180        190        200
NILIPGTLES GCFQNLTCSV PWACEQGTPP MISWMGTSVS PLHPSTTRSS
       210        220        230        240        250
VLTLIPQPQH HGTSLTCQVT LPGAGVTTNR TIQLNVSYPP QNLTVTVFQG
       260        270        280        290        300
EGTASTALGN SSSLSVLEGQ SLRLVCAVDS NPPARLSWTW RSLTLYPSQP
       310        320        330        340        350
SNPLVLELQV HLGDEGEFTC RAQNSLGSQH VSLNLSLQQE YTGKMRPVSG
       360        370        380        390        400
VLLGAVGGAG ATALVFLSFC VIFIVVRSCR KKSARPAADV GDIGMKDANT
       410        420        430        440        450
IRGSASQGNL TESWADDNPR HHGLAAHSSG EEREIQYAPL SFHKGEPQDL
       460
SGQEATNNEY SEIKIPK
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[0582] 以下实施例的目的是产生增强树突细胞、单核细胞、巨噬细胞、嗜中性粒细胞、NK细胞、T细胞和/或小神经胶质细胞的有益作用的Siglec-7结合抗体(例如,拮抗性抗体、Siglec-7特异性抗体)。使用小鼠杂交瘤技术、噬菌体展示技术和酵母展示技术产生了结合Siglec-7的细胞外结构域、特别是IgV结构域(SEQ ID NO:1的氨基酸残基39-122)的抗体。鉴定抗体,且然后在细胞中和动物体内筛选它们与Siglec-7配体竞争结合至Siglec-7、诱导Siglec-7下调、诱导Siglec-7脱敏、诱导Siglec-7降解、诱导Siglec-7靶向至溶酶体、诱导Siglec-7裂解、调节Siglec-7信号传导和/或一种或多种功能的能力,如以下实施例中所描述。由Siglec-7结合的示例性配体描绘于图2和图3中。

[0583] 例如,选择靶向Siglec-7的IgV结构域(氨基酸残基39-122)的抗Siglec-7抗体。所述IgV结构域与唾液酸靶标结合,并且这种结合可被所述抗体阻断。因此,氨基酸残基39-122对应于将阻断Siglec-7与一种或多种内源性靶标(例如配体)的结合的抗体的Siglec-7肽靶标。

[0584] 如本文所述,鉴定并表征了13种抗Siglec-7抗体。

[0585] 结果

[0586] 抗Siglec-7抗体产生

[0587] 免疫程序

[0588] 快速初免法:使用以下程序对四只50日龄雌性BALB/c小鼠进行了免疫。在19天的时间内给予一系列含有人Siglec-7抗原但不含佐剂的皮下水性注射液。小鼠被圈养在来自Lab Products的通风架系统中。使所有四只小鼠在第19天安乐死,并且收获淋巴细胞以产生杂交瘤细胞系。

[0589] 标准方法:使用以下程序对四只50日龄雌性BALB/c或NZB/W小鼠进行了免疫。小鼠被圈养在来自Lab Products的通风架系统中。每3周用混合于CpG-ODN佐剂中的人Siglec-7抗原以每只小鼠25μg蛋白质抗原(总体积125μL/小鼠)腹膜内注射小鼠。在第二次加强后7天通过隐静脉刺血来获得测试血液。通过间接ELISA测定来对测试血液(免疫血清)进行测试以确定对于融合最佳两只应答小鼠。小鼠可能需要第3次和第4次加强以及在加强后7天的另一测试血液以评估融合前的滴度。当抗体滴度足够高时,经由侧尾静脉给予最佳两只应答小鼠最后的静脉内加强。在IV加强后4天,将小鼠安乐死以进行融合。收获脾并将从脾中分离的淋巴细胞用于融合过程以产生杂交瘤。

[0590] 杂交瘤开发

[0591] 根据标准Roche方案,在聚乙二醇(PEG 1500)存在下分离淋巴细胞并与鼠SP2/0骨髓瘤细胞融合。使用单步克隆方法(HAT选择)培养融合细胞。此方法使用基于半固体甲基纤维素的HAT选择性培养基来将杂交瘤选择和克隆组合到一个步骤中。单细胞来源的杂交瘤生长以在半固体培养基上形成单克隆菌落。在融合事件后10天,将948个所得杂交瘤克隆转移至96孔组织培养板并在含有HT的培养基中生长,直到达到对数生长中期(5天)。

[0592] 杂交瘤筛选

[0593] 通过间接ELISA关于筛选抗原(初步筛选)对来自948个杂交瘤的组织培养上清液进行测试,并使用山羊抗IgG/IgM(H&L)-HRP二级抗体探测IgG和IgM抗体,并用TMB底物显影。在此测定中克隆＞0.2OD进行下一轮测试。阳性培养物关于筛选抗原进行重新测试以确认分泌并且关于不相关的抗原(人转铁蛋白)进行重新测试以消除非特异性或“粘性”mAb并排除假阳性。通过抗体捕获ELISA对所有目标克隆进行同种型分析,以确定它们是IgG还是IgM同种型。

[0594] 杂交瘤细胞培养

[0595] 将目标杂交瘤细胞系在转移至96孔板后在24孔培养板中在培养中维持32天。这被称为稳定期,并测试克隆是否保持稳定和分泌。在此稳定时间段期间,对所有目标克隆进行暂时冷冻细胞系备份以用于-80℃储存(存活6个月)。在此时间段期间定期测试杂交瘤的分泌和特异性。

[0596] 亚克隆

[0597] 对顶部杂交瘤细胞系(克隆)进行亚克隆以确保单克隆性。通过使用单步克隆系统再次涂铺亲本克隆来进行亚克隆。将24与90个之间的亚克隆转移至96孔培养板。通过间接ELISA和抗体捕获ELISA筛选亚克隆。每种亲本的顶部亚克隆被用于在培养中扩增。任何＜50%克隆的亲本克隆都进行了第二轮亚克隆。

[0598] 然后筛选抗体的Siglec-7结合。测试了对于与人Siglec-7结合为阳性的抗体在多种细胞类型中阻断配体结合的能力和降低Siglec-7的表面水平的能力。鉴定了十三种

Silgec-7抗体。表1中列出了同种型和分箱类别。

[0599] 表1:抗Siglec-7抗体

[0600]

Ab ID	Ab同种型	分箱
1A12	mIgG2a	2
1E8	mIgG1	2
2G1	mIgG2b	1
2G4	mIgG1/2a*	2
3E11	mIgG1	1
4A1	mIgG2a	2
4D7	mIgG1	5
4E3	mIgG1	1
7A3	mIgG1	4
7E11	mIgG2a	3
7F12	mIgG2a	2
10B5	mIgG2a	5
10G8	mIgG1	4

[0601] 抗体重链和轻链可变结构域序列

[0602] 使用标准技术,测定编码所产生的抗体的轻链可变结构域和重链可变结构域的氨基酸序列。表2A中列出了抗体的EU或Kabat轻链CDR序列。表2B中列出了抗体的EU或Kabat重链CDR序列。表3A中列出了抗体的EU或Kabat轻链框架(FR)序列。表3B中列出了抗体的EU或Kabat重链框架(FR)序列。

[0603] 表2A:抗Siglec-7抗体的EU或Kabat轻链CDR序列

[0604]

Ab ID	CDR L1	CDR L2	CDR L3
1A12	RSSQSLVHSTGNTY LH (SEQ ID NO: 7)	KVSNRFS (SEQ ID NO: 20)	SQNTHVPYT (SEQ ID NO: 33)
1E8	RASQSISDYLH (SEQ ID NO: 8)	YASQSIS (SEQ ID NO: 21)	QKGLNFPLT (SEQ ID NO: 34)
2G1	SANSSFIYMY (SEQ ID NO: 9)	DTSNLAS (SEQ ID NO: 22)	QQWSSSPLT (SEQ ID NO: 35)
2G4	KASDHINNWLA (SEQ ID NO: 10)	GATSLET (SEQ ID NO: 23)	HQYWNTPYT (SEQ ID NO: 36)
3E11	RSSQSLVHSTGNTY LH (SEQ ID NO: 11)	KVSNRFC (SEQ ID NO: 24)	SQNTHVPYT (SEQ ID NO: 37)
4A1	RSSQSLVHSTGNIY LH (SEQ ID NO: 12)	KVSNRFZ (SEQ ID NO: 25)	SQNTHVPYT (SEQ ID NO: 38)
4D7	KASQKVGTNVA (SEQ ID NO: 13)	SASTRHR (SEQ ID NO: 26)	HQGNSVQYT (SEQ ID NO: 39)
4E3	SANSSFTYMY (SEQ ID NO: 14)	DTSNLAS (SEQ ID NO: 27)	QQWSSSPLT (SEQ ID NO: 40)
7A3	RASQSISEYLH (SEQ ID NO: 15)	FASQSIC (SEQ ID NO: 28)	QNGHNFPYT (SEQ ID NO: 41)
7E11	LASQTIGTWLA (SEQ ID NO: 16)	AATSLAD (SEQ ID NO: 29)	QQLYSTPYT (SEQ ID NO: 42)
7F12	RSSQSLVHSTGNTY LH (SEQ ID NO: 17)	KVSNRFS (SEQ ID NO: 30)	SQNTHVPYT (SEQ ID NO: 43)
10B5	RASQDISZYLN (SEQ ID NO: 18)	LSSRLHS (SEQ ID NO: 31)	QQGHTGAWT (SEQ ID NO: 44)
10B5L1	RASQDINTYLN (SEQ ID NO: 476)	YTSRLHS (SEQ ID NO: 477)	QQGNTLPWT(SEQ ID NO: 478)
10G8	RASQSIREYLH (SEQ ID NO: 19)	FASQSIC (SEQ ID NO: 32)	QKAHNFPYT (SEQ ID NO: 45)

[0605] 表2B:抗Siglec-7抗体的EU或Kabat重链CDR序列

[0606]

Ab ID	CDR H1	CDR H2	CDR H3
1A12	SEVFPITYMN (SEQ ID NO: 46)	IGDILPSIGRTMYG (SEQ ID NO: 59)	ARSEGYLLAY (SEQ ID NO: 72)
1E8	FNIKGSLLH (SEQ ID NO: 47)	IGWIDPEDGETRFD (SEQ ID NO: 60)	ARTEYSNPAWFAY (SEQ ID NO: 73)
2G1	FTFSNYDMS	VATISSGGDYTYYP	ARHGYGNYDWYFDV (SEQ ID NO: 74)

[0607]

Ab ID	CDR H1	CDR H2	CDR H3
	(SEQ ID NO: 48)	(SEQ ID NO: 61)	
2G4	SEVFPITYMN (SEQ ID NO: 49)	IGDILPSIGRTMYG (SEQ ID NO: 62)	ARSEGYLLAY (SEQ ID NO: 75)
3E11	YIFTDYGIT (SEQ ID NO: 50)	IGEISPRSGETYFN (SEQ ID NO: 63)	AREGNPFTY (SEQ ID NO: 76)
4A1	SEVFPITYMN (SEQ ID NO: 51)	IGDILPSIGRTMYG (SEQ ID NO: 64)	ARSEGYLLAY (SEQ ID NO: 77)
4D7	YTFTNYWIN (SEQ ID NO: 52)	IGNIYSGSSRTNYN (SEQ ID NO: 65)	AREGLRAMDY (SEQ ID NO: 78)
4E3	FIFSNYDMS (SEQ ID NO: 53)	VATISSGGGYTYYP (SEQ ID NO: 66)	TRHGYGNYDWYFDV (SEQ ID NO: 79)
4E3H1	FIFSNYDMS (SEQ ID NO: 53)	VSTISSGGGYTYYA (SEQ ID NO: 480)	ARHGYGNYDWYFDV (SEQ ID NO: 74)
4E3H2	FIFSNYDMS (SEQ ID NO: 53)	VATISSGGGYTYYA (SEQ ID NO: 481)	TRHGYGNYDWYFDV (SEQ ID NO: 79)
7A3	FTFSNYAMS (SEQ ID NO: 54)	VASISSGGSYNYYP (SEQ ID NO: 67)	ASQSYGSSYWYFDV (SEQ ID NO: 80)
7E11	FSLSNYGVH (SEQ ID NO: 55)	LGVIWAGGITNYN (SEQ ID NO: 68)	AKQGGTSFSY (SEQ ID NO: 81)
7F12	SEVFPITYMN (SEQ ID NO: 56)	IGDILPSIGRTMYG (SEQ ID NO: 69)	ARSEGYLLAY (SEQ ID NO: 82)
10B5	YAFTNCWMN (SEQ ID NO: 57)	IGRIFPGNGHTNYS (SEQ ID NO: 70)	ARDYSDYYFDY (SEQ ID NO: 83)
10B5H1	GYAFTNCWMN (SEQ ID NO: 479)	RIFPGNGHTN (SEQ ID NO: 482)	DYSDYYFDY (SEQ ID NO: 483)
10G8	FTFSTYAMF (SEQ ID NO: 58)	VASISSGGRYTYYP (SEQ ID NO: 71)	VRHSYGSSYWYLDV (SEQ ID NO: 84)

[0608] 表3A:抗Siglec-7抗体的EU或Kabat轻链框架序列

[0609]

Ab ID	VL FR1	VL FR2	VL FR3	VL FR4
1A12	DVZMTQTPLSLPVS LGDQASISC (SEQ ID NO: 85)	WYLQKPGQSPKLLI Y (SEQ ID NO: 98)	GVPDRFSGSGAGTDFTL KISRVEAEDLGVYFC (SEQ ID NO: 111)	FGGGTKLEIK (SEQ ID NO: 124)
1E8	DIQMTQFPATLSVT PGDRVSLSC (SEQ ID NO: 86)	WYQHKSHESPRLLI K (SEQ ID NO: 99)	GIPSRFSGSGSGWDFTLS INSVEPEDVGIYYC (SEQ ID NO: 112)	FGGGTKLEMK (SEQ ID NO: 125)
2G1	VLTQSPAIMSASPG EKVTMTC (SEQ ID NO: 87)	WYQQKPGSSPRLLI F (SEQ ID NO: 100)	GVPIRFSGSGSGTSYSLTI SRMEAEDTATYYC (SEQ ID NO: 113)	FGGGTKLELK (SEQ ID NO: 126)
2G4	DIQMTQSLSYLSVS LGGRVTITC (SEQ ID NO: 88)	WYQQKPGNAPRLL IS (SEQ ID NO: 101)	GFPSRFSGSGSGKDYTLS ITSLQTEDVATYYC (SEQ ID NO: 114)	FGGGTRLEIK (SEQ ID NO: 127)
3E11	DVZMTQTPLSLPVS LGDQASISC (SEQ ID NO: 89)	WYLQKPGQSPKLLI Y (SEQ ID NO: 102)	GVPDRFSGSGAGTDFTL KISRVEAEDLGVYFC (SEQ ID NO: 115)	FGGGTKLEIK (SEQ ID NO: 128)
4A1	DVVMTQTPLSLPVS LGDQASISC (SEQ ID NO: 90)	WYLQKPGQSPKLLI Y (SEQ ID NO: 103)	GVPDRFSGSGSGTDFTL KISRVEAEDLGVYFC (SEQ ID NO: 116)	FGGGTKLEIK (SEQ ID NO: 129)
4D7	NZMTQFQKFMSTS VGDRVSLTC (SEQ ID NO: 91)	GFQQKPGHSPKAGI Y (SEQ ID NO: 104)	GVQDRFTARGLGSDFILP ITTZQLEDLAEYZC (SEQ ID NO: 117)	FGGGTKLEIK (SEQ ID NO: 130)
4E3	GZQNVLTQSPAILS ASPGEKVTMTC (SEQ ID NO: 92)	WYQQKPGSSPRLLI F (SEQ ID NO: 105)	GVPIRFSGSGSGTSYSLTI SRMEAEDTATYYC (SEQ ID NO: 118)	FGAGTKLELK (SEQ ID NO: 131)

[0610]

Ab ID	VL FR1	VL FR2	VL FR3	VL FR4
7A3	DIQMTQZPATLSVT PGDRVSLSC (SEQ ID NO: 93)	WYHQKSHESPRLLI K (SEQ ID NO: 106)	GIPSRFSGSGSGSDFTLTI NSVEPEDVGVYYC (SEQ ID NO: 119)	FGGGTKLEIK (SEQ ID NO: 132)
7E11	DIQMTQSPASQSAS LGESVTITC (SEQ ID NO: 94)	WYQQKPGKSPQLLI Y (SEQ ID NO: 107)	GVPSRFSGSGSGTKFSFK ISSLQAEDFVSYYC (SEQ ID NO: 120)	FGGGTKLEIK (SEQ ID NO: 133)
7F12	DVLMTQTPLSLPVS LGDQASISC (SEQ ID NO: 95)	WYLQKPGQSPKLLI Y (SEQ ID NO: 108)	GVPDRFSGSGAGTDFTL KISRVEAEDLGVYFC (SEQ ID NO: 121)	FGGGTKLEIK (SEQ ID NO: 134)
10B5	ZMTQFTSSMSGSEG DRVTISH (SEQ ID NO: 96)	WYEQKADGTANLII Y (SEQ ID NO: 109)	GZPSRLSGZGWVTDYFL PIHTSEQEDRGSYFC (SEQ ID NO: 122)	FGGGTKLEIK (SEQ ID NO: 135)
10G8	DIQMTQFPATLSGT PGDRVZLSR (SEQ ID NO: 97)	WYQQKSHESPRLZI K (SEQ ID NO: 110)	GIPSRFSGSGSGSDFTLSI NTVEPEDVGVYYC (SEQ ID NO: 123)	FGGGTKLEIK (SEQ ID NO: 136)

[0611] 表3B:抗Siglec-7抗体的EU或Kabat重链框架序列

[0612]

Ab ID	VH FR1	VH FR2	VH FR3	VH FR4
1A12	QVQLQQSGSELRSP GSSVKLSCKDFD (SEQ ID NO: 137)	WVRQKPGHGFE W (SEQ ID NO: 150)	EKFEDKATLDADTVSN TAYLELNSLTSEDSAIY YC (SEQ ID NO: 163)	WGQGTLVTVSA (SEQ ID NO: 176)
1E8	QVQLQQSGAELVR PGASVKLSCSASG (SEQ ID NO: 138)	WIKQRPLQGLEW (SEQ ID NO: 151)	PKFQDKAFLTADTSSTT AYLQLSSLTSEDTAIYY C (SEQ ID NO: 164)	WGQGTLVTVSA (SEQ ID NO: 177)
2G1	EVKLVESGGTLVKP GGSLKISCAASG (SEQ ID NO: 139)	WVRQNPEKRLE W (SEQ ID NO: 152)	DIFKGRFTISRDDAKNA LYLQMSSLRSEDTALY YC (SEQ ID NO: 165)	WGAGATVTVSS (SEQ ID NO: 178)
2G4	QVQLQQSGSELRSP GSSVKLSCKDFD (SEQ ID NO: 140)	WVRQKPGHGFE W (SEQ ID NO: 153)	EKFEDKATLDADTVSN TAYLELNSLTSEDSAIY YC (SEQ ID NO: 166)	WGQGTLVTVSA (SEQ ID NO: 179)
3E11	QVQLQQSGAELAR PGASVKLSCKASG (SEQ ID NO: 141)	WVKQRTGQGLE W (SEQ ID NO: 154)	ENYRVKATLTADKSSS TAYMQLFSLTSEDSAV YFC (SEQ ID NO: 167)	WGHGTLVTVSA (SEQ ID NO: 180)
4A1	QVQLQQSGSELRSP GSSVKLSCKDFD (SEQ ID NO: 142)	WVRQKPGHGFE W (SEQ ID NO: 155)	EKFEDKATLDADTVSN TAYLELNSLTSEDSAIY YC (SEQ ID NO: 168)	WGQGTLVTVSA (SEQ ID NO: 181)
4D7	QVQLQQSGAELVK PGASVKLSCKTSG (SEQ ID NO: 143)	WVKQRPGQGLE W (SEQ ID NO: 156)	EKFKSKATLTVDTSSST AYMQLSSLTSDDSAVY YC (SEQ ID NO: 169)	WGQGTSVTVSS (SEQ ID NO: 182)
4E3	EVKLADSGGALVN PGGSLKISCAVSG (SEQ ID NO: 144)	WVRQNPEKRLE W (SEQ ID NO: 157)	DSVKGRFTISRDNAKN ALYLQMSSLRSEDTAL YYC (SEQ ID NO: 170)	WGAGATVTVSS (SEQ ID NO: 183)
7A3	LVZSGGALVKPGGS LKLSCAASG (SEQ ID NO: 145)	WVRQTPEKRLE W (SEQ ID NO: 158)	DSVKGRFTISRDNARNT LYLQMSSLRSKDTAMY YC (SEQ ID NO: 171)	WGAGTTVTVSS (SEQ ID NO: 184)
7E11	QVQLKQSGPVLVA PSQSLSITCTVSG (SEQ ID NO: 146)	WVRQFPGKGLE W (SEQ ID NO: 159)	SVLMSRLSISKDNSKSQ VFLKMNSLQTDDTAMY YC (SEQ ID NO: 172)	WGQGTLVTVSA (SEQ ID NO: 185)
7F12	QVQLQQSGSELRSP GSSVKLSCKDFD (SEQ ID NO: 147)	WVRQKPGHGFE W (SEQ ID NO: 160)	EKFEDKATLDADTVSN TAYLELNSLTSEDSAIY YC (SEQ ID NO: 173)	WGQGTLVTVSA (SEQ ID NO: 186)
10B5	QVQLQQSGPELVKP GASVKISCKASG (SEQ ID NO: 148)	WVRQRPGKGLD W (SEQ ID NO: 161)	GKFKDKATLTEDKSSST AYMQLSSLTSEDSAVY FC (SEQ ID NO: 174)	WGQGTTLTVSS (SEQ ID NO: 187)

[0613]

Ab ID	VH FR1	VH FR2	VH FR3	VH FR4
10G8	EVKLVEFGGALVK PGGSLKLSCAALG (SEQ ID NO: 149)	RVRQTPEKREEG (SEQ ID NO: 162)	DSAKDRHPIFRDNARNT LYLQMSSLRSKDTAMY YC (SEQ ID NO: 175)	WGAGTTVTVSS (SEQ ID NO: 188)

[0614] Siglec-7抗体结合的表征

[0615] Siglec-7抗体的初始表征涉及确定其结合人原代单核细胞、人原代巨噬细胞、人

原代树突细胞、人原代嗜中性粒细胞和人原代天然杀伤(NK)细胞上表达的Siglec-7的能力。收获细胞，在96孔板中以10^6/ml涂铺，并在含有2%FBS、2mM EDTA和10μg/ml Mab以及Fc封闭试剂的100ul PBS中在冰中孵育1小时。将细胞洗涤两次并在含有2%FBS、2mM EDTA和5ug/ml PE-缀合的二级抗体的100ul PBS中在冰上孵育30分钟。将细胞在冷PBS中洗涤两次并通过BD FACS Canto上的流式细胞术进行分析。使用FlowJo(TreeStar)软件10.0.7版进行MFI值的数据分析和计算。

[0616] FACS染色分析表明Siglec-7在包括人原代单核细胞、巨噬细胞、树突细胞、嗜中性粒细胞和NK细胞的原代骨髓细胞和淋巴样细胞上表达(图4)。

[0617] 表4A展示抗体与表达Siglec-7的人原代细胞的结合。表4A中列出了由Siglec-7抗体结合的细胞类型的阳性结合百分比和平均荧光强度(MFI)值。将结合与同种型对照进行比较。所述抗体与人原代单核细胞、人原代树突细胞和人原代巨噬细胞结合。在表4A中，“缓冲液”是指仅用同上所述的PBS缓冲液处理的细胞；“二级Ab”是指仅用PE缀合的二级抗体处理的细胞；“mIgG1”、“mIgG2a”和“mIgG2b”是指同种型对照抗体；并且“RDS7”是指可商购获得的抗Siglec-7抗体Fab1138(R&D Systems；目录号MAB 1138)。图5A展示抗体与人原代树突细胞的结合。

[0618] 表4A:Siglee-7抗体与人原代细胞的结合

[0619]

抗体	单核细胞		树突细胞		巨噬细胞	
	阳性%	MFI	阳性%	MFI	阳性%	MFI
1A12	99.3	505	99.7	6092	99.4	15788
1E8	99.3	428	99.7	2936	99.5	5446
2G1	99.4	577	99.7	10245	99.5	25666
2G4	99.3	512	99.7	5752	99.5	15472
3E11	98.7	380	99.6	2522	99.6	4043
4A1	99.4	486	99.7	5450	99.3	14578
4D7	90.5	262	26.1	250	99.4	4260
4E3	98.6	362	99.7	2648	99.6	4150
7A3	97.9	407	99.7	956	99.7	2841
7E11	93.3	278	98.4	845	99.8	2381
7F12	99.3	472	99.7	4995	99.3	12325
10B5	99.2	417	99.6	3226	99.7	6028
10G8	99.1	523	99.5	897	99.7	3277
对照						
缓冲液	0.2	63	0.2	39	0.0	122
二级 Ab	9.1	107	2.4	91	23.9	398
mIgG1	10.6	115	2.8	83	21.7	368
mIgG2a	14.0	141	4.5	134	35.8	648
mIgG2b	13.9	128	5.0	130	79.5	2059
RDS7	19.9	175	73.9	1452	98.6	4219

[0620]

[0621] 将两种Siglec-7抗体4E3和10B5针对浓度范围为6.67-0.00325nM的12点曲线进行2倍滴定以评估结合并计算与原代人树突细胞结合的半最大浓度(EC_{50})(图5B)。将抗体连续稀释并与在含有1%BSA、1mM EDTA的PBS中的细胞在冰上(4℃)一起孵育1小时。将细胞沉淀

并用在缓冲液中1:200稀释的与APC缀合的山羊抗小鼠二级抗体(BD Biosciences)重新悬浮。将二级检测抗体在冰上(4℃)孵育30分钟,然后将细胞在缓冲液中洗涤3次,然后在BD FACS Canto上分析APC MFI。用FlowJo软件(TreeStar)对数据进行分析。

[0622] 体外研究证明抗Siglec-7抗体4E3和10B5与来自两个不同供体的人树突细胞结合(表4B)。抗Siglec-7抗体4E3以0.3nM的EC_{50}(95%置信区间范围为0.1701至0.4313nM)与来自359号供体的人树突细胞结合,而抗Siglec-7抗体10B5以1.58nM的EC_{50}(95%置信区间范围为0.7821至1.533nM)结合来自此供体的树突细胞。抗Siglec-7抗体4E3和10B5分别以0.3364(95%置信区间为0.1052至0.5677)和1.427(95%置信区间为0.9209至1.933)的EC_{50}结合至来自第二供体的树突细胞。

[0623] 表4B:两种Siglec-7对与原代人树突细胞结合的EC_{50}测定

[0624]

供体编号	抗体:4E3		抗体:10B5	
	EC_{50}值(nM)	95% CI (nM)	EC_{50}值(nM)	95% CI (nM)
358	0.3364	0.1052 至 0.5677	1.427	0.9209 至 1.933
359	0.3007	0.1701 至 0.4313	1.158	0.7821 至 1.533

[0625] 在测定两种抗Siglec-7抗体在人树突细胞上的EC_{50}后,通过经由表面等离子体共振(SPR)测定测量它们的K_D来测定13种抗Siglec-7抗体对Siglec-7的结合亲和力。在BiaCore T200仪器上以10Hz的速率在25℃下收集SPR数据。使用BiaCore T200评价软件2.0版进行数据分析。使用HBS-EP+(100mM HEPES,1.5M NaCl,30mM EDTA,0.5%v/v表面活性剂P20,pH 7.4)作为运行缓冲液并用于制备试剂。

[0626] 在固定有抗小鼠IgG的CM5传感器芯片(GE Healthcare)上捕获针对Siglec-7的小鼠源性抗体(25nM)(60秒接触时间,30μL/分钟流速,0秒稳定时间)。然后使组氨酸标记的人Siglec-7(NovoProtein)流过捕获的抗Siglec-7表面(120秒接触时间,30μL/分钟流速,300秒解离时间)。取决于从初始筛选获得的信息,抗原浓度范围为5nM至100nM。进行一式两份单浓度试验并用空白(0nM抗原)样品括起来。使用10mM甘氨酸-HCl(pH 1.7)(60秒接触时间,30μL/分钟流速,60秒稳定时间)在循环之间再生芯片表面。所得SPR信号作为来自空白流动池上进行的测量的响应差而获得。

[0627] 使用1:1相互作用模型进行单浓度动力学分析(Canziani,等人(2004)Analytical Biochemistry 325:301-307)以推导出每种抗体的缔合和解离速率常数(分别为k_a和k_d)。亲和常数(K_D)由比率k_d/k_a计算。对于一种抗体(克隆1E8),使用多重浓度方法(使用5种浓度的抗原,加上一个空白)验证了单一浓度分析。

[0628] 结果列于表5中。图6A显示描绘抗体亲和力的SPR传感图。

[0629] 表5:Siglec-7抗体亲和力

[0630]

抗体	mAb nM	Siglec-7 nM	K_D
1A12	25	100	0.6nM
1E8	25	5	17pM

2G1	25	20	0.1nM
2G4	25	50	0.4nM
3E11	25	25	1.0nM
4A1	25	35	0.3nM
4D7	25	100	2.9nM
4E3	25	25	0.3nM
7A3	25	20	1.0nM
7E11	25	100	9.5nM
7F12	25	35	0.4nM
10B5	25	100	3.0nM
10G8	25	10	0.6nM

[0631] 计算机抗体人源化

[0632] 抗体人源化用于通过序列和结构关系转化在不同物种中产生的抗体以最好地类似于人抗体,以便防止人施用中的免疫原性。来自不同物种的抗体共享允许将非人抗体的特异性决定区(SDR)移植到人抗体框架上的特征性序列和结构特征。这导致保留了非人抗体的特异性。人源化过程涉及鉴定非人抗体序列和特征,包括框架区和SDR。使用以下标准来人源化抗体:1)非人抗体与已知人抗体之间的框架区的相似性百分比,2)非人抗体与已知人抗体之间的SDR的长度相似性,3)用于产生人抗体的框架区的基因,以及4)先前在人源化中使用人抗体框架并作为治疗剂。框架区和SDR长度的相似性是重要的,因为差异可在抗体中产生可改变抗体的特异性的结构差异。已知用于产生人抗体框架的特异性基因对抗体的稳定性或特异性是有益的或有害的,并且因此被选择性地使用或避免。最后,具有良好耐受性和良好半衰期的的先前成功的人源化框架(包括在人治疗剂中使用的那些)可能成为未来成功人源化的候选物。

[0633] 如表6A和6B中所示,鉴定了抗体1A12、1E8、2G1、2G4、3E11、4A1、4D7、4E3、4E3H1、4E3H2、7A3、7E11、7F12、10B5、10B5L1、10B5H1以及10G8中的每种的10条人源化轻链和10条人源化重链可变区序列。在表6A和6B中,粗体字母表示CDR序列。

[0634] 表6A:人源化轻链可变区

[0635]

抗体变体	人源化序列
抗体 1A12	**抗体 1A12**
1A12V2-30	DVVMTQSPLSLPVTLGQPASISC**RSSQSLVHSTGNTYLH**WFQ QRPGQSPRRLIY**KVSNRFS**GVPDRFSGSGSGTDFTLKISRVEA EDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:189)
1A12V2-28	DIVMTQSPLSLPVTPGEPASISC**RSSQSLVHSTGNTYLH**WYL QKPGQSPQLLIY**KVSNRFS**GVPDRFSGSGSGTDFTLKISRVEA EDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:190)
1A12V4-1	DIVMTQSPDSLAVSLGERATINC**RSSQSLVHSTGNTYLH**WY QQKPGQPPKLLIY**KVSNRFS**GVPDRFSGSGSGTDFTLTISSLQ AEDVAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:191)
1A12V3-11	EIVLTQSPATLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQ QKPGQAPRLLIY**KVSNRFS**GIPARFSGSGSGTDFTLTISSLEPE DFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:192)
1A12V1-33	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQ QKPGKAPKLLIY**KVSNRFS**GVPSRFSGSGSGTDFTFTISSLQPE DIATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:193)
1A12V3-15	EIVMTQSPATLSVSPGERATLSC**RSSQSLVHSTGNTYLH**WY QQKPGQAPRLLIY**KVSNRFS**GIPARFSGSGSGTEFTLTISSLQS EDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:194)
1A12V1-5	DIQMTQSPSTLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WY QQKPGKAPKLLIY**KVSNRFS**GVPSRFSGSGSGTEFTLTISSLQP DDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:195)
1A12V1-9	DIQLTQSPSFLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQ QKPGKAPKLLIY**KVSNRFS**GVPSRFSGSGSGTEFTLTISSLQPE DFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:196)
1A12V1-39	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQ QKPGKAPKLLIY**KVSNRFS**GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:197)
1A12V3-20	EIVLTQSPGTLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQ QKPGQAPRLLIY**KVSNRFS**GIPDRFSGSGSGTDFTLTISRLEPE DFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:198)
抗体 1E8	**抗体 1E8**

[0636]

抗体变体	人源化序列
1E8V1-39	DIQMTQSPSSLSASVGDRVTITC**RASQSISDYLH**WYQQKPGK APKLLIY**YASQSIS**GVPSRFSGSGSGTDFTLTISSLQPEDFATY YC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:199)
1E8V1-5	DIQMTQSPSTLSASVGDRVTITC**RASQSISDYLH**WYQQKPGK APKLLIY**YASQSIS**GVPSRFSGSGSGTEFTLTISSLQPDDFATY YC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:200)
1E8V1-9	DIQLTQSPSFLSASVGDRVTITC**RASQSISDYLH**WYQQKPGK APKLLIY**YASQSIS**GVPSRFSGSGSGTEFTLTISSLQPEDFATY YC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:201)
1E8V3-11	EIVLTQSPATLSLSPGERATLSC**RASQSISDYLH**WYQQKPGQ APRLLIY**YASQSIS**GIPARFSGSGSGTDFTLTISSLEPEDFAVYY C**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:202)
1E8V1-33	DIQMTQSPSSLSASVGDRVTITC**RASQSISDYLH**WYQQKPGK APKLLIY**YASQSIS**GVPSRFSGSGSGTDFTFTISSLQPEDIATYY C**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:203)
1E8V3-15	EIVMTQSPATLSVSPGERATLSC**RASQSISDYLH**WYQQKPGQ APRLLIY**YASQSIS**GIPARFSGSGSGTEFTLTISSLQSEDFAVYY C**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:204)
1E8V3-20	EIVLTQSPGTLSLSPGERATLSC**RASQSISDYLH**WYQQKPGQ APRLLIY**YASQSIS**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYY C**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:205)
1E8V2-28	DIVMTQSPLSLPVTPGEPASISC**RASQSISDYLH**WYLQKPGQS PQLLIY**YASQSIS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVY YC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:206)
1E8V2-30	DVVMTQSPLSLPVTLGQPASISC**RASQSISDYLH**WFQQRPGQ SPRRLIY**YASQSIS**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:207)
1E8V4-1	DIVMTQSPDSLAVSLGERATINC**RASQSISDYLH**WYQQKPGQ PPKLLIY**YASQSIS**GVPDRFSGSGSGTDFTLTISSLQAEDVAVY YC**QKGLNFPLT**FGQGTKVEIK (SEQ ID NO:208)
抗体 2G1	**抗体 2G1**
2G1V3-11	EIVLTQSPATLSLSPGERATLSC**SANSSFIYMY**WYQQKPGQAP RLLIY**DTSNLAS**GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC **QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:209)
2G1V1-39	DIQMTQSPSSLSASVGDRVTITC**SANSSFIYMY**WYQQKPGKA PKLLIY**DTSNLAS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:210)
2G1V1-5	DIQMTQSPSTLSASVGDRVTITC**SANSSFIYMY**WYQQKPGKA PKLLIY**DTSNLAS**GVPSRFSGSGSGTEFTLTISSLQPDDFATYY C**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:211)
2G1V1-33	DIQMTQSPSSLSASVGDRVTITC**SANSSFIYMY**WYQQKPGKA PKLLIY**DTSNLAS**GVPSRFSGSGSGTDFTFTISSLQPEDIATYY C**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:212)
2G1V1-9	DIQLTQSPSFLSASVGDRVTITC**SANSSFIYMY**WYQQKPGKA PKLLIY**DTSNLAS**GVPSRFSGSGSGTEFTLTISSLQPEDFATYY C**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:213)
2G1V3-15	EIVMTQSPATLSVSPGERATLSC**SANSSFIYMY**WYQQKPGQA PRLLIY**DTSNLAS**GIPARFSGSGSGTEFTLTISSLQSEDFAVYY

抗体变体	人源化序列
	C**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:214)
2G1V3-20	EIVLTQSPGTLSLSPGERATLSC**SANSSFIYMY**WYQQKPGQAP RLLIY**DTSNLAS**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC **QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:215)
2G1V2-28	DIVMTQSPLSLPVTPGEPASISC**SANSSFIYMY**WYLQKPGQSP QLLIY**DTSNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVY YC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:216)
2G1V2-30	DVVMTQSPLSLPVTLGQPASISC**SANSSFIYMY**WFQQRPGQS PRRLIY**DTSNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVY YC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:217)
2G1V4-1	DIVMTQSPDSLAVSLGERATINC**SANSSFIYMY**WYQQKPGQP PKLLIY**DTSNLAS**GVPDRFSGSGSGTDFTLTISSLQAEDVAVY YC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:218)
抗体 2G4	**抗体 2G4**
2G4V1-5	DIQMTQSPSTLSASVGDRVTITC**KASDHINNWLA**WYQQKPG KAPKLLIY**GATSLET**GVPSRFSGSGSGTEFTLTISSLQPDDFAT YYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:219)
2G4V1-33	DIQMTQSPSSLSASVGDRVTITC**KASDHINNWLA**WYQQKPG KAPKLLIY**GATSLET**GVPSRFSGSGSGTDFTFTISSLQPEDIAT YYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:220)
2G4V1-39	DIQMTQSPSSLSASVGDRVTITC**KASDHINNWLA**WYQQKPG KAPKLLIY**GATSLET**GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:221)
2G4V1-9	DIQLTQSPSFLSASVGDRVTITC**KASDHINNWLA**WYQQKPG KAPKLLIY**GATSLET**GVPSRFSGSGSGTEFTLTISSLQPEDFAT YYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:222)
2G4V3-15	EIVMTQSPATLSVSPGERATLSC**KASDHINNWLA**WYQQKPG QAPRLLIY**GATSLET**GIPARFSGSGSGTEFTLTISSLQSEDFAV YYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:223)
2G4V3-11	EIVLTQSPATLSLSPGERATLSC**KASDHINNWLA**WYQQKPGQ APRLLIY**GATSLET**GIPARFSGSGSGTDFTLTISSLEPEDFAVY YC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:224)
2G4V3-20	EIVLTQSPGTLSLSPGERATLSC**KASDHINNWLA**WYQQKPGQ APRLLIY**GATSLET**GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:225)
2G4V4-1	DIVMTQSPDSLAVSLGERATINC**KASDHINNWLA**WYQQKPG QPPKLLIY**GATSLET**GVPDRFSGSGSGTDFTLTISSLQAEDVA VYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:226)
2G4V2-30	DVVMTQSPLSLPVTLGQPASISC**KASDHINNWLA**WFQQRPG QSPRRLIY**GATSLET**GVPDRFSGSGSGTDFTLKISRVEAEDVG VYYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:227)
2G4V2-28	DIVMTQSPLSLPVTPGEPASISC**KASDHINNWLA**WYLQKPGQ SPQLLIY**GATSLET**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**HQYWNTPYT**FGQGTKVEIK (SEQ ID NO:228)
抗体 3E11	**抗体 3E11**
3E11V2-30	DVVMTQSPLSLPVTLGQPASISC**RSSQSLVHSTGNTYLH**WFQ QRPGQSPRRLIY**KVSNRFC**GVPDRFSGSGSGTDFTLKISRVEA EDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:229)

[0637]

[0638]

抗体变体	人源化序列
3E11V2-28	DIVMTQSPLSLPVTPGEPASISC**RSSQSLVHSTGNTYLH**WYL QKPGQSPQLLIY**KVSNRFC**GVPDRFSGSGSGTDFTLKISRVEA EDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:230)
3E11V4-1	DIVMTQSPDSLAVSLGERATINC**RSSQSLVHSTGNTYLH**WY QQKPGQPPKLLIY**KVSNRFC**GVPDRFSGSGSGTDFTLTISSLQ AEDVAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:231)
3E11V3-11	EIVLTQSPATLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQ QKPGQAPRLLIY**KVSNRFC**GIPARFSGSGSGTDFTLTISSLEPE DFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:232)
3E11V1-33	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQ QKPGKAPKLLIY**KVSNRFC**GVPSRFSGSGSGTDFTFTISSLQP EDIATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:233)
3E11V3-15	EIVMTQSPATLSVSPGERATLSC**RSSQSLVHSTGNTYLH**WY QQKPGQAPRLLIY**KVSNRFC**GIPARFSGSGSGTEFTLTISSLQS EDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:234)
3E11V3-20	EIVLTQSPGTLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQ QKPGQAPRLLIY**KVSNRFC**GIPDRFSGSGSGTDFTLTISRLEPE DFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:235)
3E11V1-9	DIQLTQSPSFLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQ QKPGKAPKLLIY**KVSNRFC**GVPSRFSGSGSGTEFTLTISSLQPE DFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:236)
3E11V1-39	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQ QKPGKAPKLLIY**KVSNRFC**GVPSRFSGSGSGTDFTLTISSLQP EDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:237)
3E11V1-5	DIQMTQSPSTLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WY QQKPGKAPKLLIY**KVSNRFC**GVPSRFSGSGSGTEFTLTISSLQ PDDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:238)
抗体 4A1	**抗体 4A1**
4A1V2-30	DVVMTQSPLSLPVTLGQPASISC**RSSQSLVHSTGNIYLH**WFQ QRPGQSPRRLIY**KVSNRFZ**GVPDRFSGSGSGTDFTLKISRVEA EDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:239)
4A1V2-28	DIVMTQSPLSLPVTPGEPASISC**RSSQSLVHSTGNIYLH**WYLQ KPGQSPQLLIY**KVSNRFZ**GVPDRFSGSGSGTDFTLKISRVEAE DVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:240)
4A1V4-1	DIVMTQSPDSLAVSLGERATINC**RSSQSLVHSTGNIYLH**WYQ QKPGQPPKLLIY**KVSNRFZ**GVPDRFSGSGSGTDFTLTISSLQA EDVAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:241)
4A1V3-11	EIVLTQSPATLSLSPGERATLSC**RSSQSLVHSTGNIYLH**WYQ QKPGQAPRLLIY**KVSNRFZ**GIPARFSGSGSGTDFTLTISSLEPE DFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:242)
4A1V1-33	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNIYLH**WYQ QKPGKAPKLLIY**KVSNRFZ**GVPSRFSGSGSGTDFTFTISSLQPE DIATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:243)
4A1V3-15	EIVMTQSPATLSVSPGERATLSC**RSSQSLVHSTGNIYLH**WYQ QKPGQAPRLLIY**KVSNRFZ**GIPARFSGSGSGTEFTLTISSLQSE DFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:244)
4A1V3-20	EIVLTQSPGTLSLSPGERATLSC**RSSQSLVHSTGNIYLH**WYQ QKPGQAPRLLIY**KVSNRFZ**GIPDRFSGSGSGTDFTLTISRLEPE

[0639]

抗体变体	人源化序列
	DFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:245)
4A1V1-5	DIQMTQSPSTLSASVGDRVTITC**RSSQSLVHSTGNIYLH**WYQ QKPGKAPKLLIY**KVSNRFZ**GVPSRFSGSGSGTEFTLTISSLQP DDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:246)
4A1V1-9	DIQLTQSPSFLSASVGDRVTITC**RSSQSLVHSTGNIYLH**WYQ QKPGKAPKLLIY**KVSNRFZ**GVPSRFSGSGSGTEFTLTISSLQPE DFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:247)
4A1V1-39	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNIYLH**WYQ QKPGKAPKLLIY**KVSNRFZ**GVPSRFSGSGSGTDFTLTISSLQP EDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:248)
抗体 4D7	**抗体 4D7**
4D7V3-15	EIVMTQSPATLSVSPGERATLSC**KASQKVGTNVA**WYQQKPG QAPRLLIY**SASTRHR**GIPARFSGSGSGTEFTLTISSLQSEDFAV YYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:249)
4D7V3-11	EIVLTQSPATLSLSPGERATLSC**KASQKVGTNVA**WYQQKPG QAPRLLIY**SASTRHR**GIPARFSGSGSGTDFTLTISSLEPEDFAV YYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:250)
4D7V1-9	DIQLTQSPSFLSASVGDRVTITC**KASQKVGTNVA**WYQQKPG KAPKLLIY**SASTRHR**GVPSRFSGSGSGTEFTLTISSLQPEDFAT YYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:251)
4D7V1-5	DIQMTQSPSTLSASVGDRVTITC**KASQKVGTNVA**WYQQKPG KAPKLLIY**SASTRHR**GVPSRFSGSGSGTEFTLTISSLQPDDFAT YYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:252)
4D7V1-39	DIQMTQSPSSLSASVGDRVTITC**KASQKVGTNVA**WYQQKPG KAPKLLIY**SASTRHR**GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:253)
4D7V1-33	DIQMTQSPSSLSASVGDRVTITC**KASQKVGTNVA**WYQQKPG KAPKLLIY**SASTRHR**GVPSRFSGSGSGTDFTFTISSLQPEDIAT YYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:254)
4D7V3-20	EIVLTQSPGTLSLSPGERATLSC**KASQKVGTNVA**WYQQKPG QAPRLLIY**SASTRHR**GIPDRFSGSGSGTDFTLTISRLEPEDFAV YYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:255)
4D7V4-1	DIVMTQSPDSLAVSLGERATINC**KASQKVGTNVA**WYQQKPG QPPKLLIY**SASTRHR**GVPDRFSGSGSGTDFTLTISSLQAEDVA VYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:256)
4D7V2-28	DIVMTQSPLSLPVTPGEPASISC**KASQKVGTNVA**WYLQKPGQ SPQLLIY**SASTRHR**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:257)
4D7V2-30	DVVMTQSPLSLPVTLGQPASISC**KASQKVGTNVA**WFQQRPG QSPRRLIY**SASTRHR**GVPDRFSGSGSGTDFTLKISRVEAEDVG VYYC**HQGNSVQYT**FGQGTKVEIK (SEQ ID NO:258)
抗体 4E3	**抗体 4E3**
4E3V3-11	EIVLTQSPATLSLSPGERATLSC**SANSSFTYMY**WYQQKPGQA PRLLIY**DTSNLAS**GIPARFSGSGSGTDFTLTISSLEPEDFAVYY C**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:259)
4E3V1-33	DIQMTQSPSSLSASVGDRVTITC**SANSSFTYMY**WYQQKPGK APKLLIY**DTSNLAS**GVPSRFSGSGSGTDFTFTISSLQPEDIATY YC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:260)

[0640]

抗体变体	人源化序列
4E3V1-39	DIQMTQSPSSLSASVGDRVTITC**SANSSFTYMY**WYQQKPGK APKLLIY**DTSNLAS**GVPSRFSGSGSGTDFTLTISSLQPEDFATY YC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:261)
4E3V1-5	DIQMTQSPSTLSASVGDRVTITC**SANSSFTYMY**WYQQKPGK APKLLIY**DTSNLAS**GVPSRFSGSGSGTEFTLTISSLQPDDFATY YC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:262)
4E3V1-9	DIQLTQSPSFLSASVGDRVTITC**SANSSFTYMY**WYQQKPGKA PKLLIY**DTSNLAS**GVPSRFSGSGSGTEFTLTISSLQPEDFATYY C**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:263)
4E3V3-15	EIVMTQSPATLSVSPGERATLSC**SANSSFTYMY**WYQQKPGQ APRLLIY**DTSNLAS**GIPARFSGSGSGTEFTLTISSLQSEDFAVY YC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:264)
4E3V3-20	EIVLTQSPGTLSLSPGERATLSC**SANSSFTYMY**WYQQKPGQA PRLLIY**DTSNLAS**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYY C**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:265)
4E3V2-28	DIVMTQSPLSLPVTPGEPASISC**SANSSFTYMY**WYLQKPGQSP QLLIY**DTSNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVY YC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:266)
4E3V2-30	DVVMTQSPLSLPVTLGQPASISC**SANSSFTYMY**WFQQRPGQS PRRLIY**DTSNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVY YC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:267)
4E3V4-1	DIVMTQSPDSLAVSLGERATINC**SANSSFTYMY**WYQQKPGQ PPKLLIY**DTSNLAS**GVPDRFSGSGSGTDFTLTISSLQAEDVAV YYC**QQWSSSPLT**FGQGTKVEIK (SEQ ID NO:268)
4E3L1	EIVLTQSPATLSLSPGERATLSC**SANSSFTYMY**WYQQKPGQA PRLLIY**DTSNLAS**GIPARFSGSGSGTDFTLTISSLEPEDFAVYY C**QQWSSSPLT**FGQGTKLEIK (SEQ ID NO:484)
4E3L2	EIVLTQSPATLSLSPGERVTMSC**SANSSFTYMY**WYQQKPGQA PRLLIY**DTSNLAS**GVPARFSGSGSGTDYTLTISSMEPEDFAVY YC**QQWSSSPLT**FGQGTKLEIK (SEQ ID NO:485)
4E3L3	EIVLTQSPATLSLSPGERVTMSC**SANSSFTYMY**WYQQKPGQA PRLLIF**DTSNLAS**GVPARFSGSGSGTDYTLTISSMEPEDFAVY YC**QQWSSSPLT**FGQGTKLELK (SEQ ID NO:486)
抗体 7A3	**抗体 7A3**
7A3V1-39	DIQMTQSPSSLSASVGDRVTITC**RASQSISEYLH**WYQQKPGK APKLLIY**FASQSIC**GVPSRFSGSGSGTDFTLTISSLQPEDFATY YC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:269)
7A3V1-9	DIQLTQSPSFLSASVGDRVTITC**RASQSISEYLH**WYQQKPGK APKLLIY**FASQSIC**GVPSRFSGSGSGTEFTLTISSLQPEDFATY YC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:270)
7A3V1-5	DIQMTQSPSTLSASVGDRVTITC**RASQSISEYLH**WYQQKPGK APKLLIY**FASQSIC**GVPSRFSGSGSGTEFTLTISSLQPDDFATY YC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:271)
7A3V3-11	EIVLTQSPATLSLSPGERATLSC**RASQSISEYLH**WYQQKPGQ APRLLIY**FASQSIC**GIPARFSGSGSGTDFTLTISSLEPEDFAVYY C**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:272)
7A3V1-33	DIQMTQSPSSLSASVGDRVTITC**RASQSISEYLH**WYQQKPGK APKLLIY**FASQSIC**GVPSRFSGSGSGTDFTFTISSLQPEDIATYY

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抗体变体	人源化序列
	C**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:273)
7A3V3-15	EIVMTQSPATLSVSPGERATLSC**RASQSISEYLH**WYQQKPGQ APRLLIY**FASQSIC**GIPARFSGSGSGTEFTLTISSLQSEDFAVYY C**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:274)
7A3V3-20	EIVLTQSPGTLSLSPGERATLSC**RASQSISEYLH**WYQQKPGQ APRLLIY**FASQSIC**GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:275)
7A3V2-30	DVVMTQSPLSLPVTLGQPASISC**RASQSISEYLH**WFQQRPGQ SPRRLIY**FASQSIC**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:276)
7A3V2-28	DIVMTQSPLSLPVTPGEPASISC**RASQSISEYLH**WYLQKPGQS PQLLIY**FASQSIC**GVPDRFSGSGSGTDFTLKISRVEAEDVGVY YC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:277)
7A3V4-1	DIVMTQSPDSLAVSLGERATINC**RASQSISEYLH**WYQQKPGQ PPKLLIY**FASQSIC**GVPDRFSGSGSGTDFTLTISSLQAEDVAVY YC**QNGHNFPYT**FGQGTKVEIK (SEQ ID NO:278)
抗体 7E11	**抗体 7E11**
7E11V1-5	DIQMTQSPSTLSASVGDRVTITC**LASQTIGTWLA**WYQQKPG KAPKLLIY**AATSLAD**GVPSRFSGSGSGTEFTLTISSLQPDDFAT YYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:279)
7E11V1-39	DIQMTQSPSSLSASVGDRVTITC**LASQTIGTWLA**WYQQKPG KAPKLLIY**AATSLAD**GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:280)
7E11V1-9	DIQLTQSPSFLSASVGDRVTITC**LASQTIGTWLA**WYQQKPGK APKLLIY**AATSLAD**GVPSRFSGSGSGTEFTLTISSLQPEDFATY YC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:281)
7E11V3-15	EIVMTQSPATLSVSPGERATLSC**LASQTIGTWLA**WYQQKPG QAPRLLIY**AATSLAD**GIPARFSGSGSGTEFTLTISSLQSEDFAV YYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:282)
7E11V3-11	EIVLTQSPATLSLSPGERATLSC**LASQTIGTWLA**WYQQKPGQ APRLLIY**AATSLAD**GIPARFSGSGSGTDFTLTISSLEPEDFAVY YC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:283)
7E11V1-33	DIQMTQSPSSLSASVGDRVTITC**LASQTIGTWLA**WYQQKPG KAPKLLIY**AATSLAD**GVPSRFSGSGSGTDFTFTISSLQPEDIAT YYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:284)
7E11V3-20	EIVLTQSPGTLSLSPGERATLSC**LASQTIGTWLA**WYQQKPGQ APRLLIY**AATSLAD**GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:285)
7E11V2-28	DIVMTQSPLSLPVTPGEPASISC**LASQTIGTWLA**WYLQKPGQ SPQLLIY**AATSLAD**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:286)
7E11V4-1	DIVMTQSPDSLAVSLGERATINC**LASQTIGTWLA**WYQQKPG QPPKLLIY**AATSLAD**GVPDRFSGSGSGTDFTLTISSLQAEDVA VYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:287)
7E11V2-30	DVVMTQSPLSLPVTLGQPASISC**LASQTIGTWLA**WFQQRPG QSPRRLIY**AATSLAD**GVPDRFSGSGSGTDFTLKISRVEAEDVG VYYC**QQLYSTPYT**FGQGTKVEIK (SEQ ID NO:288)
抗体 7F12	**抗体 7F12**

[0642]

抗体变体	人源化序列
7F12V2-30	DVVMTQSPLSLPVTLGQPASISC**RSSQSLVHSTGNTYLH**WFQ QRPGQSPRRLIY**KVSNRFS**GVPDRFSGSGSGTDFTLKISRVEA EDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:289)
7F12V2-28	DIVMTQSPLSLPVTPGEPASISC**RSSQSLVHSTGNTYLH**WYL QKPGQSPQLLIY**KVSNRFS**GVPDRFSGSGSGTDFTLKISRVEA EDVGVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:290)
7F12V4-1	DIVMTQSPDSLAVSLGERATINC**RSSQSLVHSTGNTYLH**WY QQKPGQPPKLLIY**KVSNRFS**GVPDRFSGSGSGTDFTLTISSLQ AEDVAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:291)
7F12V3-11	EIVLTQSPATLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQ QKPGQAPRLLIY**KVSNRFS**GIPARFSGSGSGTDFTLTISSLEPE DFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:292)
7F12V1-33	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQ QKPGKAPKLLIY**KVSNRFS**GVPSRFSGSGSGTDFTFTISSLQPE DIATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:293)
7F12V3-15	EIVMTQSPATLSVSPGERATLSC**RSSQSLVHSTGNTYLH**WY QQKPGQAPRLLIY**KVSNRFS**GIPARFSGSGSGTEFTLTISSLQS EDFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:294)
7F12V1-5	DIQMTQSPSTLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WY QQKPGKAPKLLIY**KVSNRFS**GVPSRFSGSGSGTEFTLTISSLQP DDFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:295)
7F12V1-9	DIQLTQSPSFLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQ QKPGKAPKLLIY**KVSNRFS**GVPSRFSGSGSGTEFTLTISSLQPE DFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:296)
7F12V1-39	DIQMTQSPSSLSASVGDRVTITC**RSSQSLVHSTGNTYLH**WYQ QKPGKAPKLLIY**KVSNRFS**GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:297)
7F12V3-20	EIVLTQSPGTLSLSPGERATLSC**RSSQSLVHSTGNTYLH**WYQ QKPGQAPRLLIY**KVSNRFS**GIPDRFSGSGSGTDFTLTISRLEPE DFAVYYC**SQNTHVPYT**FGQGTKVEIK (SEQ ID NO:298)
抗体 10B5	**抗体 10B5**
10B5V1-39	DIQMTQSPSSLSASVGDRVTITC**RASQDISZYLN**WYQQKPGK APKLLIY**LSSRLHS**GVPSRFSGSGSGTDFTLTISSLQPEDFATY YC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:299)
10B5V1-33	DIQMTQSPSSLSASVGDRVTITC**RASQDISZYLN**WYQQKPGK APKLLIY**LSSRLHS**GVPSRFSGSGSGTDFTFTISSLQPEDIATY YC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:300)
10B5V1-9	DIQLTQSPSFLSASVGDRVTITC**RASQDISZYLN**WYQQKPGK APKLLIY**LSSRLHS**GVPSRFSGSGSGTEFTLTISSLQPEDFATY YC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:301)
10B5V1-5	DIQMTQSPSTLSASVGDRVTITC**RASQDISZYLN**WYQQKPGK APKLLIY**LSSRLHS**GVPSRFSGSGSGTEFTLTISSLQPDDFATY YC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:302)
10B5V3-11	EIVLTQSPATLSLSPGERATLSC**RASQDISZYLN**WYQQKPGQ APRLLIY**LSSRLHS**GIPARFSGSGSGTDFTLTISSLEPEDFAVY YC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:303)
10B5V3-15	EIVMTQSPATLSVSPGERATLSC**RASQDISZYLN**WYQQKPGQ APRLLIY**LSSRLHS**GIPARFSGSGSGTEFTLTISSLQSEDFAVY

抗体变体	人源化序列
	YC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:304)
10B5V3-20	EIVLTQSPGTLSLSPGERATLSC**RASQDISZYLN**WYQQKPGQ APRLLIY**LSSRLHS**GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:305)
10B5V2-28	DIVMTQSPLSLPVTPGEPASISC**RASQDISZYLN**WYLQKPGQS PQLLIY**LSSRLHS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVY YC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:306)
10B5V2-30	DVVMTQSPLSLPVTLGQPASISC**RASQDISZYLN**WFQQRPGQ SPRRLIY**LSSRLHS**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:307)
10B5V4-1	DIVMTQSPDSLAVSLGERATINC**RASQDISZYLN**WYQQKPGQ PPKLLIY**LSSRLHS**GVPDRFSGSGSGTDFTLTISSLQAEDVAV YYC**QQGHTGAWT**FGQGTKVEIK (SEQ ID NO:308)
10B5L1	DIQMTQSPSSLSASVGDRVTITC**RASQDINTYLN**WYQQKPGK APKLLIY**YTSRLHS**GVPSRFSGSGSGTDFTLTISSLQPEDFATY YC**QQGNTLPWT**FGQGTKLEIK (SEQ ID NO:487)
10B5L2	DIQMTQSPSSLSASVGDRVTITC**RASQDINTYLN**WYQQKPGK APKLLIY**YTSRLHS**GVPSRFSGSGSGTDYTLTISSLQPEDFATY YC**QQGNTLPWT**FGQGTKLEIK (SEQ ID NO:488)
10B5L3	DVQMTQSPSSLSASVGDRVTITC**RASQDINTYLN**WYQQKPG KAPKLLIY**YTSRLHS**GVPSRFSGSGSGTDYTLTISSLQPEDFAT YYC**QQGNTLPWT**FGQGTKLEIK (SEQ ID NO:489)
抗体 10G8	**抗体 10G8**
10G8V1-39	DIQMTQSPSSLSASVGDRVTITC**RASQSIREYLH**WYQQKPGK APKLLIY**FASQSIC**GVPSRFSGSGSGTDFTLTISSLQPEDFATY YC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:309)
10G8V1-9	DIQLTQSPSFLSASVGDRVTITC**RASQSIREYLH**WYQQKPGK APKLLIY**FASQSIC**GVPSRFSGSGSGTEFTLTISSLQPEDFATY YC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:310)
10G8V3-11	EIVLTQSPATLSLSPGERATLSC**RASQSIREYLH**WYQQKPGQ APRLLIY**FASQSIC**GIPARFSGSGSGTDFTLTISSLEPEDFAVYY C**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:311)
10G8V1-5	DIQMTQSPSTLSASVGDRVTITC**RASQSIREYLH**WYQQKPGK APKLLIY**FASQSIC**GVPSRFSGSGSGTEFTLTISSLQPDDFATY YC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:312)
10G8V3-15	EIVMTQSPATLSVSPGERATLSC**RASQSIREYLH**WYQQKPGQ APRLLIY**FASQSIC**GIPARFSGSGSGTEFTLTISSLQSEDFAVYY C**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:313)
10G8V1-33	DIQMTQSPSSLSASVGDRVTITC**RASQSIREYLH**WYQQKPGK APKLLIY**FASQSIC**GVPSRFSGSGSGTDFTFTISSLQPEDIATYY C**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:314)
10G8V3-20	EIVLTQSPGTLSLSPGERATLSC**RASQSIREYLH**WYQQKPGQ APRLLIY**FASQSIC**GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:315)
10G8V4-1	DIVMTQSPDSLAVSLGERATINC**RASQSIREYLH**WYQQKPG QPPKLLIY**FASQSIC**GVPDRFSGSGSGTDFTLTISSLQAEDVAV YYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:316)
10G8V2-30	DVVMTQSPLSLPVTLGQPASISC**RASQSIREYLH**WFQQRPGQ

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抗体变体	人源化序列
	SPRRLIY**FASQSIC**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:317)
10G8V2-28	DIVMTQSPLSLPVTPGEPASISC**RASQSIREYLH**WYLQKPGQS PQLLIY**FASQSIC**GVPDRFSGSGSGTDFTLKISRVEAEDVGVY YC**QKAHNFPYT**FGQGTKVEIK (SEQ ID NO:318)

[0645] 表6B:人源化重链可变区

抗体变体	人源化序列
抗体 1A12	**抗体 1A12**
1A12V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**SEVFPITYMN**WVR QAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:319)
1A12V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:320)
1A12V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**SEVFPITYMN**WVR QAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTITADESTSTA YMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:321)
1A12V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**SEVFPITYMN**WVRQ MPGKGLEW**IGDILPSIGRTMYG**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:322)
1A12V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:323)
1A12V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:324)
1A12V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**SEVFPITYMN**WVR QAPGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:325)
1A12V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:326)
1A12V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:327)
1A12V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**SEVFPITYMN**WIRQP

[0647]

抗体变体	人源化序列
	PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:328)
抗体 1E8	**抗体 1E8**
1E8V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FNIKGSLLH**WVRQ APGQGLEW**IGWIDPEDGETRFD**QKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYC**ARTEYSNPAWFAY**WGQGTLVT VSS (SEQ ID NO:329)
1E8V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FNIKGSLLH**WVRQM PGKGLEW**IGWIDPEDGETRFD**PSFQGQVTISADKSISTAYL QWSSLKASDTAMYYC**ARTEYSNPAWFAY**WGQGTLVTVS S (SEQ ID NO:330)
1E8V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FNIKGSLLH**WVRQA PGKGLEW**IGWIDPEDGETRFD**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**ARTEYSNPAWFAY**WGQGTLVTV SS (SEQ ID NO:331)
1E8V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FNIKGSLLH**WVRQ APGQGLEW**IGWIDPEDGETRFD**QKFQGRVTITADESTSTA YMELSSLRSEDTAVYYC**ARTEYSNPAWFAY**WGQGTLVTV SS (SEQ ID NO:332)
1E8V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FNIKGSLLH**WVRQ APGKGLEW**IGWIDPEDGETRFD**DSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYC**ARTEYSNPAWFAY**WGQGTLVT VSS (SEQ ID NO:333)
1E8V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FNIKGSLLH**WVRQA PGKGLEW**IGWIDPEDGETRFD**DSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYC**ARTEYSNPAWFAY**WGQGTLVTV SS (SEQ ID NO:334)
1E8V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FNIKGSLLH**WVRQA PGKGLEW**IGWIDPEDGETRFD**DSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYC**ARTEYSNPAWFAY**WGQGTLVTV SS (SEQ ID NO:335)
1E8V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FNIKGSLLH**WIRQPP GKGLEW**IGWIDPEDGETRFD**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**ARTEYSNPAWFAY**WGQGTLVTVSS (SEQ ID NO:336)
1E8V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FNIKGSLLH**WVRQA PGKGLEW**IGWIDPEDGETRFD**APVKGRFTISRDDSKNTLY LQMNSLKTEDTAVYYC**ARTEYSNPAWFAY**WGQGTLVTV SS (SEQ ID NO:337)
1E8V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**FNIKGSLLH**WIRQPP GKGLEW**IGWIDPEDGETRFD**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**ARTEYSNPAWFAY**WGQGTLVTVSS (SEQ ID NO:338)
抗体 2G1	**抗体 2G1**
2G1V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FTFSNYDMS**WVRQA PGKGLEW**VATISSGGDYTYYP**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**ARHGYGNYDWYFDV**WGQGTLV

[0648]

抗体变体	人源化序列
	TVSS (SEQ ID NO:339)
2G1V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSNYDMS**WVRQ APGKGLEW**VATISSGGDYTYYP**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARHGYGNYDWYFDV**WGQGTL VTVSS (SEQ ID NO:340)
2G1V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FTFSNYDMS**WVRQ APGKGLEW**VATISSGGDYTYYP**DSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYC**ARHGYGNYDWYFDV**WGQGTL VTVSS (SEQ ID NO:341)
2G1V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSNYDMS**WVRQ APGKGLEW**VATISSGGDYTYYP**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARHGYGNYDWYFDV**WGQGTL VTVSS (SEQ ID NO:342)
2G1V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FTFSNYDMS**WVRQ APGQGLEW**VATISSGGDYTYYP**QKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYC**ARHGYGNYDWYFDV**WGQGTLV TVSS (SEQ ID NO:343)
2G1V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FTFSNYDMS**WVRQ APGQGLEW**VATISSGGDYTYYP**QKFQGRVTITADESTSTA YMELSSLRSEDTAVYYC**ARHGYGNYDWYFDV**WGQGTLV TVSS (SEQ ID NO:344)
2G1V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FTFSNYDMS**WVRQ MPGKGLEW**VATISSGGDYTYYP**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**ARHGYGNYDWYFDV**WGQGTLV TVSS (SEQ ID NO:345)
2G1V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FTFSNYDMS**WIRQPP GKGLEW**VATISSGGDYTYYP**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**ARHGYGNYDWYFDV**WGQGTLVTVS S (SEQ ID NO:346)
2G1V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FTFSNYDMS**WVRQ APGKGLEW**VATISSGGDYTYYP**APVKGRFTISRDDSKNTL YLQMNSLKTEDTAVYYC**ARHGYGNYDWYFDV**WGQGTL VTVSS (SEQ ID NO:347)
2G1V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**FTFSNYDMS**WIRQPP GKGLEW**VATISSGGDYTYYP**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**ARHGYGNYDWYFDV**WGQGTLVTVS S (SEQ ID NO:348)
抗体 2G4	**抗体 2G4**
2G4V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**SEVFPITYMN**WVR QAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:349)
2G4V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:350)
2G4V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**SEVFPITYMN**WVR QAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTITADESTSTA

[0649]

抗体变体	人源化序列
	YMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:351)
2G4V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**SEVFPITYMN**WVRQ MPGKGLEW**IGDILPSIGRTMYG**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:352)
2G4V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:353)
2G4V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:354)
2G4V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**SEVFPITYMN**WVR QAPGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:355)
2G4V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYM**NWIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:356)
2G4V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:357)
2G4V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:358)
抗体 3E11	**抗体 3E11**
3E11V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**YIFTDYGIT**WVRQM PGKGLEW**IGEISPRSGETYFN**PSFQGQVTISADKSISTAYLQ WSSLKASDTAMYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:359)
3E11V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**YIFTDYGIT**WVRQ APGQGLEW**IGEISPRSGETYFN**QKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:360)
3E11V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**YIFTDYGIT**WVRQA PGKGLEW**IGEISPRSGETYFN**DSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:361)
3E11V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**YIFTDYGIT**WVRQA PGQGLEW**IGEISPRSGETYFN**QKFQGRVTITADESTSTAYM ELSSLRSEDTAVYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:362)
3E11V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**YIFTDYGIT**WVRQA

抗体变体	人源化序列
	PGKGLEW**IGEISPRSGETYFN**DSVKGRFTISRDNAKNSLYL QMNSLRAEDTAVYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:363)
3E11V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**YIFTDYGIT**WVRQA PGKGLEW**IGEISPRSGETYFN**DSVKGRFTISRDNAKNSLYL QMNSLRAEDTAVYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:364)
3E11V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**YIFTDYGIT**WVRQA PGKGLEW**IGEISPRSGETYFN**DSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:365)
3E11V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**YIFTDYGIT**WIRQPPG KGLEW**IGEISPRSGETYFN**PSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:366)
3E11V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**YIFTDYGIT**WVRQA PGKGLEW**IGEISPRSGETYFN**APVKGRFTISRDDSKNTLYL QMNSLKTEDTAVYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:367)
3E11V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**YIFTDYGIT**WIRQPP GKGLEW**IGEISPRSGETYFN**PSLKSRVTISVDTSKNQFSLKL SSVTAADTAVYYC**AREGNPFTY**WGQGTLVTVSS (SEQ ID NO:368)

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抗体 4A1	抗体 4A1
4A1V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**SEVFPITYMN**WVR QAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:369)
4A1V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:370)
4A1V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**SEVFPITYMN**WVR QAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTITADESTSTA YMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:371)
4A1V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**SEVFPITYMN**WVRQ MPGKGLEW**IGDILPSIGRTMYG**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:372)
4A1V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:373)
4A1V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:374)

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抗体变体	人源化序列
4A1V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**SEVFPITYMN**WVR QAPGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:375)
4A1V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:376)
4A1V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:377)
4A1V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:378)
抗体 4D7	**抗体 4D7**
4D7V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**YTFTNYWIN**WVRQ MPGKGLEW**IGNIYSGSSRTNYN**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ ID NO:379)
4D7V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**YTFTNYWIN**WVRQ APGKGLEW**IGNIYSGSSRTNYN**DSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ ID NO:380)
4D7V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**YTFTNYWIN**WVRQ APGQGLEW**IGNIYSGSSRTNYN**QKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ ID NO:381)
4D7V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**YTFTNYWIN**WVRQ APGKGLEW**IGNIYSGSSRTNYN**DSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ ID NO:382)
4D7V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**YTFTNYWIN**WVRQ APGQGLEW**IGNIYSGSSRTNYN**QKFQGRVTITADESTSTAY MELSSLRSEDTAVYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ ID NO:383)
4D7V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**YTFTNYWIN**WVRQ APGKGLEW**IGNIYSGSSRTNYN**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ ID NO:384)
4D7V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**YTFTNYWIN**WVRQ APGKGLEW**IGNIYSGSSRTNYN**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ ID NO:385)
4D7V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**YTFTNYWIN**WIRQPP GKGLEW**IGNIYSGSSRTNYN**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ

[0652]

抗体变体	人源化序列
	ID NO:386)
4D7V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**YTFTNYWIN**WVRQ APGKGLEW**IGNIYSGSSRTNYN**APVKGRFTISRDDSKNTLY LQMNSLKTEDTAVYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ ID NO:387)
4D7V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**YTFTNYWIN**WIRQPP GKGLEW**IGNIYSGSSRTNYN**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**AREGLRAMDY**WGQGTLVTVSS (SEQ ID NO:388)
抗体 4E3	**抗体 4E3**
4E3V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FIFSNYDMS**WVRQA PGKGLEW**VATISSGGGYTYYP**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**TRHGYGNYDWYFDV**WGQGTLV TVSS (SEQ ID NO:389)
4E3V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FIFSNYDMS**WVRQA PGKGLEW**VATISSGGGYTYYP**DSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYC**TRHGYGNYDWYFDV**WGQGTLV TVSS (SEQ ID NO:390)
4E3V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FIFSNYDMS**WVRQA PGKGLEW**VATISSGGGYTYYP**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**TRHGYGNYDWYFDV**WGQGTLV TVSS (SEQ ID NO:391)
4E3V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FIFSNYDMS**WVRQA PGKGLEW**VATISSGGGYTYYP**DSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYC**TRHGYGNYDWYFDV**WGQGTLV TVSS (SEQ ID NO:392)
4E3V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FIFSNYDMS**WVRQ APGQGLEW**VATISSGGGYTYYP**QKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYC**TRHGYGNYDWYFDV**WGQGTL VTVSS (SEQ ID NO:393)
4E3V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FIFSNYDMS**WVRQ APGQGLEW**VATISSGGGYTYYP**QKFQGRVTITADESTSTA YMELSSLRSEDTAVYYC**TRHGYGNYDWYFDV**WGQGTLV TVSS (SEQ ID NO:394)
4E3V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FIFSNYDMS**WVRQM PGKGLEW**VATISSGGGYTYYP**PSFQGQVTISADKSISTAYL QWSSLKASDTAMYYC**TRHGYGNYDWYFDV**WGQGTLVT VSS (SEQ ID NO:395)
4E3V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FIFSNYDMS**WIRQPP GKGLEW**VATISSGGGYTYYP**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**TRHGYGNYDWYFDV**WGQGTLVTVS S (SEQ ID NO:396)
4E3V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FIFSNYDMS**WVRQA PGKGLEW**VATISSGGGYTYYP**APVKGRFTISRDDSKNTLY LQMNSLKTEDTAVYYC**TRHGYGNYDWYFDV**WGQGTLVT VSS (SEQ ID NO:397)
4E3V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**FIFSNYDMS**WIRQPPG KGLEW**VATISSGGGYTYYP**PSLKSRVTISVDTSKNQFSLKL

抗体变体	人源化序列
	SSVTAADTAVYYC**TRHGYGNYDWYFDV**WGQGTLVTVSS (SEQ ID NO:398)
4E3H1	EVQLVESGGGLVKPGGSLRLSCAASG**FIFSNYDMS**WVRQA PGKGLEWVS**TISSGGGYTY**YADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAR**HGYGNYDWYFDV**WGQGTLV TVSS (SEQ ID NO:490)
4E3H2	EVQLVESGGGLVKPGGSLRLSCAV**SGFIFSNYDMS**WVRQA PGKGLEWVA**TISSGGGYTY**YADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCTR**HGYGNYDWYFDV**WGQGTLVT VSS (SEQ ID NO:491)
4E3H3	EVQLVESGGGLVKPGGSLRISCA**VSGFIFSNYDMS**WVRQA PGKGLEWVA**TISSGGGYTY**YADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYC**TRHGYGNYDWYFDV**WGQGALV TVSS (SEQ ID NO:492)
抗体 7A3	**抗体 7A3**
7A3V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSNYAMS**WVRQ APGKGLEW**VASISSGGSYNYYP**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ASQSYGSSYWYFDV**WGQGTLV TVSS (SEQ ID NO:399)
7A3V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FTFSNYAMS**WVRQA PGKGLEW**VASISSGGSYNYYP**DSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYC**ASQSYGSSYWYFDV**WGQGTLVTV SS (SEQ ID NO:400)
7A3V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FTFSNYAMS**WVRQ APGKGLEW**VASISSGGSYNYYP**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**ASQSYGSSYWYFDV**WGQGTLVT VSS (SEQ ID NO:401)
7A3V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSNYAMS**WVRQ APGKGLEW**VASISSGGSYNYYP**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ASQSYGSSYWYFDV**WGQGTLV TVSS (SEQ ID NO:402)
7A3V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FTFSNYAMS**WVRQ APGQGLEW**VASISSGGSYNYYP**QKFQGRVTITADESTSTAY MELSSLRSEDTAVYYC**ASQSYGSSYWYFDV**WGQGTLVTV SS (SEQ ID NO:403)
7A3V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FTFSNYAMS**WVRQ APGQGLEW**VASISSGGSYNYYP**QKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYC**ASQSYGSSYWYFDV**WGQGTLVT VSS (SEQ ID NO:404)
7A3V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FTFSNYAMS**WVRQ MPGKGLEW**VASISSGGSYNYYP**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**ASQSYGSSYWYFDV**WGQGTLVT VSS (SEQ ID NO:405)
7A3V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FTFSNYAMS**WIRQPP GKGLEW**VASISSGGSYNYYP**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**ASQSYGSSYWYFDV**WGQGTLVTVSS (SEQ ID NO:406)
7A3V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FTFSNYAMS**WVRQ

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抗体变体	人源化序列
	APGKGLEW**VASISSGGSYNYYP**APVKGRFTISRDDSKNTLY LQMNSLKTEDTAVYYC**ASQSYGSSYWYFDV**WGQGTLVT VSS (SEQ ID NO:407)
7A3V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**FTFSNYAMS**WIRQPP GKGLEW**VASISSGGSYNYYP**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**ASQSYGSSYWYFDV**WGQGTLVTVSS (SEQ ID NO:408)
抗体 7E11	**抗体 7E11**
7E11V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FSLSNYGVH**WIRQPP GKGLEW**LGVIWAGGITNYN**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:409)
7E11V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FSLSNYGVH**WVRQ APGKGLEW**LGVIWAGGITNYN**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:410)
7E11V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FSLSNYGVH**WVRQ APGKGLEW**LGVIWAGGITNYN**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:411)
7E11V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FSLSNYGVH**WVRQ APGKGLEW**LGVIWAGGITNYN**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:412)
7E11V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FSLSNYGVH**WVRQA PGKGLEW**LGVIWAGGITNYN**DSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:413)
7E11V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FSLSNYGVH**WVRQ MPGKGLEW**LGVIWAGGITNYN**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:414)
7E11V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FSLSNYGVH**WVRQ APGQGLEW**LGVIWAGGITNYN**QKFQGRVTITADESTSTAY MELSSLRSEDTAVYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:415)
7E11V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FSLSNYGVH**WVRQ APGQGLEW**LGVIWAGGITNYN**QKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:416)
7E11V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**FSLSNYGVH**WIRQPP GKGLEW**LGVIWAGGITNYN**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:417)
7E11V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**FSLSNYGVH**WIRQPP GKGLEW**LGVIWAGGITNYN**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**AKQGGTSFSY**WGQGTLVTVSS (SEQ ID NO:418)

[0655]

抗体变体	人源化序列
抗体 7F12	**抗体 7F12**
7F12V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**SEVFPITYMN**WVR QAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:419)
7F12V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:420)
7F12V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**SEVFPITYMN**WVR QAPGQGLEW**IGDILPSIGRTMYG**QKFQGRVTITADESTSTA YMELSSLRSEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:421)
7F12V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**SEVFPITYMN**WVRQ MPGKGLEW**IGDILPSIGRTMYG**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:422)
7F12V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:423)
7F12V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**SEVFPITYMN**WVRQ APGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:424)
7F12V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**SEVFPITYMN**WVR QAPGKGLEW**IGDILPSIGRTMYG**DSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:425)
7F12V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:426)
7F12V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:427)
7F12V4-30	QVQLQESGPGLVKPSQTLSLTCTVSG**SEVFPITYMN**WIRQP PGKGLEW**IGDILPSIGRTMYG**PSLKSRVTISVDTSKNQFSL KLSSVTAADTAVYYC**ARSEGYLLAY**WGQGTLVTVSS (SEQ ID NO:428)
抗体 10B5	**抗体 10B5**
10B5V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**YAFTNCWMN**WVRQ MPGKGLEW**IGRIFPGNGHTNYS**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:429)
10B5V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**YAFTNCWMN**WVR QAPGQGLEW**IGRIFPGNGHTNYS**QKFQGRVTMTRDTSTST

[0656]

抗体变体	人源化序列
	VYMELSSLRSEDTAVYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:430)
10B5V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**YAFTNCWMN**WVRQAPGQGLEW**IGRIFPGNGHTNYS**QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:431)
10B5V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPGNGHTNYS**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:432)
10B5V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPGNGHTNYS**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:433)
10B5V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPGNGHTNYS**DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:434)
10B5V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPGNGHTNYS**DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:435)
10B5V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**YAFTNCWMN**WIRQPPGKGLEW**IGRIFPGNGHTNYS**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:436)
10B5V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**YAFTNCWMN**WVRQAPGKGLEW**IGRIFPGNGHTNYS**APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:437)
10B5V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**YAFTNCWMN**WIRQPPGKGLEW**IGRIFPGNGHTNYS**PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC**ARDYSDYYFDY**WGQGTLVTVSS (SEQ ID NO:438)
10B5H1	QVQLVQSGAEVKKPGASVKVSCKAS**GYAFTNCWMN**WVRQAPGQGLEWMG**RIFPGNGHTN**YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**DYSDYYFDY**WGQGTLVTVSS(SEQ ID NO:493)
10B5H2	QVQLVQSGAEVKKPGASVKVSCKAS**GYAFTNCWMN**WVRQAPGQGLEWIG**RIFPGNGHTN**YAQKFQGRVTMTEDTSTSTVYMELSSLRSEDTAVYYCAR**DYSDYYFDY**WGQGTLVTVSS(SEQ ID NO:494)
10B5H3	QVQLVQSGAEVKKPGASVKISCKAS**GYAFTNCWMN**WVRQAPGQGLEWIG**RIFPGNGHTN**YAQKFQGRATLTEDTSTSTAYMELSSLRSEDTAVYYCAR**DYSDYYFDY**WGQGTLLTVSS(SEQ ID NO:495)
10B5H4	QVQLVQSGAEVKKPGASVKISCKAS**GYAFTNCWMN**WVRQAPGQGLEWIG**RIFPGNGHTN**YAQKFQGRATLTEDKSTST

抗体变体	人源化序列
	AYMELSSLRSEDTAVYYCAR**DYSDYYFDY**WGQGTLLTVS S(SEQ ID NO:496)
抗体 10G8	**抗体 10G8**
10G8V3-23	EVQLLESGGGLVQPGGSLRLSCAASG**FTFSTYAMF**WVRQA PGKGLEW**VASISSGGRYTYYP**DSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYC**VRHSYGSSYWYLDV**WGQGTLVTV SS (SEQ ID NO:439)
10G8V3-48	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSTYAMF**WVRQ APGKGLEW**VASISSGGRYTYYP**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**VRHSYGSSYWYLDV**WGQGTLV TVSS (SEQ ID NO:440)
10G8V3-7	EVQLVESGGGLVQPGGSLRLSCAASG**FTFSTYAMF**WVRQ APGKGLEW**VASISSGGRYTYYP**DSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYC**VRHSYGSSYWYLDV**WGQGTLV TVSS (SEQ ID NO:441)
10G8V3-30	QVQLVESGGGVVQPGRSLRLSCAASG**FTFSTYAMF**WVRQ APGKGLEW**VASISSGGRYTYYP**DSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYC**VRHSYGSSYWYLDV**WGQGTLV TVSS (SEQ ID NO:442)
10G8V1-46	QVQLVQSGAEVKKPGASVKVSCKASG**FTFSTYAMF**WVRQ APGQGLEW**VASISSGGRYTYYP**QKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYC**VRHSYGSSYWYLDV**WGQGTLVT VSS (SEQ ID NO:443)
10G8V1-69	QVQLVQSGAEVKKPGSSVKVSCKASG**FTFSTYAMF**WVRQ APGQGLEW**VASISSGGRYTYYP**QKFQGRVTITADESTSTA YMELSSLRSEDTAVYYC**VRHSYGSSYWYLDV**WGQGTLVT VSS (SEQ ID NO:444)
10G8V5-51	EVQLVQSGAEVKKPGESLKISCKGSG**FTFSTYAMF**WVRQ MPGKGLEW**VASISSGGRYTYYP**PSFQGQVTISADKSISTAY LQWSSLKASDTAMYYC**VRHSYGSSYWYLDV**WGQGTLVT VSS (SEQ ID NO:445)
10G8V4-59	QVQLQESGPGLVKPSETLSLTCTVSG**FTFSTYAMF**WIRQPP GKGLEW**VASISSGGRYTYYP**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**VRHSYGSSYWYLDV**WGQGTLVTVSS (SEQ ID NO:446)
10G8V3-15	EVQLVESGGGLVKPGGSLRLSCAASG**FTFSTYAMF**WVRQ APGKGLEW**VASISSGGRYTYYP**APVKGRFTISRDDSKNTL YLQMNSLKTEDTAVYYC**VRHSYGSSYWYLDV**WGQGTLV TVSS (SEQ ID NO:447)
10G8V4-39	QLQLQESGPGLVKPSETLSLTCTVSG**FTFSTYAMF**WIRQPP GKGLEW**VASISSGGRYTYYP**PSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYC**VRHSYGSSYWYLDV**WGQGTLVTVSS (SEQ ID NO:448)

[0657]

[0658] 抗体4E3的人源化

[0659] 使用鼠抗Siglec-7抗体4E3(S7-4E3)的重链可变区(VH)序列和轻链可变区(VL)序列作为NCBI网站上的IgBLAST程序的输入(Ye,J.等人Nucleic Acids Research 41:W34-W40(2013))。IgBLAST采用鼠VH或VL序列并将其与已知人种系序列的文库进行比较。所使用的数据库是IMGT人VH基因(F+ORF,273条种系序列)和IMGT人VLκ基因(F+ORF,74条种系序

列)。对于4E3抗体VL,选择人种系IGKV3-11(等位基因1)作为受体序列,并且从在IMGT® the international ImMunoGeneTics information system®编译的人连接区序列选择人轻链IGKJ2(等位基因1)连接区(J基因)(图6B)。对于4E3抗体VH,选择人种系IGHV3-21(等位基因1)作为受体序列,并且从在IMGT® the international ImMunoGeneTics information system®编译的人连接区序列选择人重链IGHJ4(等位基因1)连接区(J基因)(图6C)。根据AbM定义(AbM抗体建模软件)定义抗体VL和VH的互补决定区(CDR)。

[0660] 可能需要将人种系框架(即VH和VL中的非CDR残基)位置改变为相应的亲本鼠序列以优化人源化抗体的结合。每条人源化序列的潜在变化在图6B和6C中注释。

[0661] 图6B和6C显示抗Siglec-7抗体4E3的人源化型式的序列。在抗体4E3的VL结构域中,CDR-L1内的Asp26和CDR-L2内的Asn52基于序列和构象具有较低脱酰胺潜力,并且可能显示低水平的这种翻译后修饰(图6B)。抗体4E3的CDR-L3内的Trp90似乎是溶剂暴露的,并且可显示较低水平的氧化,在应力条件下尤其如此(图6B)。基于上述的变体VL序列列于表6A中。

[0662] 在抗体4E3的VH结构域中,CDR-H1内的Asn31和CDR-H3内的Asn103基于序列和构象具有较低脱酰胺潜力,但可显示低水平的这种翻译后修饰(图6C)。CDR-H3内的Trp106似乎是溶剂暴露的,并且可显示低水平的氧化,在应力条件下尤其如此(图6C)。基于上述的变体VH序列列于表6B中。

[0663] 抗体10B5的人源化

[0664] 使用鼠抗Siglec-7抗体10B5(S7-10B5)的重链可变区(VH)序列和轻链可变区(VL)序列作为NCBI网站上的IgBLAST程序的输入(Ye,J.等人Nucleic Acids Research 41:W34-W40(2013))。IgBLAST采用鼠VH或VL序列并将其与已知人种系序列的文库进行比较。所使用的数据库是IMGT人VH基因(F+ORF,273条种系序列)和IMGT人VLκ基因(F+ORF,74条种系序列)。对于10B5抗体VL,选择人种系IGKV1-39(等位基因1)作为受体序列,并且从在IMGT® the international ImMunoGeneTics information system®编译的人连接区序列选择人轻链IGKJ2(等位基因1)连接区(J基因)(图6D)。对于10B5抗体VH,选择人种系IGHV1-46(等位基因1)作为受体序列,并且从在IMGT® the international ImMunoGeneTics information system®编译的人连接区序列选择人重链IGHJ4(等位基因1)连接区(J基因)(图6E)。根据AbM定义(AbM抗体建模软件)定义抗体VL和VH的互补决定区(CDR)。

[0665] 可能需要将人种系框架(即VH和VL中的非CDR残基)位置改变为相应的亲本鼠序列以优化人源化抗体的结合。每条人源化序列的潜在变化在图6D和6E中注释。

[0666] 图6D和6E示出抗Siglec-7抗体10B5的人源化型式的序列。在抗体10B5的VL结构域中,CDR-L1内的Asp30和CDR-L3内的Asn92基于序列和构象具有低至中等脱酰胺潜力,并且可显示低水平的这种翻译后修饰(图6D)。抗体10B5的CDR-L1内的Trp33似乎是溶剂暴露的,并且可显示较低水平的氧化,在应力条件下尤其如此(图6D)。CDR-L1内还存在游离Cys,其可能是溶剂暴露的并且可被改变为Ser以评价其对结合的影响。基于上述的变体VL序列列于表6A中。

[0667] 在抗体10B5的VH结构域中,CDR-H2内的Asp54-Gly55具有中等脱酰胺、随后异天冬氨酸形成的潜力(图6E)。在此位点的翻译后修饰可影响抗体与靶标的结合。可对亲本小鼠抗体进行分析以确定翻译后修饰的水平。或者,可将抗体10B5人源化,且然后在最后一步中

可将NG修饰成例如QG,以确定是否保持结合。CDR-H1内的Asn31和CDR-H2内的Asn58基于序列和构象具有较低脱酰胺潜力,但可显示低水平的这种翻译后修饰(图6E)。对CDR的修饰可在人源化后进行,如通过分析CDR-H2内的Asn54-Gly55并改变CDR-H1内的Cys32Ser(图6E)。基于上述的变体VH序列列于表6B中。

[0668] 实施例2:Siglec-7抗体的表位作图

[0669] 测试了Siglec-7抗体结合跨越整个人Siglec-7的15或25聚体肽的能力。通过确定它们的Siglec-7结合区,还将Siglec-7抗体与参考Siglec-7抗体进行了比较。

[0670] 方法

[0671] 基于人Siglec-7(SEQ ID NO:1)的序列合成了线性15聚体肽,其中14个残基重叠。此外,基于人Siglec-7(SEQ ID NO:1)的序列合成了具有单个残基移位的线性25聚体肽。在基于ELISA的方法中测试了Siglec-7抗体与每种合成肽的结合。在此测定中,将肽阵列与一级抗体溶液一起孵育(在4℃下过夜)。在洗涤后,将肽阵列与抗体过氧化物酶缀合物(SBA,目录号2010-05)的1/1000稀释液在25℃下孵育1小时。在洗涤后,加入过氧化物酶底物2,2′-连氮基-二-3-乙基苯并噻唑啉磺酸盐(ABTS)和2μl/ml的3%H_2O_2。在一小时后,测量颜色显色。用电荷耦合装置(CCD)照相机和图像处理系统对颜色显色进行量化。

[0672] 使用标准夹心形式分箱测定(参见Estep等人,(2013)MAbs 5(2):270-8),在Forte Bio Octet Red384系统(Pall Forte Bio Corporation,Menlo Park,CA)上进行了抗体的表位分箱。将对照抗靶标IgG负载到AHQ传感器上,并用不相关的人IgG1抗体阻断传感器上未占据的Fc结合位点。然后将传感器暴露于100nM靶抗原,然后暴露于第二抗靶标抗体。使用ForteBio的数据分析软件7.0对数据进行处理。抗原缔合后第二抗体的另外结合指示未被占据的表位(非竞争物),而无结合指示表位阻断(竞争物)。

[0673] 或者,为了重新构建靶分子的表位,合成了成环肽和组合肽的文库。氨基官能化聚丙烯载体通过以下步骤获得:与专有亲水性聚合物制剂接枝、随后使用二环己基碳二亚胺(DCC)与N-羟基苯并三唑(HOBt)与叔丁氧基羰基-六亚甲基二胺(BocHMDA)反应,并且随后使用三氟乙酸(TFA)裂解Boc-基团。标准Fmoc-肽合成用于通过定制修改的JANUS液体处理站(Perkin Elmer)合成氨基官能化固体载体上的肽。

[0674] 结构模拟物的合成使用Pepscan专有的支架上化学连接肽(CLIPS)技术完成。CLIPS技术允许将肽构造成单环和双环。将CLIPS模板偶联至半胱氨酸残基。将肽中多个半胱氨酸的侧链偶联至一个或两个CLIPS模板。例如,将mP2CLIPS(2,6-双(溴甲基)吡啶)的0.5mM溶液溶解于碳酸氢铵(20mM,pH 7.8)/乙腈(1:3(v/v))中。将该溶液添加至肽阵列上。所述CLIPS模板将结合至如以肽阵列(具有3μl孔的455孔板)的固相结合肽存在的两个半胱氨酸的侧链。将所述肽阵列在完全覆盖于溶液中的同时在溶液中轻轻振荡30至60分钟。最后,将肽阵列用过量的H2O充分洗涤并在70℃下在含有PBS(pH 7.2)中的1%SDS/0.1%β-巯基乙醇的破碎缓冲液中超声处理30分钟,随后再在H2O中超声处理45分钟。携带肽的T3CLIPS(2,4,6-三(溴甲基)吡啶)以类似的方式制备,但现在使用三个半胱氨酸。

[0675] 成环肽:长度为17的限制性肽。位置2-16是源自靶序列的15聚体。天然Cys残基受乙酰氨基甲基基团(ACM)保护。位置1和17是通过mP2CLIPS部分连接的Cys。组合肽(不连续模拟物):长度为33的限制性肽。位置2-16和18-32是源自靶序列的15-聚体肽,其中天然Cys残基受ACM保护。位置1、17和33是通过T3 CLIPS部分连接的Cys。

[0676] 在基于PEPSCAN的ELISA中测试了抗体与每条合成肽的结合。将肽阵列与由实验优化浓度的测试抗体和封闭溶液(例如4％马血清、5％卵白蛋白(w/v)于PBS/1％Tween 80中)组成的测试抗体溶液一起孵育。将肽阵列与测试抗体溶液一起在4℃下孵育过夜。在用洗涤缓冲液(1×PBS,0.05％Tween80)充分洗涤后,将肽阵列与适当抗过氧化物酶缀合物的1/1000稀释液一起在25℃下孵育1小时。在用洗涤缓冲液洗涤后,添加过氧化物酶底物2,2′-连氮基-二-3-乙基苯并噻唑啉磺酸盐(ABTS)和2μl/ml的3％H2O2。在一小时后,测量颜色显色。颜色显色是用电荷耦合装置(CCD)-照相机和图像处理系统量化的。

[0677] 或者使用质谱法来鉴定构象表位。为了以高分辨率确定抗Siglec 7抗体所结合的Siglec 7蛋白上的构象表位的关键残基,将抗体/抗原复合物与氘化交联剂一起孵育并经受多酶促蛋白水解裂解。在富集所交联的肽后,通过高分辨质谱法(nLC-轨道阱MS(nLC-Orbitrap MS))分析样品,并使用XQuest软件分析所产生的数据。具体地说,Siglec 7 ECD/抗体复合物通过混合Siglec-7抗原和抗体的等摩尔溶液(各自于5μl中的4μM)而产生。将1μl的所得混合物与1μl由乙腈/水(1∶1,v/v)中的重结晶芥子酸基质(10mg/ml)、TFA 0.1％(K200 MALDI试剂盒)组成的基质混合。在混合后,将1μl的每种样品点在MALDI板(SCOUT 384)上。在室温下结晶后,将板引入MALDI质谱仪中并立即分析。将分析一式三份重复。代表单体抗体、抗原和抗体以及抗原/抗体复合物的峰以预测的分子量进行检测。

[0678] 然后确定构象结合中的表位是否与通过蛋白水解产生的非结构化C1q肽竞争。具体地说,为了确定Siglec-7 ECD/抗体复合物是否可与线性肽竞争,将Siglec-7 ECD抗原用固定的胃蛋白酶消化。将25μl浓度为10μM的抗原与固定的胃蛋白酶5μM混合并在室温下孵育30分钟。在孵育时间后,将样品离心并吸移上清液。蛋白质水解的完成由线性模式下的高质量MALDI质谱法控制。优化胃蛋白酶蛋白水解以便获得大量1000-3500Da范围内的肽。接着,将5μl通过蛋白水解产生的抗原肽与5μl抗体(8μM)混合,并在37℃下孵育6小时。在将抗体与Siglec-7抗原肽一起孵育后,将5μl混合物与5μl完整Siglec-7抗原(4μM)混合,以使得最终混合物含有2μM/2uM/2.5μM Siglec-7/抗体/Siglec-7抗原肽。MALDI ToF MS分析使用CovalX的HM3相互作用模块与标准氮激光器进行,并且聚焦于0至2000kDa的不同质量范围。对于分析,以下参数适用于质谱仪:线性和正模式;离子源1:20kV;离子源2:17kV;脉冲离子引出:400ns;对于HM3:增益电压:3.14kV;增益电压:3.14kV;加速电压:20kV。为了校准仪器,施加使用胰岛素、BSA和IgG簇的外部校准。对于每种样品,分析3个斑点(每个斑点300次激光发射)。所呈现的光谱对应于300次激光发射的总和。使用Complex Tracker分析软件2.0版(CovalX Inc)分析MS数据。为了鉴定用于Siglec-7与抗体结合的构象表位,使用化学交联、高质量MALDI质谱法和nLC轨道阱质谱法,按照以下程序进行抗原与抗体之间的相互作用界面。将5μl样品抗原(浓度4μM)与5μl样品抗体(浓度4μM)混合以便获得最终浓度为2μM/2μM的抗体/抗原混合物。将混合物在37℃下孵育180分钟。在第一步骤中,将1mg的二琥珀酰亚胺辛二酸酯H12(DSS-H12)交联剂与1mg的二琥珀酰亚胺辛二酸酯D12(DSS-D12)交联剂混合。将制备的2mg与1ml的DMF混合以获得2mg/ml的DSS H12/D12溶液。将10μl预先制备的抗体/抗原混合物与1μl制备的交联剂d0/d12溶液(2mg/ml)混合。将溶液在室温下孵育180分钟以便实现交联反应。

[0679] 为了促进蛋白质水解,有必要减少蛋白质中存在的二硫键。将交联的样品与20μl碳酸氢铵(25mM,pH 8.3)混合。在混合后,将2.5μl的DTT(500mM)添加至溶液中。然后将混合

物在55℃下孵育1小时。在孵育后，在室温下在暗室中孵育1小时之前加入2.5μl碘代乙酰胺(1M)。在孵育后，通过添加120μl用于蛋白质水解的缓冲液来将溶液1/5稀释。将145μl的还原/烷基化的交联样品与2μl胰蛋白酶(Sigma，T6567)混合。将蛋白水解混合物在37℃下孵育过夜。对于a-胰凝乳蛋白酶蛋白水解，蛋白水解的缓冲液是Tris-HCL 100mM，CaCl2 10mM，pH 7.8。将145μl的还原/烷基化的交联复合物与2μl的α-胰凝乳蛋白酶200μM混合，并在30℃下孵育过夜。对于这种分析，使用与轨道阱质谱法组合的nLC。使用Xquest 2.0版和stavrox软件分析交联剂肽。然后鉴定肽和交联的氨基酸。

[0680] 结果

[0681] 确定了4种抗Siglec-7抗体的Siglec-7结合区域。表7A中列出了结合区域。图1B-1E示出人Siglec-7的示意图，其指示由抗Siglec-7抗体结合的区域。

[0682] 表7A:Siglec-7抗体结合区

[0683]

抗体	Siglec-7 结合区	SEQ ID:1 的氨基酸区
1A12 4D7	^{111}RDARMSDAGRYF^{122} 和 ^{282}PPARLSWTWR^{291}	111-122 和 282-291
1A12 1E8 2G1 4D7	^{113}ARMSDAGRYFF^{123}	113-123
4A1	^{113}ARMSDAGRYFFRM^{125}	113-125
7E11	^{68}AGNDISWKAPV^{78}	68-78
10G8	^{60}PVHGYWFRAG^{69} and^{84}AWAVQEETRDRF^{95}	60-69 和 84-95
2G4 3E11 10B5 2G1 7F12	^{60}PVHGYWFRAG^{69} 和 ^{117}DAGRYFFRMEK^{127}	60-69 和 117-127

[0684] 如表7A中所示，抗体1A12和4D7显示仅对于Siglec-7的两个细胞外结构域(包括IgV结构域和第二Ig样C2-型结构域)内的肽的稳健结合。如表7A中所示，由抗体1A12和4D7识别的肽对应于SEQ ID NO:1的氨基酸残基111-122和282-291，并且具有氨基酸序列：RDARMSDAGRYF和PPARLSWTWR。

[0685] 如表7A中进一步指出的，抗体1A12、1E8、2G1、4D7、4A1、7E11、10G8、2G4、3E11、10B5、2G1以及7F12显示仅对于Siglec-7的细胞外结构域(包括IgV结构域)内的肽的稳健结合。如表7A中所示，由抗体1A12、1E8、2G1和4D7识别的肽对应于SEQ ID NO:1的氨基酸残基113-123，并且具有氨基酸序列:ARMSDAGRYFF。被抗体4A1识别的肽对应于SEQ ID NO:1的氨基酸残基113-125并具有氨基酸序列:ARMSDAGRYFFRM。由抗体7E11识别的肽对应于SEQ ID NO:1的氨基酸残基68-78，并且具有氨基酸序列:AGNDISWKAPV。由抗体10G8识别的肽对应于SEQ ID NO:1的氨基酸残基60-69和84-95，并且具有氨基酸序列:PVHGYWFRAG和AWAVQEETRDRF。由抗体2G4、3E11、10B5、2G1和7F12识别的肽对应于SEQ ID NO:1的氨基酸残

基60-69和117-127,并且具有氨基酸序列:PVHGYWFRAG和DAGRYFFRMEK。

[0686] 在图1B-1E中描绘了由抗体4A1、10G8、2G4、3E11、10B5、2G1、7F12和7E11结合的Siglec-7肽。在图1B和1E中示出了由抗体4A1识别的不连续肽。在图1C中描绘了由抗体2G4、3E11、10B5、2G1和7F12识别的不连续肽。在图1D中描绘了由抗体10G8识别的肽。图1E描绘了由抗体7E11结合的Siglec-7的构象表位的推定结合位点。推定表位包括对应于SEQ ID NO:1的氨基酸残基68-78并具有氨基酸序列AGNDISWKAPV的结合区。

[0687] 功能作图

[0688] 使用用于siglec-7蛋白的丙氨酸扫描文库进行抗siglec-7抗体的鸟枪诱变表位作图。对编码C-末端V5表位标签的siglec-7表达构建体(Uniprot id Q9Y286)进行高通量丙氨酸扫描诱变(概述于Davidson和Doranz,2014 Immunology 143,13-20中)以产生综合突变文库。残基19至353中的每一个都发生突变,从而代表siglec-7细胞外结构域,最多发生于丙氨酸,而丙氨酸密码子被突变为丝氨酸。总共产生了335个siglec-7突变体表达构建体,确认序列,并将其排列到384孔板中,每孔一个突变体。

[0689] 将排列在384孔微板中的siglec-7突变文库克隆分别转染到HEK-293T细胞中并使其表达22小时。然后将细胞与稀释于10%正常山羊血清(NGS)(Sigma-Aldrich,St.Louis,MO)中的MAb一起孵育。在文库筛选之前,使用针对表达野生型siglec-7的细胞的独立免疫荧光滴定曲线确定一级MAb浓度,以确保信号在线性检测范围内。使用3.75μg/ml AlexaFluor488缀合的二级抗体(Jackson ImmunoResearch Laboratories,Westgrove,PA)在10%NGS中检测MAb。将细胞用PBS-/-洗涤两次并重新悬浮于含有0.1%BSA(Sigma-Aldrich,St.Louis,MO)的Cellstripper(Cellgro,Manassas,VA)中。使用Intellicyt高通量流式细胞仪(HTFC,Intellicyt,Albuquerque,NM)检测平均细胞荧光。相对于野生型siglec-7蛋白反应性,通过从模拟转染的对照中减去信号并且归一化至来自野生型siglec-7转染的对照的信号来计算针对每种突变体克隆的MAb反应性。

[0690] 如果关键克隆内的突变残基不支持测试MAb的反应性但确实支持可商购获得的参考MAb 6-434或S7.7(Biolegend,目录号:339202、347702)或其它抗siglec-7MAb的反应性,则所述突变残基被鉴定为对于MAb表位而言是关键的。这种反向筛选策略有助于排除局部错误折叠或具有表达缺陷的siglec-7突变体。

[0691] 图1F描绘筛选中鉴定的所有关键残基的平均结合反应性和范围。所述范围是一式两份实验结合值之间的差异。主要关键残基被鉴定为其中所述突变对于测试抗体结合为阴性(<30%的与WT的结合)但对于对照抗体为阳性(>80%WT)的残基。图1G描绘Siglec-7的IgV结构域的晶体结构模型(PDB ID 1O7V;Alphey等人,2003),从而指示对于每种测试的抗体,关键残基为红球且二级残基为粉球。表7B中列出了对抗体结合关键的氨基酸残基以及二级残基。

[0692] 表7B:参与抗Siglec-7抗体结合的残基

[0693]

抗体	关键 Siglec-7 残基	二级 Siglec-7 残基
4E3 Fab	I_{72}；W_{74}；N_{81}；以及 R_{124}	
10B5 MAb	K_{104}	
10B5 Fab	R_{45}；S_{47}；T_{103}；K_{104}；以及 T_{107}	M_{30}；Q_{31}；V_{44}；F_{48}；以及 Y_{50}

[0694] 如表7B中所示，参与由抗体4E3结合的关键Siglec-7残基对应于SEQ ID NO:1的氨基酸残基I_{72}、W_{74}、N_{81}和R_{124}。参与由抗体10B5结合的关键Siglec-7残基对应于SEQ ID NO:1的氨基酸残基R_{45}、S_{47}、T_{103}、K_{104}和T_{107}；并且参与由抗体10B5结合的二级残基对应于SEQ ID NO:1的氨基酸残基M_{30}、Q_{31}、V_{44}、F_{48}和Y_{50}。

[0695] 实施例3:Siglec-7抗体诱导的体外和体内Siglec-7的细胞表面水平的降低

[0696] Siglec-7的体外表达

[0697] 以下实施例的目的是测试抗Siglec-7和/或Siglec-7双特异性抗体是否降低单核细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、T细胞和/或小神经胶质细胞上Siglec-7的细胞表面水平。

[0698] 对抗Siglec-7抗体降低组织细胞淋巴瘤细胞系U937以及人原代单核细胞、源自外周血单核细胞的人原代树突细胞(DC)、源自外周血单核细胞的人原代巨噬细胞和NK细胞以及人原代小神经胶质细胞上的Siglec-7的细胞表面水平的能力进行了评价。将细胞样品以200,000个细胞/ml涂铺在24孔板中，或者以在2ml补充有10％Hyclone FBS、2mM谷氨酰胺、pen/strep和非必需氨基酸的RPMI中500,000个细胞接种于6孔皿中。以1.0μg/ml加入Siglec-7抗体或对照同种型，并在37℃、5％CO_2下孵育24小时。

[0699] 为了评估受体动力学，允许抗体结合细胞1小时，洗出并在24小时和48小时后测定Siglec-7的表面水平。

[0700] 通过FACS分析来检测细胞表面受体表达。将细胞与抗Siglec-7-PE克隆6-434(Biolegend)以及对照表面标志物(U937:Siglec-5，人单核细胞:CD14，人树突细胞:CD11c，人巨噬细胞:CD11b，人NK细胞:CD56)在黑暗中冰上一起孵育30分钟。将细胞在FACS缓冲液(PBS+2％FBS，2mM EDTA)中洗涤2次，并在BD FACS Canto上进行流式细胞术。使用TreeStar FlowJo软件分析数据。使用相应荧光团的MFI值，将数据计算为不存在抗体时受体表达的百分比。

[0701] 表8A和8B描绘来自人细胞的Siglec-7细胞表面水平的结果。在表8A和8B中，“无Ab”是指未用抗体处理的细胞；“mIgG1”、“mIgG2a”和“mIgG2b”是指同种型对照抗体；并且“RDS7”是指可商购获得的抗Siglec-7抗体Fab1138(R&D Systems;目录号MAB1138)。

[0702] 表8A:Siglec-7抗体降低人细胞系和人原代细胞中的Siglec-7的细胞表面水平

[0703]

	Siglec-7 表面表达%					
	U937 细胞		单核细胞		DC	
Ab	Siglec-7 %	对照%	Siglec-7 %	对照%	Siglec-7 %	对照%
1A12	87.3	136.8	39.9	93.4	100.5	95.7
1E8	114.0	134.2	36.7	94.1	23.0	97.0
2G1	121.4	129.5	139.5	98.6	110.4	102.2
2G4	84.6	136.2	29.3	95.1	98.1	96.2
3E11	82.4	128.1	23.9	89.0	19.9	97.6

[0704]

	Siglec-7 表面表达%					
	U937 细胞		单核细胞		DC	
Ab	Siglec-7 %	对照%	Siglec-7 %	对照%	Siglec-7 %	对照%
4A1	89.5	131.9	39.8	90.4	99.6	95.1
4D7	84.7	119.0	33.9	83.5	73.3	106.5
4E3	30.8	94.0	15.1	87.8	11.2	96.9
7A3	76.3	136.3	23.7	69.7	11.0	119.3
7E11	75.2	127.1	8.1	77.4	19.3	103.9
7F12	86.3	124.4	39.0	88.4	96.9	91.5
10B5	36.5	122.6	6.7	75.3	16.8	112.1
10G8	83.8	133.4	30.9	70.1	10.5	121.4
无 Ab	100	100	100	100	100	100
mIgG 1	101.8	100.4	96.2	93.9	100.8	97.7
mIgG 2a	99.8	100.4	99.4	93.3	100.5	97.4
mIgG 2b	99.3	99.0	96.2	94.9	100.1	95.1
RDS7	98.2	96.0	99.6	81.3	96.7	105.9

[0705] 表8B:Siglec-7抗体降低人原代细胞中的Siglec-7的细胞表面水平

[0706]

	Siglec-7 表面表达%					
	巨噬细胞		NK 细胞		小神经胶质细胞	
Ab	Siglec-7%	对照%	Siglec-7%	对照%	Siglec-7%	对照%
1A12	13.4	103.6	136.5	99.6	28.6	88.6
1E8	9.1	88.8	143.6	98.5	41.3	71.1
2G1	95.7	92.3	113.9	98.8	106.2	82.6
2G4	14.1	96.2	126.1	101.5	23.0	81.9
3E11	7.4	85.7	107.9	101.6	34.2	82.1
4A1	13.1	96.0	132.4	98.8	26.3	85.8
4D7	24.1	74.8	87.6	101.2	44.3	84.1
4E3	4.2	78.3	31.2	100.8	20.9	92.7
7A3	8.3	85.0	77.1	102.1	ND	ND
7E11	5.7	83.9	50.7	101.6	11.5	74.1
7F12	13.1	93.0	124.1	98.5	28.1	78.8

[0707]

	Siglec-7 表面表达%					
	巨噬细胞		NK 细胞		小神经胶质细胞	
Ab	Siglec-7%	对照%	Siglec-7%	对照%	Siglec-7%	对照%
10B5	3.2	84.0	25.5	101.9	5.5	72.1
10G8	9.2	84.0	74.7	103.7	ND	ND
无 Ab	100	100	100	100	100	100
mIgG1	100.0	90.9	99.6	98.4	88.7	76.8
mIgG2a	100.0	96.0	100.9	99.2	84.2	85.2
mIgG2b	100.3	89.9	101.3	99.6	88.8	83.6
RDS7	98.7	90.4	102.6	100.4	80.2	74.6

[0708] 如表8A和8B中所示，大多数抗体能够降低多种类型的人细胞上Siglec-7的细胞表面水平。然而，使用Siglec-7的80％或更高的细胞表面表达水平的阈值，发现抗体2G1不降低任何测试的人细胞上Siglec-7的细胞表面水平。

[0709] 图7A-7F进一步证明，大多数抗体能够降低U937细胞(图7A)、人原代单核细胞(图7B)、人原代树突细胞(图7C)、人原代巨噬细胞(图7D)、人原代NK细胞(图7E)和人原代小神经胶质细胞(图7F)上Siglec-7的细胞表面水平。

[0710] 另外，进行体外表面Siglec-7下调研究，其中将Siglec-7抗体4E3和10B5针对12点曲线进行2倍滴定。在第5天收获从分离的人单核细胞用GM-CSF和IL-4分化的原代人树突细胞，并以每孔100,000个细胞涂铺在圆底96孔非TC处理的板中。将Siglec-7抗体针对浓度范围为6.67-0.00325nM的12点曲线进行2倍滴定以评估结合并计算半最大有效浓度(EC_{50})值。将抗体连续稀释，并将其与细胞在37℃下在含有10％FBS(Hyclone)和常规补充物的RPMI培

养基中一起孵育过夜。第二天，将细胞沉淀并与非竞争性FACS检测Siglec-7APC缀合的抗体克隆6-434(Biolegend)和对照受体CD11c PE-Cy7抗体(BD Biosciences)一起重悬浮于含有1％BSA和1mM EDTA的PBS中。将细胞与检测抗体一起在冰上孵育30分钟，然后在缓冲液中洗涤3次，然后在BD FACS Canto上分析。用FlowJo软件(TreeStar)对数据进行分析。

[0711] 如图7M中所示，抗Siglec-7抗体4E3和10B5能够下调原代人树突细胞上Siglec-7的细胞表面表达。CD11c对照受体的细胞表面表达不受用任一Siglec-7抗体处理影响(图7N)。表8C总结了从四种不同的供体分离的原代人树突细胞上所指示抗体对Siglec-7的细胞表面下调的结果。

[0712] 表8C.通过两种Siglec-7抗体进行的原代人树突细胞上的Siglec-7细胞表面下调

[0713]

供体编号	抗体：4E3		抗体：10B5	
	EC_{50} 值(pM)	95% CI (pM)	EC_{50} 值(pM)	95% CI (pM)
365	33.56	18.58 至 48.53	71.33	54.41 至 88.24
364	49.94	23.09 至 76.80	102.5	67.33 至 137.6
362	114.1	78.37 至 149.8	143.7	113.2 至 174.3
363	94.96	27.75 至 162.2	350.4	220.2 至 480.5

[0714] 其中抗体4E3和10B5针对12点曲线进行2倍滴定的体外研究表明用小鼠Siglec-7抗体的稳健Siglec-7受体下调，而CD11c对照受体在抗体处理后未受影响。这些数据显示小鼠Siglec-7抗体4E3下调50％的取自供体363的人原代骨髓细胞上的Siglec-7受体，EC50为94.96pM(95％置信区间为27.75至162.2pM)，并且小鼠Siglec-7抗体10B5下调50％的取自同一供体的人原代骨髓细胞上的Siglec-7受体，EC_{50}为350.4pM(95％置信区间为220.2-480.5pM)。

[0715] Siglec-7抗体对TREM2表达的作用

[0716] 为了测试降低Siglec-7的细胞表面水平的Siglec-7抗体调节TREM2表达的能力，在第6天收获了用GM-CSF和IL-4分化的人单核细胞来源的树突细胞，并且以每孔500,000个细胞与1.0μg/ml抗Silglec-7抗体10B5、同种型对照抗体一起涂铺于24孔皿中过夜或不处理。在第二天通过FACS分析检测CD11c、TREM2和Siglec-7的细胞表面受体表达。将细胞与生物素化的抗Siglec-7克隆10A9一起在冰上孵育20分钟。在一次洗涤后，将细胞在具有APC缀合的链霉亲和素(BD Biosciences，1:150稀释)、抗Siglec-7-PE克隆6-434(Biolegend)和抗CD11c-PECy7(BD Biosciences)的FACS缓冲液中在黑暗中在冰上孵育30分钟。将细胞在FACS缓冲液(PBS+2％FBS，2mM EDTA)中洗涤3次，并在BD FACS Canto上进行流式细胞术。使用TreeStar FlowJo软件分析数据。使用相应荧光团的MFI值，将数据计算为不存在抗体时受体表达的百分比。

[0717] 如图7G和7H中所示，能够降低Siglec-7的细胞表面水平的抗Siglec-7抗体10B5不影响TREM2表达。

[0718] TREM2中的功能丧失突变与严重的神经变性(包括那须哈科拉病、额颞叶痴呆和阿尔茨海默氏病)相关。据信含有ITIM的Siglec受体的调节可影响TREM2表达。因此，不会降低人免疫细胞上的TREM2表达的抗SIglec-7抗体可能是积极治疗结果的关键。图7G和7H中的

结果表明抗Siglec-7抗体克隆10B5(其稳健降低Siglec-7的细胞表面水平)不降低人树突细胞上的TREM2表达。

[0719] Siglec-7的体内表达

[0720] 为了测试Siglec-7抗体在体内降低Siglec-7的细胞表面水平的能力,使用了人源化NOG小鼠(hu-NOG)。Hu-NOG小鼠的遗传背景是NOD.Cg-Prkdc^{scid} Il2rg^{tm1Sug}/JicTac并植入人CD34^{+}造血干细胞。雌性Hu-NOG小鼠购自Taconic并在植入人细胞后15周使用。小鼠在第0天接受腹膜内注射40mg/kg抗Siglec-7抗体4E3或10B5或同种型对照小鼠IgG1抗体(克隆MOPC-21)。在第1天,将血液样品从小鼠抽取到肝素中,并且进行处理以用于FACS分析。简言之,首先将血液样品在冰冷的ACK裂解缓冲液中孵育5分钟以裂解红细胞,且然后用冷PBS充分洗涤。此程序重复两次。然后将细胞在抗人CD45-Pe-Cy7、抗小鼠CD45-APC-Cy7、抗人CD3-PerCP-Cy5.5、抗人CD14-FITC、抗人CD11c-PB、抗Siglec-7-APC、抗CD33-PE以及存活力染料(Life Technologies,目录号L34957)存在下在FACS缓冲液(PBS+2%FBS,2mM EDTA)中在冰上在Fc封闭溶液存在下孵育30分钟,然后用冷FACS缓冲液洗涤两次。然后获得4%PFA固定的样品。数据在BD FACS CANTO^{TM} II细胞计数器(Becton Dickinson)上采集并用TreeStar的FlowJo软件进行分析。在抗体处理后第-7、1、7和14天测定hCD45+、hCD14+细胞群中Siglec 7和CD33的表达水平。

[0721] 如图7I-7L中所示,当与同种型对照MOPC21抗体处理相比时,用抗Siglec-7抗体4E3和10B5处理能够降低经处理的hu-NOG小鼠的外周血的细胞中Siglec-7的细胞表面水平。早在用抗体4E3进行抗体处理后第1天,Siglec-7表达降低约60%,并且早在用抗体10B5进行抗体处理后第1天降低约80%(图7J)。作为比较,与在用mIgG1对照抗体处理后CD33的细胞表面水平相比,在抗Siglec-7抗体处理后无关表面受体CD33的细胞表面表达未显著降低(图7K)。

[0722] 这些结果证明,当使用人源化小鼠时,Siglec-7抗体体内接合Siglec-7并且功能性地下调人免疫细胞上的Siglec-7。所述结果进一步证明Siglec-7抗体4E3和10B5当注射到人源化小鼠中时,接合小鼠血液中循环的外周单核细胞上的Siglec-7。Siglec-7的抗体接合导致对Siglec-7具有特异性的受体下调而不是对照受体CD33。在单次注射10B5抗体后,在人单核细胞上表达的80%的Siglec-7在处理后第1天下调。对于4E3和10B5抗体,在用单一处理处理后7和14天,受体损失持续。

[0723] 实施例4:Siglec-7抗体与Siglec-7配体竞争结合至人Siglec-7

[0724] 以下实施例的目的是测试抗Siglec-7抗体是否识别Siglec-7上的配体结合位点并与配体竞争结合在Siglec-7受体上。

[0725] 为了确定哪些抗体与配体竞争结合至Siglec-7,根据标准方案(Kelm等人,Current Biology,1994)进行红细胞(RBC)固体粘附测定。将红细胞用含有唾液酸的糖蛋白高度修饰;因此,抗体阻断RBC与固定化Siglec-7结合的能力可用于确定配体干扰。简言之,将5μg/ml Siglec-7-Fc在室温下在96孔Immunolon板中涂覆过夜,然后用PBS洗涤,用结合缓冲液(含有%0.25 BSA 1mM $CaCl_2$的PBS)封闭1小时。使Siglec-7抗体(0.5μg/ml或1.0μg/ml)在室温下在轻轻摇动下结合1小时。在除去未结合的抗体后,将红细胞以3.0x10^{6}个细胞/ml的浓度添加至每个孔,并在室温下孵育1小时。然后将未结合的RBC用PBS小心地洗涤3次,并向每个孔中加入水用于低张性裂解结合的RBC。将板转移至-80℃持续10分钟,然后37

℃持续15分钟。通过过氧化物酶活性检测结合的RBC，然后用2N硫酸终止反应。在450nM处检测到信号。数据被计算为在不存在抗体的情况下与板结合的Siglec-7-Fc结合的RBC的百分比。

[0726] 表9中描绘了配体竞争测定的结果。在表9中，“mIgG1”和“mIgG2b”是指同种型对照抗体；“RDS7”是指可商购获得的抗Siglec-7抗体Mab1138(R&D Systems；目录号MAB 1138)；并且“仅RBC”是指不与抗体一起孵育的RBC。

[0727] 表9:Siglec-7抗体与配体竞争结合

[0728]

抗体	结合至 Siglec-7 的 RBC%
1A12	16.5
1E8	16.4
2G1	14.5
2G4	11.6
3E11	26.8
4A1	11.2
4D7	96.5
4E3.	20.2
7A3	89.5
7E11	89.3
7F12	7.9
10B5	88.4

[0729]

抗体	结合至 Siglec-7 的 RBC%
10G8	111.4
mIgG1	106.9
mIgG2b	101.6
RDS7	97.1
仅 RBC	100.0

[0730] 如表9中所示，抗体1A12、1E8、2G1、2G4、3E11、4A1、4E3和7F12能够阻断RBC与Siglec-7的结合，因此表明抗体与Siglec-7上的配体结合位点的竞争性结合，以及其抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(即阻断配体与Siglec-7的结合)的能力。然而，使用与Siglec-7结合的RBC的阈值为80％或更高，发现抗体4D7、7A3、7E11、10B5和10G8不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。

[0731] 图8进一步证明，抗体1A12、1E8、2G1、2G4、3E11、4A1、4E3和7F12能够阻断RBC与Siglec-7的结合，因此表明抗体与Siglec-7上的配体-结合位点的竞争性结合，以及其抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用(即阻断配体与Siglec-7的结合)的能力。

[0732] 实施例5:Siglec-7抗体功能研究的总结。

[0733] 表10总结了以上实施例3和4中描述的细胞表面表达和配体结合研究的结果。如表10中所示，存在三种一般类别的Siglec-7抗体。一类抗体降低Siglec-7的细胞表面水平而不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。第二类抗体既降低Siglec-7

的细胞表面水平，又抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用。第三类抗体抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用而不降低Siglec-7的细胞表面水平。

[0734] 在降低Siglec-7的细胞表面水平而不抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的抗体类别中的抗体包括:4D7、7A3、7E11、10B5以及10G8。

[0735] 在降低Siglec-7的细胞表面水平并抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用的抗体类别中的抗体包括:1A12、1E8、2G1、2G4、3E11、4A1、4E3以及7F12。

[0736] 在抑制Siglec-7与一种或多种Siglec-7配体之间的相互作用而不降低Siglec-7的细胞表面水平的抗体类别中的抗体包括:2G1。

[0737] 表10:Siglec-7抗体功能研究

[0738]

抗体	减少细胞表面Siglec-7	抑制Siglec-7配体结合
1A12	X	X
1E8	X	X
2G1		X
2G4	X	X
3E11	X	X
4A1	X	X
4D7	X	
4E3	X	X
7A3	X	
7E11	X	
7F12	X	X
10B5	X	
10G8	X	

[0739] 实施例6:配体与树突细胞上的Siglec-7的结合抑制T细胞增殖和吞噬

[0740] 用GM-CSF和IL-4使人树突细胞(DC)从外周血单核细胞中分化，并将其培养5天。收获未成熟(悬浮)DC并在12孔皿中以200,000个细胞/ml的密度接种。用TNFa(50μg/ml)、IL-1b(50μg/ml)、IL-6(150ng/ml)和前列腺素E2(1μg/ml)的细胞因子混合物活化DC 24小时。通过流式细胞术用可商购获得的针对LIN、CD11c、HLA-DR、CD86和CD83的抗体(BD Biosciences)确定树突细胞成熟。就在与同种异体分离的T细胞共培养之前，将活化的DC在无血清培养基中用唾液酸酶处理或不处理，在37℃下与来自霍乱弧菌(Vibrio cholera)的100mU/ml神经氨酸苷酶处理2小时。通过加入含血清的培养基猝灭酶促活性，将细胞沉淀并重新悬浮于完全培养基中。将唾液酸酶活化的、未处理的活化的或未活化的DC与同种异体CFSE标记的T细胞以1:10的比率共培养。将CD3/CD28 Dynal珠粒添加至仅T细胞作为阳性对照。在5天后，通过BD FACS Canto上的CFSE稀释来测量T细胞增殖。

[0741] 图9和10示出树突细胞上的唾液酸在混合淋巴细胞反应(MLR)期间限制T细胞增殖。图10示出正常表达抑制性配体的DC诱导低水平的T细胞增殖(左图)，而除去DC上的抑制性配体增加T细胞增殖(右图)。

[0742] 如图9和10中所示，当与未处理的活化的DC相比时，从活化的DC酶促除去唾液酸增加了T细胞增殖。这些结果表明，当与同种异体DC共培养时，存在于DC上的唾液酸以抑制性方式作用于T细胞以限制T细胞增殖。这些结果表明阻断T细胞或树突细胞上的Siglec-7的抗体增强了T细胞和/或树突细胞功能性。使用CD3/CD28Dynal珠粒作为阳性对照。此外，这些结果表明阻断唾液酸与DC或任何其它细胞或生物来源的相互作用可增加T细胞功能。

[0743] 实施例7：炎性病况诱导骨髓细胞中的Siglec-7唾液酸配体表达

[0744] 用GM-CSF和IL-4使人树突细胞(DC)从外周血单核细胞中分化并将其培养5天。未成熟的人DC在第5天收获并与来自B16、Lewis肺、MC38肿瘤上清液或10ng/ml LPS的无菌过滤上清液共培养。在24小时后，用直接缀合的Siglec-7-PE抗体通过流式细胞术测定Siglec-7表达。通过在冰上与50μg/ml的与人IgG1-Fc融合的可溶性Siglec-7孵育30分钟评估唾液酸配体表达，在存在人Fc阻断的情况下使用仅IgG1-Fc作为阴性对照。在洗涤步骤并在冰上与缀合至PE的抗人二级抗体一起孵育30分钟后，检测可溶性受体与细胞上唾液酸的结合。流式细胞术分析在BD FACS Canto上进行。

[0745] 为了引发原代巨噬细胞，分离来自外周人血液样品的人单核细胞并直接使用或用50μg/ml M-CSF分化成巨噬细胞5天。为了确定Siglec-7在炎性细胞因子产生中的作用，将人巨噬细胞与各种炎症介质一起培养，并且测量培养上清液中的细胞因子水平。为了产生人巨噬细胞，分离来自外周人血液样品的单核细胞并直接使用或用50μg/ml M-CSF分化成巨噬细胞或用100μg/ml GM-CSF和100μg/ml IL-4分化成树突细胞持续5天。将细胞培养5天，并且用PBS中的1mM EDTA分离粘附细胞。将细胞以10^5个细胞/孔涂铺在96孔板上并使其在37℃下粘附4小时。然后用浓度范围为0.01-100ng/ml(LPS)或0.01-100μg/ml(酵母聚糖)的TLR激动剂LPS(马流产沙门菌(Salmonella abortus equi))或酵母聚糖(酿酒酵母(Saccharomyces cerevisiae))刺激细胞。或者，在10ng/ml的细胞因子IL-4或50ng/ml的IFN-g存在下培养巨噬细胞。在刺激后24或48小时收集细胞培养物上清液，并根据制造商的方案通过使用细胞计量珠粒阵列炎症试剂盒(Cytometric Bead Array Inflammation Kit,BD)测量TNFα、IL-6、IL-10和MCP-1细胞因子的水平。预期用炎性介质LPS或酵母多糖刺激的巨噬细胞当用Siglec-7拮抗性抗体或用除去抑制性二醇配体的酶处理时分泌更多的炎性细胞因子TNFα、IL-6、IL-10和MCP-1。

[0746] 图11A和11B示出在暴露于肿瘤上清液后，Siglec-7表达在人树突细胞上维持。图11C和11D示出肿瘤上清液增加唾液酸(一种Siglec-7配体)的表达。图11E和11F示出在LPS诱导的炎症期间Siglec-7表达在人树突细胞上维持。图11G和11H示出LPS诱导的炎症增加唾液酸(一种Siglec-7配体)的表达。

[0747] 这些结果表明炎性病状和肿瘤环境导致Siglec-7和唾液酸配体两者的上调。所述结果还表明增加的Siglec-7功能可免疫抑制人原代树突细胞。这些结果表明，用下调或阻断抗体抑制Siglec-7可减轻免疫抑制的骨髓来源的或肿瘤相关的骨髓细胞并恢复免疫功能。这些结果进一步表明，阻断骨髓细胞上的Siglec-7的抗体增强骨髓细胞功能。

[0748] 实施例8：用唾液酸酶处理增加树突细胞对大肠杆菌的吞噬

[0749] 以下实施例的目的是测试拮抗性抗Siglec-7抗体和/或Siglec-7双特异性抗体是否诱导凋亡神经元、神经组织碎片、非神经组织碎片、细菌、其它异物以及致病蛋白(如Aβ肽、α突触核蛋白蛋白、Tau蛋白、TDP-43蛋白、朊病毒蛋白、亨廷顿蛋白)、RAN翻译产物抗原

(包括由来自骨髓谱系的细胞如单核细胞、树突细胞、巨噬细胞和小神经胶质细胞中的甘氨酸-丙氨酸(GA)、甘氨酸-脯氨酸(GP)、甘氨酸-精氨酸(GR)、脯氨酸-丙氨酸(PA)或脯氨酸-精氨酸(PR)组成的二肽重复序列(DPR肽))的吞噬。双特异性抗体可以是识别Siglec-7抗原和包括但不限于以下各项的第二抗原的抗体:CD3、Aβ肽、抗原或α突触核蛋白蛋白抗原或Tau蛋白抗原或TDP-43蛋白抗原或朊病毒蛋白抗原或亨廷顿蛋白抗原或RAN翻译产物抗原,包括由甘氨酸-丙氨酸(GA)、甘氨酸-脯氨酸(GP)、甘氨酸-精氨酸(GR)、脯氨酸-丙氨酸(PA)或脯氨酸-精氨酸(PR)组成的二肽重复序列(DPR肽)。

[0750] 使用RosetteSep™单核细胞分离抗体混合物(StemCell Technologies)分离来自外周人血液样品的单核细胞,并用GM-CSF和IL-4(PeproTech)分化成树突细胞并培养5天。将细胞在培养皿上涂铺在含有10%胎牛血清(Hyclone)的RPMI培养基(Invitrogen)中并在37℃下5%CO_2中培养。收集非粘附细胞并用于吞噬实验。

[0751] 为了进行细菌吞噬测定,收获树突细胞并涂铺在无细胞因子的96孔平底板中持续2小时。根据制造商的方案将pHrodo标记的大肠杆菌BioParticles重新悬浮,并且用来自霍乱弧菌的0.2U/ml或0.4U/ml唾液酸酶或仅PBS在37℃下处理2.5小时。将BioParticles洗涤,重新悬浮于RPMI中并添加20μg/孔。将树突细胞和大肠杆菌细胞混合、沉淀并在37℃下孵育30分钟。将细胞松弛素D以10μM添加至对照孔中。就在FACS分析之前,将细胞转移至冰并在4℃下在FACS缓冲液中洗涤2X。在BD FACS Canto上通过流式细胞术在PE通道中检测到pHrodo标记的大肠杆菌吞噬。

[0752] 图12示出唾液酸酶处理增加了大肠杆菌的树突细胞介导的吞噬。这些结果表明,例如降低Siglec-7的细胞表面表达和/或抑制一种或多种Siglec-7配体与Siglec-7的结合的拮抗性抗Siglec-7抗体和/或Siglec-7双特异性抗体也可用于诱导或以其它方式增加吞噬。

[0753] 实施例9:阿尔茨海默氏病患者的脑切片中Siglec-7配体的表达增加

[0754] 用生物素化的Siglec-7-Fc(R&D)通过免疫组织化学在正常和阿尔茨海默氏病(AD)患者的脑中检测到唾液酸配体表达。根据制造商的说明书用EZ-Link磺基-NHS-生物素(Thermo Scientific)将Siglec-7-Fc蛋白生物素化。除了过夜孵育之外,在振荡器上进行IHC程序。将样品在10%MeOH、3%H_2O_2(于PBS中)中孵育15分钟,随后在含有4%血清的PBS中洗涤3次。接下来,将样品在含0.2%triton-X、4%血清、0.019%L-赖氨酸的PBS中孵育30分钟,接着在一级抗体中孵育1小时,然后在4C下在PBS中与4%血清一起孵育过夜。第二天将样品置于振荡器上1小时,然后洗涤3次,然后将样品在ABC缓冲液中孵育1小时并洗涤3次。将样品用Vector DAB过氧化物酶试剂盒显色,洗涤3次并脱水,并用带有彩色照相机的尼康90i显微术成像(放大200倍)。使用Nikon Elements BR图像分析软件进行定量。

[0755] 图13A和13B示出唾液酸Siglec-7配体在来自两名AD患者(供体1和供体2)的脑切片中上调。来自5名AD和5名非AD人脑的数据通过单向ANOVA显示Siglec-7唾液酸配体表达的统计上显著的增加,p=0.0159(图13B)。

[0756] 这些结果表明从细胞表面除去Siglec-7或阻断增加的配体相互作用的抗体可减轻对大脑中小神经胶质细胞或其它骨髓细胞的抑制性Siglec-7-依赖性信号传导并恢复这些细胞的正常功能,对阿尔茨海默氏病具有有益作用。

[0757] 实施例10:癌细胞中Siglec-7配体的表达增加

[0758] 体外研究

[0759] 培养小鼠黑素瘤(B16)、Lewis肺肿瘤细胞或结肠癌(MC38)并在冰上与50ug/ml Siglec-7-Fc或IgG1-Fc对照一起孵育30分钟以确定这些细胞类型上的Siglec-7结合唾液酸配体表达的水平。结合相互作用在含有0.25％BSA、1mM $CaCl_2$的PBS中进行。为了检测Siglec-7受体结合,将山羊抗人Fc-PE二级抗体在洗去未结合的Siglec-7-Fc后在冰上孵育30分钟。将细胞在结合缓冲液中洗涤三次并在BD FACS Canto上通过流式细胞术进行分析。

[0760] 图14示出在黑色素瘤细胞、肺肿瘤细胞和结肠癌细胞中,抑制性Siglec-7配体的表达相对于本底增加至少20倍。不希望受理论束缚,在这些肿瘤细胞上抑制性唾液酸配体表达的鉴定表明癌细胞逃避免疫识别和清除的促成机制。肿瘤细胞上的唾液酸配体可经由在骨髓和淋巴免疫细胞上表达的Siglec-7介导免疫抑制相互作用。这些结果表明,从细胞表面移除Siglec-7或阻断增加的配体相互作用的抗体可减轻肿瘤对免疫系统的抑制作用并增强癌症疗法。

[0761] 体内研究

[0762] 在通过静脉内注射植入人胎儿肝$CD34^+$细胞(100,000个细胞/小鼠)前大约24小时,将四周龄的雌性Taconic NOG小鼠清髓化。通过外周血的流式细胞术监测免疫细胞的重建。在植入后12周,皮下植入Champions肿瘤移植黑色素瘤模型。大约8-10周后,当肿瘤达到150-200mm^3的大小时,收获血液、脾脏和肿瘤并在BD FACS Canto上通过流式细胞术处理以用于分析。进行流式细胞分析以确定Siglec-7在人($hCD45^+$)免疫系统的不同区室中的表达。具体地说,在$CD3^+$ T细胞、$CD14^+$单核细胞/巨噬细胞和其它CD3-CD14-人免疫细胞中分析表达。用TreeStar的FlowJo软件10.0.6版分析数据。

[0763] 如图15中所描绘,结果表明Siglec-7在人源化小鼠的移植的黑色素瘤肿瘤中在外周血、脾脏和肿瘤浸润免疫细胞中表达。重要的是,Siglec-7在人免疫细胞浸润黑色素瘤肿瘤中显著上调。这证明了此小鼠模型评估S Siglec-7抗体的治疗能力的相关性。

[0764] 实施例11:通过拮抗性和/或双特异性Siglec-7抗体减少骨髓细胞中的抗炎细胞因子IL-10

[0765] 此实施例的目的是测试在用拮抗性抗Siglec-7抗体和/或Siglec-7双特异性抗体处理并用100ng/ml LPS(Sigma)刺激、通过与凋亡细胞共培养或通过类似的刺激进行刺激后骨髓来源的骨髓细胞是否显示抗炎细胞因子IL-10和其它抗炎介质的减少。

[0766] 如先前所述进行人骨髓前体细胞的分离。在5天后更换培养基,并且将细胞再培养10-11天。在24小时后收集上清液,并且根据制造商的说明书(R&D Systems)通过IL-10ELISA测定从细胞释放的IL-10和其它抗炎细胞因子的水平(JEM(2005),201;647-657;以及PLoS Medicine(2004),4|第4期|e124)。

[0767] 实施例12:通过拮抗性和/或双特异性Siglec-7抗体诱导来自骨髓谱系的细胞中的吞噬

[0768] 此实施例的目的是测试拮抗性抗Siglec-7抗体和/或Siglec-7双特异性抗体是否诱导凋亡神经元、神经组织碎片、非神经组织碎片、细菌、其它异物以及致病蛋白(如Aβ肽、α突触核蛋白蛋白、Tau蛋白、TDP-43蛋白、朊病毒蛋白、亨廷顿蛋白)、RAN翻译产物抗原(包括由来自骨髓谱系的细胞如单核细胞、树突细胞、巨噬细胞和小神经胶质细胞中的甘氨酸-丙氨酸(GA)、甘氨酸-脯氨酸(GP)、甘氨酸-精氨酸(GR)、脯氨酸-丙氨酸(PA)或脯氨酸-精氨酸

(PR)组成的二肽重复序列(DPR肽))的吞噬。双特异性抗体可以是识别Siglec-7抗原和包括但不限于以下各项的第二抗原的抗体:Aβ肽、抗原或α突触核蛋白蛋白抗原或Tau蛋白抗原或TDP-43蛋白抗原或朊病毒蛋白抗原或亨廷顿蛋白抗原或RAN翻译产物抗原,包括由甘氨酸-丙氨酸(GA)、甘氨酸-脯氨酸(GP)、甘氨酸-精氨酸(GR)、脯氨酸-丙氨酸(PA)或脯氨酸-精氨酸(PR)组成的二肽重复序列(DPR肽)。

[0769] 使用RosetteSep单核细胞分离抗体混合物(StemCell Technologies)分离来自外周人血液样品的单核细胞,并用50μg/ml M-CSF(PeproTech)分化成巨噬细胞、嗜中性粒细胞和NK细胞持续5天。将细胞涂铺在培养皿上的含有10%胎牛血清(Hyclone)的RPMI培养基(Invitrogen)中并在37℃下5%CO_2中培养。通过轻轻刮取收集粘附细胞并用于吞噬实验。

[0770] 根据在Etemad等人,JI(2012)和Ohgidani等人,Scientific Reports(2014)中描述的方法通过在含有1%Pen/Strep、10ng/ml GM-CSF、10ng/ml M-CSF、10ng/mlβ-NGF、100ng/ml CCL-2、100ng/ml IL-34的无血清RPMI中培养,从外周血单核细胞制备人小神经胶质细胞。当出现分枝形态时,在第7-10天收获细胞。

[0771] 为了进行吞噬测定,将小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞或树突细胞与凋亡神经元、神经组织碎片、非神经组织碎片、细菌、其它异物和致病蛋白一起培养。将神经元培养5-10天,且然后以30nM的最终浓度加入冈田酸持续3小时以诱导细胞凋亡。用CellTracker CM-DiI膜染料(Molecular Probes)标记神经元细胞膜。在孵育后,将凋亡神经元或吞噬的其它靶标洗涤两次,并以1:20的效应子/靶标比添加至转导的小神经胶质细胞培养物中。在添加凋亡神经元后1小时和24小时,在共焦荧光显微术(Leica)下对具有吞噬神经元细胞膜的小神经胶质细胞的数量计数。在60的放大倍数下在三个不同区域中对凋亡细胞计数。通过流式细胞术确认吞噬的量。此外,在添加凋亡神经元后24、48或72小时,收集细胞并用于细胞因子的RT-PCR。

[0772] 为了进行微球珠粒或细菌吞噬测定,将小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞或树突细胞用抗Siglec-7激动性抗体处理。收获细胞并涂铺在无细胞因子的96孔平底板中持续2小时。根据制造商的方案将pHrodo标记的大肠杆菌BioParticles重新悬浮,并且用来自霍乱弧菌的0.2U/ml或0.4U/ml唾液酸酶或仅PBS在37C下处理2.5小时。将BioParticles洗涤,重新悬浮于RPMI中并添加20ug/孔。将细胞和大肠杆菌混合、沉淀并在37C下孵育30分钟。将细胞松弛素D以10uM添加至对照孔中。就在FACS分析之前,将细胞转移至冰并在4C下在FACS缓冲液中洗涤2次。在BD FACS Canto上通过流式细胞术在PE通道中检测到pHrodo标记的大肠杆菌吞噬。

[0773] 在24小时后,添加1.00μm的红色荧光微球珠粒(Fluoresbrite Polychromatic Red Mi-crospheres;Polysciences Inc.)持续1小时。通过荧光显微术分析小神经胶质细胞对微球珠粒的吞噬。此外,从培养板收集小神经胶质细胞并通过流式细胞术分析。测定具有吞噬珠粒的小神经胶质细胞的百分比。因为吞噬因实验而异,所以吞噬的相对变化也被确定。数据被显示为用激动性抗体和对照抗体培养的小神经胶质细胞之间的吞噬的相对变化。

[0774] 为了进行用于分析炎性基因转录物的RT-PCR,用Siglec-7载体或GFP1对照载体转导小神经胶质细胞。然后将细胞在培养皿上培养并用抗Siglec-7激动性抗体处理。在24、48和72小时后,使用Rneasy迷你试剂盒(Rneasy Mini Kit,QIAGEN)从小神经胶质细胞分离

RNA。还从已用sh-Siglec-7RNA、sh-对照RNA、wSiglec-7、GFP2、mtDAP12-GFP以及GFP1载体转导并与凋亡神经元共培养48小时的小神经胶质细胞中收集RNA。

[0775] 然后进行RNA的逆转录。SYBR Green的定量RT-PCR在ABI Prism 5700序列检测系统(Prism 5700 Sequence Detection System,PerkinElmer)上进行。GAPDH的扩增用于样品归一化。扩增方案遵循GeneAmp 5700序列检测系统软件(1.3版)。为了检测GAPDH、TNF-α、IL-1、NOS2和TGF-β转录物,以200nM的最终浓度使用以下正向和反向引物:

[0776] GAPDH正向引物:5′-CTCCACTCACGGCAAATTCAA-3′(SEQ ID NO:526),和GAPDH反向引物:5′-GATGACAAGCTTCCCATTCTCG-3′(SEQ ID NO:527);

[0777] TNF-α正向引物:5′-CCGTCAGCCGATTTGCTATCT-3′(SEQ ID NO:528),和TNF-α反向引物:5′-ACGGCAGAGAGGAGGTTGACTT-3′(SEQ ID NO:529);

[0778] IL-1α正向引物:5′-ACAA-CAAAAAAGCCTCGTGCTG-3′(SEQ ID NO:530),和IL-1α反向引物:5′-CCATTGAGGTGGAGAGCTTTCA-3′(SEQ ID NO:531);

[0779] NOS2正向引物:5′-GGCAAACCCAAGGTCTACGTTC-3′(SEQ ID NO:532),NOS2反向引物:5′-TACCTCATTGGCCAGCTGCTT-3′(SEQ ID NO:533);以及

[0780] TGF-β1正向引物:5′-AGGACCTGGGTTGGAAGTGG-3′(SEQ ID NO:534),和TGF-β1反向引物:5′-AGTTGGCATGGTAGCCCTTG-3′(SEQ ID NO:535)。

[0781] 为了进行淀粉样蛋白吞噬测定,将HiLyteFluor™ 647(Anaspec)-Aβ-(1-40)以20mM重新悬浮于Tris/EDTA(pH 8.2)中,且然后在37℃下在黑暗中孵育3天以促进聚集。将小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞或树突细胞在低血清(补充有胰岛素的0.5%FBS)、LPS(50ng/ml)、IFNc(100单位/ml)和抗Siglec-7拮抗性抗体中预处理24小时,之后添加聚集的荧光标记的aβ肽。在添加100nM聚集的HiLyteFluor™ 647-Ab-(1-40)(ASN NEURO(2010)2(3):157-170)后5小时通过流式细胞术分析确定Siglec-7的淀粉样蛋白吞噬和表面表达。以类似的方式进行其它致病蛋白的吞噬。

[0782] 实施例13:通过拮抗性Siglec-7抗体和/或双特异性抗体诱导SYK和/或ERK活化

[0783] 此实施例的目的是测试激动性抗Siglec-7抗体和/或Siglec-7双特异性抗体是否诱导Syk和ERK活化。

[0784] 将小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞或树突细胞暴露于激动性抗Siglec-7和/或Siglec-7双特异性抗体1小时。在刺激后,将细胞在还原样品缓冲液中裂解以用于蛋白质印迹分析。通过蛋白质印迹分析(JEM(2005),201,647-657)分别用抗磷酸-Syk或ERK和抗Syk或ERK抗体(均来自Cell Signaling Technology)通过免疫检测确定ERK的磷酸化和Syk和/或ERK的总量。

[0785] 实施例14:Siglec-7抗体和/或双特异性抗体诱导Syk磷酸化

[0786] 脾酪氨酸激酶(Syk)是一种细胞内信号传导分子,其通过磷酸化若干底物而在Siglec-7下游起作用,由此促进形成导致细胞活化和炎性过程的信号传导复合物。通过培养人巨噬细胞、人嗜中性粒细胞、人NK细胞和人原代树突细胞并测量细胞提取物中Syk蛋白的磷酸化状态来测定激动剂Siglec-7抗体诱导Syk活化的能力。

[0787] 将人原代树突细胞在1%血清RPMI中饥饿4小时,且然后用PBS-EDTA从组织培养皿中移出,用PBS洗涤并计数。将细胞用全长激动剂Siglec-7抗体或对照抗体在冰上涂覆15分钟。在用冷PBS洗涤后,将细胞在山羊抗人IgG存在下在37℃下孵育指定的时间段。在刺激

后，将细胞用裂解缓冲液(1％v/v NP-40％、50Mm Tris-HCl(pH 8.0)、150mM NaCl、1mM EDTA、1.5mM $MgCl_2$、10％甘油加上蛋白酶和磷酸酶抑制剂)裂解，然后在4℃下以16,000g离心10分钟以除去不溶性物质。然后用抗Syk Ab(4D10用于人DC，Santa Cruz Biotechnology)免疫沉淀裂解物。将沉淀的蛋白质通过SDS-PAGE分级分离，转移至PVDF膜并用抗磷酸酪氨酸Ab(4G10，Millipore)探测。为了证实所有底物都被充分免疫沉淀，用抗Syk(Novus Biological，用于人DC)重新探测免疫印迹。如所描述(例如，Peng等人，(2010)Sci Signal.，3(122)：ra38)，使用增强的化学发光(ECL)系统(GE healthcare)进行可视化。

[0788] 实施例15：通过拮抗性Siglec-7抗体和/或双特异性抗体诱导小神经胶质细胞、巨噬细胞、嗜中性粒细胞，NK细胞和树突细胞中的CCR7和朝向CCL19和CCL21的迁移

[0789] 此实施例的目的是测试抗Siglec-7抗体和/或Siglec-7双特异性抗体是否在小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞和树突细胞中诱导CCR7和朝向CCL19和CCL21的迁移。

[0790] 将小神经胶质细胞、巨噬细胞或树突细胞与激动性抗Siglec-7和/或Siglec-7/DAP12双特异性抗体或与对照抗体一起培养。在72小时后收集细胞，用CCR7特异性抗体免疫标记，并通过流式细胞术分析。

[0791] 为了确定增加的CCR7表达的任何功能性后果，进行趋化性测定。用拮抗性抗Siglec-7和/或Siglec-7/DAP12双特异性抗体经由Siglec-7刺激小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞或树突细胞并置于双室系统中。量化朝向趋化因子配体CCL19和CCL21迁移的小神经胶质细胞的数量(JEM(2005)，201，647-657)。

[0792] 对于趋化性测定，将小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞或树突细胞暴露于拮抗性抗Siglec-7抗体或Siglec-7双特异性抗体并用1μg/ml LPS处理。将小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞或树突细胞转移到transwell系统(3μm孔滤器；Millipore)的含有450μl培养基的上室中，其中下室中具有100ng/ml CCL19或CCL21(均来自PeproTech)。在1小时孵育期后，通过显微术在三个独立区域对已经迁移到下室的小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞或树突细胞的数量计数(JEM(2005)，201，647-657)。

[0793] 实施例16：通过拮抗性Siglec-7抗体和/或双特异性抗体诱导小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞和树突细胞中的F-肌动蛋白

[0794] 此实施例的目的是测试拮抗性抗Siglec-7抗体或Siglec-7双特异性抗体是否在小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞和树突细胞中诱导F-肌动蛋白。

[0795] 将用Siglec-7转导或表达Siglec-7的目标小神经胶质细胞、巨噬细胞、嗜中性粒细胞、NK细胞或树突细胞和其它目标细胞添加至培养板，且然后暴露于拮抗性抗Siglec-7和/或Siglec-7双特异性抗体或对照抗体。将细胞固定、封闭，且然后在1小时后用Alexa Fluor 546缀合的鬼笔环肽(Molecular Probes)染色，并用荧光染料标记F-肌动蛋白。通过共聚焦激光扫描显微术用40倍物镜收集图像(Leica)。(JEM(2005)，201，647-657)。

[0796] 实施例17：通过拮抗性Siglec-7抗体和/或双特异性抗体诱导破骨细胞产生并提高破骨细胞生成速率

[0797] 此实施例的目的是测试拮抗性抗Siglec-7抗体和/或Siglec-7双特异性抗体是否

诱导破骨细胞产生并提高破骨细胞生成速率。

[0798] 将人单核细胞来源的单核细胞/巨噬细胞维持于补充有10％FBS(Atlantic Biologics,Atlanta,GA,USA)和青霉素-链霉素-谷氨酰胺(Mediatech)的RPMI-1640培养基(Mediatech)或另一适当培养基中。将细胞以3000个细胞/孔在96孔板中接种在补充有10％FBS、青霉素-链霉素-谷氨酰胺、50ng/ml RANKL和20ng/ml M-CSF的α-MEM培养基中。培养基每3天更换一次,暴露于抗Siglec-7拮抗性抗体,并对多核(至少3个细胞核)$TRACP^+$破骨细胞的数量进行计数并通过光学显微术评分。为了确定复杂性和大小,将破骨细胞通过细胞核的数量(>10或3-10个细胞核)进行计数。还通过使用Image J软件(NIH)测量破骨细胞的表面积。另外,测定破骨细胞基因的表达水平。使用TRIzol试剂(Invitrogen)在不同时间点从破骨细胞生成培养物中提取总RNA。在使用SuperScript III试剂盒(Invitrogen)进行第一链cDNA合成后,针对Nfatc1、Acp5、Ctsk、Calcr和Ccnd1进行实时定量PCR反应。计算靶mRNA表达的相对定量并归一化至亲环蛋白的表达并表达为(靶基因的mRNA/亲环蛋白的mRNA)$3X10^6$.(J.OF BONE AND MINERAL RESEARCH(2006),21,237-245;J Immunol 2012;188:2612-2621)。

[0799] 或者,将巨噬细胞、嗜中性粒细胞或NK细胞一式三份接种到板上,并用RANKL、M-CSF和抗Siglec-7和/或Siglec-7双特异性抗体或同种型匹配的对照单克隆抗体进行处理。将培养基每3天更换一次,直到出现大量多核细胞。在培养3至5天后,将细胞用PBS中的3.7％甲醛固定10分钟。然后将板在PBS中洗涤两次,在50％丙酮和50％乙醇的溶液中孵育30秒,并用PBS洗涤。用来自Sigma的试剂盒(产品435)对细胞进行抗酒石酸酸性磷酸酶(TRAP)染色。如所描述(例如,Peng等人,(2010)Sci Signal.,3(122):ra38),然后通过光学显微术对多核(多于两个细胞核)TRAP阳性细胞进行计数。

[0800] 实施例18:在整个动物中体内保护免遭EAE和铜宗

[0801] 将成年7-9周龄的雌性C57BL/6小鼠(获自Charles River Laboratories)在尾根部双侧注射200μl含在不完全弗氏佐剂(Difco)中的100μg的髓磷脂少突胶质细胞糖蛋白肽35-55(氨基酸MEVGWYRSPFSRVVHLYRNGK(SEQ ID NO:536);Seqlab)的接种物和1mg结核分枝杆菌H37 Ra(Difco)。在免疫后第0天和第2天注射百日咳毒素(200ng;List Bio-logical Laboratories)。临床体征评分如下:0,无临床体征;1,完全尾松软;2,完全尾松软和步态异常;3,一个后肢轻瘫;4,完全后肢轻瘫;以及5,前肢和后肢瘫痪或垂死。仅在第14天具有疾病发作(临床评分为1或更高)的小鼠才用于实验。将激动性抗Siglec-7和/或Siglec-7双特异性抗体在第一次临床症状当天或在任何其它所需时间腹膜内或静脉内注射于EAE患病小鼠中(PLoS Med(2007)4(4):e124)。

[0802] 向年轻或老龄野生型(WT)小鼠饲喂含有0.2％铜宗(CPZ)粉状草酸双(亚环己基酰肼)(Sigma-Aldrich)的标准饮食(Harlan)持续4、6或12周。对于组织学和免疫组织化学分析,在用4％多聚甲醛(PFA)小鼠灌注后除去大脑,在4％PFA中固定24小时,然后在30％蔗糖中浸泡24-48小时。为了评价髓磷脂完整性和损伤以及细胞增殖和炎症,将切片或小鼠脑用抗MBP(1:100;Abcam,ab7349)、抗dMBP(1:2000;Millipore;ab5864)、抗βAPP(1:100;Invitrogen,51-2700)、抗SMI-31(1:1000;Covance,smi-31R)、抗Iba1(1:600;Wako,019-19741)、抗BrdU(1:250;Abcam,ab1893)、抗GFAP(1:200;Invitrogen,13-0300)、抗iNOS(1:100;BD Pharmingen,610329)、抗LPL(1:400,来自Dr.G.Olivecrona)以及抗MHC II(1:100;

BD Pharmingen,553549)染色。对于抗体的行为作用,使用透明聚苯乙烯外壳和计算机化光感仪器分析小鼠的自主活动。对一般活动变量(总步行、垂直后退站立)以及情绪指数(包括所花费的时间、行进距离和条目)进行分析。进行一系列感觉运动测试来评估平衡(台架和平台)、强度(倒屏)、协调(极点和倾斜屏幕)和开始运动(步行开始)。使用转棒方案研究运动协调和平衡(Cantoni等人,Acta Neuropathol(2015)129(3):429-47)。

[0803] 实施例19:拮抗性Siglec-7抗体和/或Siglec-7双特异性抗体在建立的创伤性脑损伤动物模型中的治疗用途的表征

[0804] 在创伤性脑损伤的建立的动物模型中测试拮抗性抗Siglec-7和/或Siglec-7双特异性抗体的治疗效用(Tanaka,Y等人(2013)Neuroscience 231 49-60)。可使用一般小鼠或在细菌人工染色体下或在骨髓启动子下表达人Siglec-7基因的小鼠。例如,使用诱导小神经胶质细胞和星形胶质细胞的活化的创伤性脑损伤模型。使用8或9周龄的雄性C57BL/6J WT小鼠(购自Charles River Laboratories或Jackson Laboratories)。通过腹膜内施用溶于无菌盐水中的甲苯噻嗪盐酸盐(8mg/kg)和水合氯醛(300mg/kg)将小鼠麻醉,且随后置于立体定位仪(Narishige,Tokyo,Japan)中。将头皮切开,且露出颅骨。将骨膜从头骨上清除,用牙钻在右大脑半球上钻一个孔,并用针尖除去硬脑膜。使用外径为0.5mm的不锈钢套管在右半球取得纵向刺伤伤口。将套管定位在中线侧面1.3mm和前囟后1mm处,并将其引入脑中直到尖端达到2mm的深度。然后将套管尾端移动2mm(前囟3mm),且然后向后移回2mm直到其初始位置。最后,从脑中取出套管,并缝合头皮伤口。然后根据标准程序用拮抗性抗Siglec-7和/或Siglec-7双特异性抗体处理小鼠,且然后通过组织学和免疫荧光染色和行为测试进行分析。这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0805] 实施例20:拮抗性Siglec-7抗体和/或Siglec-7双特异性抗体在毒素诱导的损伤后的神经炎症和神经元损失模型中的治疗用途的表征

[0806] 在毒素诱导的损伤后的神经炎症和神经元损失模型中测试了激动性抗Siglec-7和/或Siglec-7双特异性抗体的治疗效用(Martens,LH等人,(2012)The Journal of Clinical Investigation,122,3955)。将三个月大的一般小鼠每天用4次腹膜内注射MPTP(1-甲基-4-苯基-1,2,3,6-四氢吡啶)(4μg/g体重)(Sigma-Aldrich)或PBS处理2天。如所描述,根据标准方案用激动性抗Siglec-7和/或Siglec-7双特异性抗体处理小鼠,且然后使用体视学计数进行分析以定量黑质致密部(SNpc)中的多巴胺神经元和小神经胶质细胞。这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0807] 实施例21:拮抗性Siglec-7抗体和/或Siglec-7双特异性抗体在衰老、癫痫发作、脊髓损伤、视网膜营养不良、额颞叶痴呆和阿尔茨海默氏病的动物模型中的治疗用途的表征

[0808] 在老化、癫痫发作、脊髓损伤、视网膜营养不良、额颞叶痴呆、亨廷顿疾病、帕金森氏病、肌萎缩性侧索硬化和阿尔茨海默氏病的动物模型中测试了拮抗性抗Siglec-7和/或Siglec-7双特异性抗体的治疗效用,如先前所描述(例如,Beattie,MS等人,(2002)Neuron 36,375-386;Volosin,M等人,(2006)J.Neurosci.26,7756-7766;Nykjaer,A等人,(2005)

Curr.Opin.Neurobiol.15,49-57;Jansen,P等人,(2007)Nat.Neurosci.10,1449-1457;Volosin,M等人,(2008)J.Neurosci.28,9870-9879;Fahnestock,M等人,(2001)Mol.Cell Neurosci.18,210-220;Nakamura,K等人,(2007)Cell Death.Differ.14,1552-1554;Yune,T等人,(2007)Brain Res.1183,32-42;Wei,Y等人,(2007)Neurosci.Lett.429,169-174;Provenzano,MJ等人,(2008)Laryngoscope 118,87-93;Nykjaer,A等人,(2004)Nature 427,843-848;Harrington,AW等人,(2004)Proc.Natl.Acad.Sci.U.S.A.101,6226-6230;Teng,HK等人,(2005)J.Neurosci.25,5455-5463;Jansen,P等人,(2007)Nat.Neurosci.10,1449-1457;Volosin,M等人,(2008)J.Neurosci.28,9870-9879;Fan,YJ等人,(2008)Eur.J.Neurosci.27,2380-2390;Al-Shawi,R等人,(2008)Eur.J.Neurosci.27,2103-2114;以及Yano,H等人,(2009)J.Neurosci.29,14790-14802)。这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0809] 实施例22:拮抗性Siglec-7抗体和/或Siglec-7双特异性抗体在感染模型中的治疗用途的表征

[0810] 在感染模型中测试了拮抗性抗Siglec-7抗体和/或Siglec-7双特异性抗体的治疗效用。例如,如先前所描述(例如,Yin,F等人,(2009)J.Exp.Med,207,117-128),可使用正常小鼠中的单核细胞增多性李斯特氏菌或其它感染。可使用一般小鼠或在细菌人工染色体下或在骨髓启动子下表达人Siglec-7基因的小鼠。

[0811] 实施例23:拮抗性Siglec-7抗体和/或Siglec-7双特异性抗体在炎性疾病模型中的治疗用途的表征

[0812] 在炎性疾病模型中测试了拮抗性抗Siglec-7抗体和/或Siglec-7双特异性抗体的治疗效用。例如,类风湿性关节炎或另一种炎性疾病的建立模型中(Mizoguchi(2012)Prog Mol Biol Transl Sci.,105:263-320;以及Asquith等人,(2009)Eur J Immunol.39:2040-4)。这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0813] 实施例24:筛选诱导或抑制Siglec-7和下游信号传导分子的磷酸化的抗Siglec-7抗体和/或Siglec-7双特异性抗体。

[0814] 用PBS-EDTA从组织培养皿中移出细胞(J774、RAW 264.7、BMM细胞、人原代单核细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、T细胞、小神经胶质细胞或破骨细胞),用PBS洗涤并计数。将细胞与抗Siglec-7抗体和/或Siglec-7双特异性抗体或与1μg/10^6细胞的同种型匹配的对照抗体在冰上或在其它条件下孵育20分钟。将细胞在冰冷的放射免疫沉淀测定(RIPA)缓冲液中裂解20分钟,然后在4℃下以16,000g离心10分钟以除去不溶物质。使所得上清液与所指示抗体(DAP12,ERK或AKT)和蛋白质A-或蛋白质G-琼脂糖(Sigma)进行免疫沉淀反应。将珠粒用RIPA缓冲液充分洗涤并通过SDS-聚丙烯酰胺凝胶电泳(SDS-PAGE)分离蛋白质。然后通过蛋白质印迹将蛋白质转移至硝酸纤维素膜,与适当的抗体(特异性地识别磷酸化酪氨酸或磷酸化形式的DAP12、ERK、Svk、LCK、FYN、C-Cbl、VAV或AKT的抗体)一起孵育并用增强的化学发光(ECL)系统(Pierce)可视化,如所描述(例如,Peng等人,(2010)Sci Signal.,3(122):ra38)。

[0815] 实施例25:筛选诱导或抑制钙通量的抗Siglec-7和/或Siglec-7双特异性抗体

[0816] 将BMM细胞用含HEPES的缓冲液[20mM HEPES(pH 7.3)、120mM NaCl、1mM CaCl、1mM MgCl、5mM KCl、葡萄糖(1mg/ml)、牛血清白蛋白(1mg/ml)]洗涤两次,然后在37℃下在0.05%Pluronic F-127(Invitrogen)和1μM Indo-1 AM(Invitrogen)中孵育20分钟。将细胞用HEPES缓冲液洗涤两次,且然后用抗Siglec-7抗体和/或Siglec-7双特异性抗体(16μg/ml)或用对照抗体(16μg/ml)刺激,并通过分光光度计(PTL Photon Technology Intemational)监测。根据制造商的说明书(例如,Peng等人,(2010)Sci Signal.,3(122):ra38)将Indo-1荧光发射转化为钙(Ca^{2+})。

[0817] 实施例26:Siglec-7增加巨噬细胞、嗜中性粒细胞、NK细胞和树突细胞的存活

[0818] 为了评价Siglec-7在细胞存活中的作用,在存在炎性介质的情况下培养人或小鼠巨噬细胞、嗜中性粒细胞、NK细胞、小神经胶质细胞、T细胞和树突细胞,并测量细胞存活。

[0819] 通过用冷PBS冲洗胫骨和股骨骨髓细胞获得来自表达Siglec-7的小鼠或WT小鼠的鼠骨髓前体细胞。用PBS洗涤一次后,将红细胞使用ACK裂解缓冲液(Lonza)裂解,用PBS洗涤两次并以$0.5x10^6$个细胞/ml与指示量的50ng/ml M-CSF一起悬浮于完全RPMI培养基(10%FCS、Pen/Strep、Gln、neAA)中以产生巨噬细胞、嗜中性粒细胞或NK细胞,或者与10ng/ml GM-CSF一起悬浮于所述完全RPMI培养基中以产生树突细胞。对于M2型巨噬细胞,将10ng/ml IL-4添加至培养的细胞。对于M1型巨噬细胞,添加50ng/ml IFN。在一些实验中,将LPS或酵母聚糖在第5天以1μg/ml-0.01ng/ml的浓度范围添加至细胞培养物。重组细胞因子购自Peprotech。

[0820] 为了分析骨髓源性巨噬细胞、嗜中性粒细胞或NK细胞的存活力,如上制备细胞并在MCSF中培养。在非组织培养物处理的板中将细胞以10^5/200μL涂铺于96孔板(用于使用基于荧光素酶的测定的存活力分析)或以$0.5x10^6$/1ml涂铺于6孔板中(用于台盼蓝排除细胞计数)。在第3天添加含有新鲜M-CSF的培养基。在所指示的时间点,用3mM EDTA从板中轻轻分离细胞,并使用Burker室计数。对于活细胞的FACS分析,将巨噬细胞在50ng/ml MCSF中培养6天(+MCSF)或在50ng/ml MCSF中培养4天,之后将MCSF除去持续另外36小时(-MCSF)。将细胞使用CD11b抗体和DAPI染色。对于荧光素酶存活力测定,在分级浓度的生长因子GMCSF(树突细胞)、MCSF(M1巨噬细胞)或MCSF+IL-4(M2巨噬细胞)中培养的第5天测量细胞存活力。将细胞直接与ToxGlo试剂(Promega)一起孵育,并测定荧光素酶活性(发光)。对于在炎性介质IFN、LPS或酵母聚糖存在下培养的存活巨噬细胞的FACS分析,在第5天收集细胞并使用CD11b抗体和DAPI染色。

[0821] 实施例27:Siglec-7增加巨噬细胞、嗜中性粒细胞或NK细胞上炎性细胞表面标志物的表达

[0822] 为了确定Siglec-7在炎症标志物表达中的作用,将巨噬细胞、嗜中性粒细胞和NK细胞与各种炎性介质一起培养,并且在存在或不存在Siglec-7抗体下测量表面标志物(例如CD86和CD206)的表达。

[0823] 将巨噬细胞、嗜中性粒细胞和NK细胞涂铺并使其在37℃下粘附4小时,并且以0.01-100ng/ml(LPS)或0.01-10μg/ml(酵母聚糖)范围内的浓度添加TLR激动剂LPS(马流产沙门氏菌)和酵母聚糖(酿酒酵母)。或者,在细胞因子IL-4(10ng/ml)或IFN(0.5-50ng/ml)存在下培养巨噬细胞、嗜中性粒细胞和NK细胞。48小时后在BD FACS Canto上进行CD86和CD206的FACS分析。使用FlowJo(TreeStar)软件10.0.7版进行数据分析。

[0824] 实施例28:Siglec-7抗体和/或双特异性抗体的抗癌作用的分析

[0825] 将8周龄(+/-2周龄)的10只C57B16/NTac小鼠组(一般小鼠或表达来自细菌人工染色体或来自骨髓启动子的人Siglec-7基因的小鼠)用悬浮在100ul PBS中的肿瘤细胞(例如$1x10^5$至$1x10^6$个MC38 Lewis肺或B16细胞)皮下激发。在植入前将动物用异氟烷麻醉。从第2天开始,将各组小鼠用200ug的每种拮抗性抗Siglec-7抗体每3天4个剂量i.p.注射。用卡尺每两周监测肿瘤生长以在第4天开始测量肿瘤生长。实验的终点是2000mm^3的肿瘤体积或60天。肿瘤生长和存活%是结果量度。肿瘤摄取和生长速率降低、肿瘤浸润性免疫抑制性巨噬细胞、嗜中性粒细胞和/或NK细胞数量减少以及效应性T细胞流入肿瘤增加指示阻断抗Siglec-7抗体的抗癌作用。

[0826] 表达人IL-3、人GM-CSF、人IL-6、人IL-2并用来自人胎盘、胎肝、外周血或另一来源的人免疫细胞接种的免疫缺陷小鼠或免疫缺陷转基因小鼠也可用于此类研究(Ito M等人,(2008)Curr Top Microbiol Immunol.;324:53-76;Ito R.,等人,(2012)Cellular& Molecular Immunology 9,208-214;Brehm等人,(2010)Curr Opin Endocrinol Diabetes Obes.17(2):120-125;Zhou等人,(2013)Cancer Letters.344,13-19)。此类小鼠可与细胞系肿瘤或患者来源的人肿瘤异种移植物结合使用(Siolas等人,(2013)Cancer Res.;73(17):5315-5319)。

[0827] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0828] 实施例29:将Siglec-7抗体和/或双特异性抗体与针对抑制性检查点蛋白或抑制性细胞因子/趋化因子及其受体的抗体组合的组合疗法的累加抗肿瘤作用的分析

[0829] 如实施例28中所述,将8周龄(+/-2周龄)的15只C57B16/NTac小鼠组用肿瘤细胞皮下激发。在植入前将动物用异氟烷麻醉。从第2天开始,在第3天、第6天和第9天将小鼠用200ug抗Siglec-7抗体单独或与针对检查点蛋白的抗体(例如,抗PDL1 mAb克隆10F.9G2和/或抗CTLA4 mAb克隆UC10-4F10-11)组合每3天4个剂量i.p.注射。处理组包括抗Siglec-7;抗CTLA-4;抗PDL1;抗Siglec-7+抗CTLA4;抗Siglec-7+抗PDL1;以及同种型对照。用卡尺每两周监测肿瘤生长以在第4天开始测量肿瘤生长。实验的终点是2000mm^3的肿瘤体积或60天。肿瘤生长和存活%是结果量度。在组合疗法情况下肿瘤生长减少和存活%增加表明抗Siglec-7抗体与抗检查点抗体具有累加或协同的治疗作用。针对检查点分子的拮抗性抗体包括针对PDL1、PDL2、PD1、CTLA4、B7-H3、B7-H4、HVEM、BTLA、KIR、GAL9、TIM3、A2AR、LAG-3和磷脂酰丝氨酸的抗体。针对抑制性细胞因子的拮抗剂抗体包括针对CCL2、CSF-1和IL-2的抗体。表达人IL-3、人GM CSF、人IL-6、人I12并用来自人胎盘、胎肝、外周血或另一来源的人免疫细胞接种的免疫缺陷小鼠或免疫缺陷转基因小鼠也可用于此类研究(Ito M等人,(2008)Curr Top Microbiol Immunol.;324:53-76;Ito R.,等人,(2012)Cellular&Molecular Immunology 9,208-214;Brehm等人,(2010)Curr Opin Endocrinol Diabetes Obes.17(2):120-125;Zhou等人,(2013)Cancer Letters.344,13-19)。此类小鼠可与细胞系肿瘤或患者来源的人肿瘤异种移植物结合使用(Siolas等人,(2013)Cancer Res.;73(17):5315-5319)。

[0830] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人

Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0831] 实施例30:将Siglec-7抗体和/或双特异性抗体与活化刺激性检查点蛋白的抗体组合的组合疗法的累加抗肿瘤作用的分析

[0832] 如实施例28中所述,将8周龄(+/-2周龄)的15只C57B16/NTac小鼠组用肿瘤细胞皮下激发。在植入前将动物用异氟烷麻醉。从第2天开始,在第3天、第6天和第9天将小鼠用200ug抗Siglec-7抗体单独或与活化刺激性检查点蛋白的激动性抗体(例如OX40或ICOS mAb)组合每3天4个剂量i.p.注射。用卡尺每两周监测肿瘤生长以在第4天开始测量肿瘤生长。实验的终点是2000mm^{3}的肿瘤体积或60天。肿瘤生长和存活%是结果量度。在组合疗法情况下肿瘤生长减少和存活%增加表明抗Siglec-7抗体与刺激性检查点抗体具有累加或协同的治疗作用。刺激性检查点抗体包括针对CD28、ICOS、CD137、CD27、CD40和GITR的激动性/刺激性抗体。

[0833] 表达人IL-3、人GM CSF、人IL-6、人Il2并用来自人胎盘、胎肝、外周血或另一来源的人免疫细胞接种的免疫缺陷小鼠或免疫缺陷转基因小鼠也可用于此类研究(Ito M等人,(2008)Curr Top Microbiol Immunol.;324:53-76;Ito R.,等人,(2012)Cellular& Molecular Immunology 9,208-214;Brehm等人,(2010)Curr Opin Endocrinol Diabetes Obes.17(2):120-125;Zhou等人,(2013)Cancer Letters.344,13-19)。此类小鼠可与细胞系肿瘤或患者来源的人肿瘤异种移植物结合使用(Siolas等人,(2013)Cancer Res.;73(17):5315-5319)。

[0834] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有人Siglec-7cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0835] 实施例31:将Siglec-7抗体和/或双特异性抗体与刺激性细胞因子组合的组合疗法的累加抗肿瘤作用的分析

[0836] 如实施例28中所述,将8周龄(+/-2周龄)的15只C57B16/NTac小鼠组用肿瘤细胞皮下激发。在植入前将动物用异氟烷麻醉。从第2天开始,将小鼠用200ug抗Siglec-7抗体单独或与刺激性细胞因子(例如IL-12、IFN-a)组合每3天4个剂量i.p.注射。用卡尺每两周监测肿瘤生长以在第4天开始测量肿瘤生长。实验的终点是2000mm^{3}的肿瘤体积或60天。肿瘤生长和存活%是结果量度。在组合疗法情况下肿瘤生长减少和存活%增加表明抗Siglec-7抗体与免疫刺激性细胞因子具有累加或协同的治疗作用。刺激性细胞因子包括IFN-a/b、IL-2、IL-12、IL-18、GM-CSF和G-CSF。

[0837] 表达人IL-3、人GM CSF、人IL-6、人Il2并用来自人胎盘、胎肝、外周血或另一来源的人免疫细胞接种的免疫缺陷小鼠或免疫缺陷转基因小鼠也可用于此类研究(Ito M等人,(2008)Curr Top Microbiol Immunol.;324:53-76;Ito R.,等人,(2012)Cellular& Molecular Immunology 9,208-214;Brehm等人,(2010)Curr Opin Endocrinol Diabetes Obes.17(2):120-125;Zhou等人,(2013)Cancer Letters.344,13-19)。此类小鼠可与细胞系肿瘤或患者来源的人肿瘤异种移植物结合使用(Siolas等人,(2013)Cancer Res.;73(17):5315-5319)。

[0838] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人

Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0839] 实施例32:Siglec-7抗体和/或双特异性抗体Fab刺激先天免疫细胞的存活力的能力的分析

[0840] 在先天免疫细胞(例如巨噬细胞、嗜中性粒细胞和NK细胞)中评价板结合的交联抗Siglec-7抗体Fab片段的激动功能性。

[0841] 巨噬细胞、嗜中性粒细胞和NK细胞在M-CSF和板结合的Siglec-7抗体Fab存在下培养,并测量细胞存活力。

[0842] 将源自人单核细胞的巨噬细胞、嗜中性粒细胞、NK细胞和DC以及源自人单核细胞的T细胞和人小神经胶质细胞涂铺在用12.5nM或100nM交联Siglec-7 Fab预先涂覆的未经组织培养物处理的96孔板上。将细胞在10ng/ml M-CSF存在下培养48小时。使用CellTiter-Glo®试剂盒(Promega)进行存活力分析。使用GEN5 2.04软件,用BioTek Synergy微板读数器读取板。

[0843] 实施例33:Siglec-7抗体和/或双特异性抗体调节NFAT依赖性基因的能力的分析

[0844] 在NFAT(活化的T细胞的核因子)启动子控制下,使用荧光素酶报道基因评价拮抗性抗Siglec-7抗体活化NFAT依赖性基因的能力。

[0845] 将源自表达含有ITAM基序的共受体DAP12及其配体结合配偶体TREM2的小鼠T淋巴细胞BW5147.G.1.4(ATCC® TIB48™)的细胞系用人Siglec-7和Cignal Lenti NFAT-荧光素酶病毒(Qiagen)感染。荧光素酶信号传导通过板结合的抗TREM2抗体活化。将全长和Fab片段抗Siglec-7抗体与TREM2抗体一起共涂铺或者施加在溶液中。对于板结合,将抗体以10μg/ml施加在组织培养物处理的透明底部白色96孔板(100ul/孔)上的DPBS中在4℃下过夜。将孔用DPBS冲洗三次,且随后以100,000个细胞/孔涂铺在含有1%血清的培养基中。作为信号传导的阳性对照,一起添加PMA(0.05ug/ml)和离子霉素(0.25uM)。将细胞孵育6小时,并通过向每个孔添加ONE-Glo™试剂(Promega)并在板振荡器上在室温下孵育3分钟来测量荧光素酶活性。使用BioTek板读数器测量荧光素酶信号。

[0846] 实施例34:Siglec-7抗体和/或双特异性抗体的抗中风作用的分析

[0847] 大脑中动脉(MCAO)的瞬时闭塞-一种非常类似于人中风的模型被用于诱导小鼠的脑梗塞。将单丝(7OSPRe,Doccol Corp,USA)通过右颈总动脉的切口引入颈内动脉中。将大脑中动脉闭塞30分钟,伴随再灌注时间范围(6小时、12小时、24小时、2天、7天和28天)。在第12小时和第7天时使用假手术动物控制手术的作用。假手术动物经历相同的手术程序而不闭塞大脑中动脉。测试用拮抗性抗Siglec-7抗体或对照抗体处理的MCAO动物的梗塞体积、急性炎性应答(12小时再灌注)、促炎性细胞因子TNFa、IL-1a和IL-1b的转录、小神经胶质细胞活性(CD68、Iba1)、趋化因子CCL2(MCP1)、CCL3(MIP1a和趋化因子受体CX3CR1的转录,以及CD3阳性T细胞的侵袭(Sieber等人(2013)PLoS ONE 8(1):e52982.doi:10.1371/journal.pone.0052982.)这种实验可在一般小鼠或可替代地表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0848] 实施例35:抗Siglec-7抗体和/或双特异性抗体的抗阿尔茨海默氏病作用的分析

[0849] 为了评价拮抗性抗Siglec-7抗体延迟、预防或逆转阿尔茨海默氏病(AD)的发展的

能力,使用了5X FAD小鼠。5X FAD小鼠过度表达具有瑞典(K670N,M671L)、佛罗里达(I716V)和伦敦(V717I)家族性阿尔茨海默氏病(FAD)突变的突变体人APP(695)以及携带两种FAD突变M146L和L286V的人PS1。这两种转基因都受小鼠Thy1启动子调控,以驱动大脑上的过度表达并概述AD的主要特征。用组织提取物的免疫组织化学和通过ELISA测试了用激动性抗Siglec-7抗体或用对照抗体处理的小鼠的Aβ斑块负载。将它们针对脑中小神经胶质细胞的数目以及针对使用Morris水迷宫(一种空间学习和记忆任务)、八臂水迷宫(一种空间学习和记忆任务)、Y迷宫(将自发更迭量化为空间认知的量度)、在旷场中的新颖性偏好、评估学习和记忆的操作性学习以及恐惧条件反射(mousebiology.org网站;Wang等人,(2015)Cell.pii:S0092-8674(15)00127-0)的认知缺陷进行测试。这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0850] 实施例36:Siglec-7抗体和/或双特异性抗体在呼吸道感染中的保护作用的分析

[0851] 为了评价拮抗剂Siglec-7抗体延迟、预防或治疗细菌呼吸道感染的能力,使用了涉及用肺炎链球菌(Streptococcus pneumoniae)激发C57B16小鼠的临床前小鼠模型。此模型涉及如所描述(参见例如Sharif O等人,2014 PLoS Pathog.2014年6月;10(6):e1004167;以及Schabbauer G等人,2010 J Immunol 185:468-476),鼻内(i.n.)施用105个CFU肺炎链球菌血清型3(ATCC 6303)。在此模型中,大约90%的WT C57B16小鼠在感染后6天内死于感染。

[0852] 将10至15只小鼠/组用肺炎链球菌激发,并且从第0天开始每隔一天用拮抗剂抗Siglec-7抗体伴随处理。第一剂量的抗Siglec-7抗体在用肺炎链球菌激发前3小时施用。每天监测小鼠持续15天以检查死亡事件。确定在细菌激发后存活的小鼠的%。

[0853] 在单独实验中,还测定血液和肺中的细菌负荷和细胞因子表达的计数。在感染后24或48小时,将血液收集在含有EDTA的管中,并涂铺在琼脂板上以计算血浆中的细菌CFU。通过ELISA将血浆储存在-20℃下以进行细胞因子分析。收获肺,均质化并涂铺在琼脂板上以计算细菌CFU,或在裂解缓冲液中孵育30分钟并分析上清液的细胞因子测量值。

[0854] 在单独的实验中,在细菌感染后40小时收集肺,将其固定在10%福尔马林中,并包埋在石蜡中用于H&E病理学分析。

[0855] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0856] 实施例37:Siglec-7抗体和/或双特异性抗体在脓毒症中的保护作用的分析

[0857] 为了评价拮抗剂Siglec-7抗体延迟、预防或治疗败血症的能力,使用了涉及用LPS全身激发C57B16小鼠的临床前小鼠模型。

[0858] 此模型涉及如所描述(参见例如,Gawish R等人,2014 FASEB J)腹膜内(i.p.)施用37mg/ml LPS。在此模型中,>95%WT C57Bl6小鼠在LPS注射后40小时内死于感染。

[0859] 将小鼠群组用LPS激发,并且从第0天开始每天用拮抗剂抗Siglec-7抗体伴随处理。第一剂量的抗Siglec-7抗体在用LPS激发前3小时施用。在白天约每4小时监测小鼠,以检查死亡事件。确定从LPS激发存活的小鼠的百分比。

[0860] 在单独的实验中,收集腹膜灌洗液(PLF)。将上清液储存在-20℃下以用于通过

ELISA进行细胞因子分析;对沉淀的细胞计数以定量腹腔内募集的炎性细胞。可进行类似的研究以测试Siglec-7抗体在其它感染模型中的功效(参见例如,Sun等人,(2013)Invest Ophthalmol Vis Sci.17;54(5):3451-62)。

[0861] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0862] 实施例38:Siglec-7抗体和/或双特异性抗体在急性和慢性结肠炎中的保护作用的分析

[0863] 为了评价拮抗剂抗Siglec-7抗体延迟、预防或治疗结肠炎的能力,使用了急性或慢性结肠炎的临床前小鼠模型。对于DSS诱导的结肠炎,小鼠在饮用水中自由接受3%DSS持续8天。对于TNBS诱导的结肠炎,将小鼠麻醉并用直肠内注射3mg于20%乙醇(vol/vol)中的TNBS或作为对照的单独媒介物进行处理。对于慢性结肠炎模型,将所有小鼠用3个循环的2%DSS处理5天,随后10天恢复期。对于所有模型,每天监测重量减轻、粪便稠度和大便潜血的存在并将其用于计算疾病活动指数,如所描述(参见例如,Correale C,2013,Gastroenterology,2013年2月,第346-356页.e3)。

[0864] 从第0天开始每天用拮抗剂抗Siglec-7抗体处理小鼠群组,并进行DSS或TNBS施用。如所描述(参见例如,S.Vetrano,Gastroenterology,135(2008),第173-184页),每天监测小鼠以检查重量减轻、粪便稠度并且大便潜血的存在并将其用于计算疾病活动指数。

[0865] 在单独的实验中,收集粘膜损伤的内窥镜和组织学图像以评价炎性细胞浸润和粘膜损伤。可进行类似的研究以测试Siglec-7抗体在其它自身免疫性(包括克罗恩氏病、炎性肠病和溃疡性结肠炎)模型中的益处(参见例如,Low等人,(2013)Drug Des Devel Ther.;7:1341-1357;以及Sollid等人,(2008)PLoS Med 5(9):e198)。

[0866] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0867] 实施例39:Siglec-7抗体和/或双特异性抗体在伤口愈合中的保护作用的分析

[0868] 为了评价激动性抗Siglec-7抗体在损伤后增加结肠创伤修复的能力,使用结肠中活检损伤的小鼠模型。在此模型中,将具有外操作鞘的内窥镜插入到中降结肠中,并且检查粘膜到非直肠连接处。然后,用直径为3 French的柔性活检钳除去整个粘膜和粘膜下层的单个全厚度区域,避免固有肌层的穿透。将每只小鼠在沿结肠背侧的3-5个部位进行活检损伤(参见例如,Seno H,2008,Proc Natl Acad Sci U S A.20091月6日;106(1):256-261)。

[0869] 在活检损伤后2或3天用激动剂抗Siglec-7抗体处理小鼠群组。每天监测小鼠持续15天,以通过测量损伤的表面积来检查重量减轻和伤口愈合。

[0870] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0871] 实施例40:Siglec-7抗体和/或双特异性抗体在视网膜变性中的保护作用的分析

[0872] AMD是外视网膜的退行性疾病。认为炎症,特别是炎性细胞因子和巨噬细胞、嗜中性粒细胞和/或NK细胞促成AMD疾病进展。

[0873] 在玻璃疣、布鲁赫氏膜(Bruch's membrane)、脉络膜和视网膜中记录了AMD病变附近的巨噬细胞、嗜中性粒细胞和NK细胞的存在。巨噬细胞、嗜中性粒细胞和NK细胞释放组织因子(TF)和血管内皮生长因子(VEGF),这触发显示脉络膜新生血管化患者中新血管形成的扩大。

[0874] 存在于黄斑脉络膜中的巨噬细胞的类型随年龄而变化,从而显示与年轻人的眼睛相比,老年人眼中升高水平的M2巨噬细胞、嗜中性粒细胞和NK细胞。然而,与相似年龄的正常解剖眼睛相比,晚期AMD黄斑具有更高的M1至M2定量。(参见例如,Cao X等人,(2011),pathol Int 61(9):pp528-35)。这表明在AMD进展的晚发中,眼内经典M1巨噬细胞活化之间存在联系。

[0875] 视网膜小神经胶质细胞是通常也存在于内层视网膜中的组织驻留巨噬细胞。在损伤的情况下,小神经胶质细胞可被活化并充当炎症介体。已在AMD组织样品中检测到活化的小神经胶质细胞,并已被认为是导致AMD发病机制的炎性过程的一个潜在促成因子(Gupta等人,(2003)Exp Eye Res.,76(4):463-71.)。在一个或多个AMD模型中测试了Siglec-7抗体预防、延迟或逆转AMD的能力(参见例如,Pennesi等人,(2012)Mol Aspects Med.;33(4):487-509)。

[0876] 记载总炎性巨噬细胞、嗜中性粒细胞和NK细胞(M1和/或活化的小神经胶质细胞)与AMD疾病进展相关,且因此代表拮抗剂Siglec-7抗体的治疗靶标。可在青光眼和遗传形式或视网膜变性如视网膜色素变性中获得类似的治疗益处。

[0877] 在青光眼模型中测试了Siglec-7抗体预防、延迟或逆转青光眼中的视网膜神经节细胞变性的能力(参见例如,E1-Danaf等人,(2015).J Neurosci.11;35(6):2329-43)。同样地,如Chang等人,(2002)Vision Res.;42(4):517-25和"Retinal Degeneration Rat Model Resource Availability of P23H and S334ter Mutant Rhodopsin Transgenic Rats and RCS Inbred and RCS Congenic Strains of Rats,"MM LaVail,2011年6月30日中所描述对REM2在遗传诱导的视网膜变性和视网膜色素变性中的治疗益处进行测试。

[0878] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0879] 实施例41:Siglec-7抗体和/或双特异性抗体在脂肪形成和饮食诱导的肥胖症中的保护作用的分析

[0880] 为了测试Siglec-7抗体在脂肪形成和肥胖症中的作用,使用高脂肪饮食(HFD)的小鼠模型(参见例如,Park等人,(2015)Diabetes.64(1):117-27)。

[0881] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0882] 实施例42:拮抗剂Siglec-7抗体和/或双特异性抗体在骨质疏松症中的保护作用的分析

[0883] 骨是不断重塑以支持钙稳态和结构需求的动态器官。破骨细胞是负责除去骨的有机和无机组分的细胞。破骨细胞来源于巨噬细胞谱系中的造血祖细胞并且响应于NFκB配体的肿瘤坏死因子家族细胞因子受体活化因子而分化。破骨细胞(唯一的骨再吸收细胞)对骨

质疏松症的发病机理和骨质疏松症至关重要(Novack等人,(2008)Annual Rev Pathol.,3:457-84)。

[0884] 骨质疏松症是一种进行性骨疾病,其特征在于骨质量和密度的降低,可导致骨折风险增加。它主要表现在绝经后的前几年,当骨转换加速时,破骨细胞和成骨细胞两者的活性增加。然而,由于再吸收和合成过程的不平衡,净作用是骨质流失,主要是骨小梁。因此,骨质疏松症中最普遍的骨折部位是腕关节、股骨颈和椎体,其中骨小梁结构是整体骨强度的关键。

[0885] 如在缺乏DAP12 ITAM信号转导适体并且导致破骨细胞样细胞分化的显著缺陷的动物模型中所观察到,破骨细胞功能降低导致骨质疏松症,伴随骨量增加和骨髓空间消除(Koga等人,(2004)Nature 428:758-763)。

[0886] 因此,施用本公开的拮抗剂抗Siglec-7抗体可预防骨质疏松症、降低骨质疏松症的风险和/或治疗骨质疏松症。在一些实施方案中,施用激动剂抗Siglec-7抗体可诱导患有骨质疏松症的个体中的一种或多种Siglec-7活性(例如,DAP12磷酸化、Syk活化和加速分化成破骨细胞)(Peng等人(2010).Sci Signal.2010 18;3 122;以及Humphrey等人,(2006)J Bone Miner Res.,21(2):237-45)。

[0887] 这种实验也可在表达来自细菌人工染色体或来自由骨髓启动子驱动的cDNA的人Siglec-7基因的小鼠中或在用含有hSiglec-7 cDNA的慢病毒或AAV病毒转导的小鼠中进行。

[0888] 实施例43:Siglec-7抗体和/或双特异性抗体调节Siglec-7与SHP1、SHP2和其它信号传导分子的结合的能力的分析

[0889] 用PBS-EDTA从组织培养皿中移出人原代单核细胞、巨噬细胞、嗜中性粒细胞、NK细胞、树突细胞、T细胞、小神经胶质细胞或破骨细胞,用PBS洗涤并计数。将细胞与抗Siglec-7抗体和/或Siglec-7双特异性抗体或与同种型匹配的对照抗体以1μg/10^6个细胞在冰上或在其它条件下一起孵育20分钟。将细胞在冰冷的放射免疫沉淀测定(RIPA)缓冲液中裂解20分钟,然后在4℃下以16,000g离心10分钟以除去不溶物质。使所得上清液与所指示抗体(SHP1、SHP2、c-Cbl、Vav、Syk、LcK、Fyn、GRb2、PLC-γ、Toll样受体、DAMP受体、模式识别受体)以及蛋白质A-或蛋白质G-琼脂糖(Sigma)进行免疫沉淀反应。将珠粒用RIPA缓冲液充分洗涤并通过SDS-聚丙烯酰胺凝胶电泳(SDS-PAGE)分离蛋白质。然后通过蛋白质印迹将蛋白质转移至硝酸纤维素膜,与适当的Siglec-7抗体一起孵育并用增强的化学发光(ECL)系统(Pierce)可视化,如所描述(例如,Peng等人,(2010)Sci Signal.,3(122):ra38)。或者,将细胞与抗Siglec-7抗体和/或Siglec-7双特异性抗体或与同种型匹配的对照抗体以1μg/10^6个细胞在冰上或在其它条件下孵育20分钟。将细胞在冰冷的放射免疫沉淀测定(RIPA)缓冲液中裂解20分钟,然后在4℃下以16,000g离心10分钟以除去不溶物质。将所得上清液与第二Siglec-7抗体进行免疫沉淀反应。然后通过蛋白质印迹将蛋白质转移至硝酸纤维素膜,并与所指示的抗体(SHP1、SHP2、c-Cbl、Vav、Syk、LcK、Fyn、GRb2、PLC-γ Toll样受体、DAMP受体、模式识别受体)一起孵育。

[0890] 实施例44:抗Siglec-7和抗PD1抗体组合治疗的体内作用

[0891] 在植入人源化小鼠之前,将CTG-0202患者来源的黑色素瘤肿瘤首先在预研究动物中传代。当储备动物中肿瘤达到1-1.5cm^3时,将所述肿瘤收获以重新植入预研究动物中。预

研究动物在左侧腹上单侧植入肿瘤片段。CTG-0202黑色素瘤肿瘤以传代数为6使用。

[0892] 将免疫受损的雌性小鼠(Taconic NOG)用胎儿肝来源的$CD34^+$造血细胞人源化。将小鼠在68-74°F(20℃-23℃)和30%-70%湿度下按12小时光暗循环圈养在单独的HEPA通风笼(Innocage® IVC,Innovive USA)中的经辐照的富含纸捻的1/8″玉米芯草垫(Sheperd)上。小鼠自由喂水(反渗透,2ppm Cl_2)和辐照的由19%蛋白质、9%脂肪和4%纤维组成的测试啮齿动物饮食(Teklad 2919)。植入48只人源化小鼠,并且在植入后7至10天开始的每个实验记录研究前肿瘤体积。当肿瘤体积达到大约80-200mm^3时,通过肿瘤体积将小鼠与处理组或对照组匹配以用于给药,并且在第0天开始给药。测试组施用抗PD-1抗体Keytruda®(派姆单抗)与对照单克隆抗体(组1)的组合,或与抗Siglec-7抗体10B5(组2)的组合。表11和图16A描绘给药方案、给药量和施用途径。

[0893] 表11:用于Siglec-7抗体10B5的体内癌症功效研究的抗体给药方案和施用途径

[0894]

组	n	抗体处理	剂量体积(mg/kg)	ROA	方案	剂量总数
1	8	Keytruda	5/2.5	IP	q5dx6	6
		Alector CTR mAb	40	IP	q5dx6	6
2	8	Keytruda	5/2.5	IP	q5dx6	6
		Alector 10B5	40	IP	q5dx6	6

[0895] 在表11中,“n”是指每个处理组中的小鼠数量;“Alector CTR mAb”是指同种型对照抗体;“Alector 10B5”是指抗Siglec-7抗体10B5;“ROA”是指施用途径;“IP”是指腹膜内;“q5dx6”是指每五天施用总共六个剂量的给药方案。

[0896] 从第0天开始,每天观察小鼠并使用数字秤每周称量两次。每周通过数字卡尺测量肿瘤尺寸两次,并记录每组的数据,包括个体肿瘤体积和平均估计肿瘤体积(平均TV±SEM)。使用公式(1)计算肿瘤体积:TV=宽度2x长度x0.52。在研究完成时,使用公式(2)的初始(i)和最终(f)肿瘤测量值,计算并报告每个处理组(T)对比对照组(C)的肿瘤生长抑制百分比(%TGI)值:%TGI=1-(Tf-Ti)/(Cf-Ci)。

[0897] 报道两次连续测量的第0天测量的肿瘤体积≤50%的各个小鼠被认为是部分应答者(PR)。缺乏可触及肿瘤的各个小鼠(连续两次测量<4x4mm^2)被归类为完全应答者(CR);一直坚持到研究完成的CR被认为是无肿瘤存活者(TFS)。使用DT=(Di-Df)*log2/(logTVi-logTV)$_f$其中D=天数和TV=肿瘤体积测定媒介物处理的组的肿瘤倍增时间(DT)。使用双向ANOVA确定肿瘤体积的统计学差异。当对照组的平均肿瘤体积在第28天达到1500mm^3时,研究结束。

[0898] 在研究终止时,将收获的肿瘤在冰包装上的培养基中过夜运输并在第二天处理。通过心脏穿刺收集全血样品并在肝素钠中运输并在递送后第二天处理。将肿瘤样品在37℃下用胶原酶处理30分钟。将样品通过细胞过滤器解离并重新悬浮于PBS中的2%FBS中。将全血样品中的红细胞使用ACK裂解缓冲液裂解,且然后将细胞在PBS中的2%FBS中洗涤两次。使用血细胞计数器对细胞进行计数,并将一百万个细胞用荧光染料缀合的抗体在冰上染色30分钟,然后用PBS中的2%FBS洗涤。将细胞用PBS中的4%多聚甲醛固定。将所有染色的细

胞在FACS Canto(BD Biosciences)上分析并且用FlowJo软件(TreeStar)分析数据。为了评估受体下调,使用小鼠(m)CD45、人(h)CD45、人(h)CD3和人(h)CD14抗体来门控$CD14^+$群体。为了鉴定肿瘤浸润免疫细胞,根据标准程序使用hCD45、hCD3、hCD4、hCD8和hCD14抗体来对群体进行门控。

[0899] 如图16B和16C中所示,在移植人免疫干细胞的小鼠中,用Siglec-7抗体10B5和抗PD-1抗体Keytruda®(派姆单抗)的组合治疗在患者来源的黑色素瘤肿瘤模型中显著抑制体内肿瘤生长。使用Rlm()函数通过多元线性回归针对供体、时间0处的肿瘤大小和小鼠体重校正在每个时间点的肿瘤体积。在每个时间点,通过使用R lm()函数来评估统计显著性。

[0900] 如图16D和16E中所示,用Siglec-7抗体10B5和抗PD-1抗体Keytruda®(派姆单抗)的组合治疗在患者来源的黑色素瘤肿瘤模型中体内抑制肿瘤生长,所述肿瘤模型植入来自不同人供体的人免疫干细胞(供体编号:984480112、165547112和17509112)。使用R lm()函数通过多元线性回归针对供体、时间0处的肿瘤大小和小鼠体重校正在每个时间点的肿瘤体积。在每个时间点,通过使用R lm()函数来评估统计显著性。

[0901] 图16B-16E描绘抗Siglec-7抗体10B5作为治疗人癌症的治疗剂的临床前功效。Siglec-7抗体10B5当与抗PD1抗体Keytruda®(派姆单抗)组合递送时显著降低黑色素瘤肿瘤中的肿瘤体积(图16B-16E)。值得注意的是,Keytruda®(派姆单抗)与同种型对照(Alector CTR mAb)的组合不抑制肿瘤生长(图16B-16E)。

[0902] 如图16F中所示,使用Siglec-7抗体10B5和抗PD-1抗体Keytruda®(派姆单抗)的组合治疗降低小鼠肿瘤模型中来自外周血的外周血$hCD45^+$ $CD14^+$骨髓细胞中Siglec-7的细胞表面水平,所述肿瘤模型植入人免疫干细胞和患者来源的异种移植物CTG-0202黑色素瘤肿瘤。通过使用R lm()函数评估统计显著性。

[0903] 如图16G中所示,用Siglec-7抗体10B5和抗PD-1抗体Keytruda®(派姆单抗)的组合治疗减少小鼠肿瘤模型中的肿瘤浸润性$hCD45^+$ $CD14^+$骨髓细胞的数量,所述肿瘤模型植入人免疫干细胞和患者来源的异种移植物CTG-0202黑色素瘤肿瘤。通过使用R lm()函数评估统计显著性。

[0904] 如图16H中所示,用Siglec-7抗体10B5和抗PD-1抗体Keytruda®(派姆单抗)的组合治疗增加小鼠肿瘤模型中肿瘤浸润$hCD45^+$ $CD3^+$ T细胞的数量,所述肿瘤模型植入人免疫干细胞和患者来源的异种移植物CTG-0202黑色素瘤肿瘤。通过使用R lm()函数评估统计显著性。

[0905] 如图16I中所示,使用Siglec-7抗体10B5和抗PD-1抗体Keytruda®(派姆单抗)的组合治疗减少小鼠肿瘤模型中的外周血$hCD45^+$ $CD14^+$骨髓细胞的数量,所述肿瘤模型植入人免疫干细胞和患者来源的异种移植物CTG-0202黑色素瘤肿瘤。通过使用R lm()函数评估统计显著性。

[0906] 对于本文描述的研究来说重要的是,肿瘤和对肿瘤应答的免疫系统两者都是人的。使用小鼠免疫系统经遗传消融和辐射清除骨髓的方法将小鼠的免疫系统人源化,然后用再生并发育骨髓和淋巴免疫细胞的人供体$CD34^+$造血干细胞和祖细胞替换。所述肿瘤是一种患者来源的黑色素瘤。人特异性Siglec-7抗体10B5显示人Siglec-7的靶标特异性接合

和下调。受体下调在外周和肿瘤CD14$^+$骨髓细胞上显著。因此，对肿瘤体积、肿瘤生长速率、增加的CD3$^+$ T细胞的肿瘤浸润以及减少的CD14+细胞的任何作用是10B5抗体介导的人骨髓免疫细胞上Siglec-7下调的结果。

[0907] 上述数据表明Siglec-7抗体10B5是外周和肿瘤浸润骨髓细胞上有效且显著的受体下调抗体。对肿瘤浸润免疫细胞群体的分析表明CD3$^+$ T细胞的显著增加。此外，骨髓细胞群体也受到Siglec-7抗体处理的影响。在肿瘤以及外周血细胞群体中观察到CD14$^+$骨髓细胞的显著减少。此数据表明下调Siglec-7功能性地改变肿瘤浸润免疫细胞群体。总之，这些研究证明抗Siglec-7抗体作为治疗人癌症的治疗剂的临床前功效。

[0908] 实施例45:Siglec-7抗体对骨髓源性抑制细胞(MDSC)的作用

[0909] 通过聚蔗糖离心从全血中分离外周血单核细胞(PBMC)。在红细胞的ACK裂解后，将人PBMC在补充有10％FBS(Hyclone)、L-谷氨酰胺、Pen/Strep、非必需氨基酸、丙酮酸钠以及含有10ng/ml重组IL-6(Sigma-Aldrich)、IL-8(R&D Systems)和GM-CSF(R&D Systems)的抑制性细胞因子混合物的RPMI培养基中培养。在一些实验中，将人PBMC与补充有10ng/ml GM-CSF的肿瘤条件培养基一起培养。肿瘤条件培养基是含有上述补充物的RPMI培养基，除了从肿瘤细胞系培养物中收获的IL-6和IL-8外，并且用0.2μm膜无菌过滤。将细胞因子、抗体(抗Siglec-7抗体4E3或10B5或同种型对照抗体)或rhGM-CSF加标的肿瘤上清液每2-3天添加至人PBMC持续一周。

[0910] 对于FACS分析，收获悬浮和粘附细胞，并通过标准FACS程序测试指定受体的表达。重要的是，死细胞从表达分析中被门控出来，并且所有MFI值都来源于活细胞。与同种型处理的条件相比，将作图值计算为ΔMFI。

[0911] 对于T细胞增殖测定，在培养7天后，使用针对CD2、CD3、CD8、CD19和CD56的抗体混合物(STEMCELL Technologies)，通过基于磁性的阴性选择分离骨髓来源的抑制细胞(MDSC)。将分离的MDSC以每孔50,000个细胞涂铺在平底96孔非TC板中，并用指定的抗体处理，之后添加T细胞。

[0912] 使用用CFSE(Life Technologies)标记的RosetteSep选择技术(STEMCELL Technologies)从全血中分离非自体供体CD3或CD8T细胞，并将其用10U/mL IL-2和1:1比率的CD3/CD28 T-活化剂Dynabeads(Life Technologies)活化。将MDSC和T细胞以每孔1:2或50,000:100,000个细胞的比率共培养。在共培养后3天在FACS Canto(BD Biosciences)上检测到CFSE。使用FlowJo 10.1版(TreeStar)软件分析数据。

[0913] 如图17A和图17B中所示，MDSC表面上的抗Siglec-7抗体10B5和4E3降低PD-L1和PD-L2(PD-1配体)、B7-H3(强效T细胞检查点抑制剂)、CD200R(抑制信号传导受体)以及CD163和CD206(M2型标志物)的表达。这些结果表明抗Siglec-7抗体介导的靶标接合和随后的Siglec-7下调导致MDSC的表型改变，包括抑制性配体和受体的表达降低。

[0914] 如图17C和图17D中所示，抗Siglec-7抗体10B5和4E3在MDSC存在下增加T细胞增殖，从而允许产生更多的抵抗肿瘤T细胞。与活化的T细胞共培养的MDSC将T细胞增殖抑制约25％。在这些研究中，用Siglec-7抗体10B5或4E3处理的MDSC诱导更少的T细胞增殖抑制(图17C和图17D)。同种型对照(mIgG1)抗体不影响T细胞增殖的MDSC依赖性抑制。用Siglec-7靶向抗体处理MDSC在减轻MDSC介导的T细胞抑制方面比PD-L1阻断抗体更有效(图17C和图17D)。

[0915] 最后，测试了抗Siglec-7抗体诱导MDSC的细胞死亡的能力。将人外周血细胞聚蔗糖分离、用ACK裂解缓冲液裂解红细胞，并将细胞洗涤3次，然后涂铺在含有10％FBS、Pen/Strep、1mM谷氨酰胺、非必需氨基酸和丙酮酸钠的RPMI中。将人PBMC在37℃下在5％CO_2中与以下细胞因子一起培养1周：10ng/ml rhGM-CSF(R&D)、10ng/ml rhIL-8(R&D)和10ng/ml rhIL-6(Sigma)。向一些烧瓶中添加mIgG1(BioXcell)同种型抗体或Siglec-7抗体4E3或10B5。每2-3天在观察到时补充培养基、细胞因子和抗体。在培养7天后，通过刮擦和滴定收获细胞，并重新悬浮于含有2％FBS和1mM EDTA的PBS中用于FACS分析。为了评估活细胞和死细胞群体，将Live/Dead Fixable Aqua死细胞染色剂(Thermo Fisher)在具有2％FBS和1mM EDTA的PBS中1:500稀释，并在冰上孵育30分钟。将细胞在缓冲液中洗涤3次并在BD FACS Canto(BD Biosciences)上分析正向和侧向散射以及AmCyan荧光。用FlowJo(Tree Star Software)分析数据。

[0916] 如图18中所示，抗Siglec-7抗体4E3和10B5能够在分化的MDSC的子集中诱导细胞死亡。相对于单独培养基或同种型处理的细胞，两种抗Siglec-7抗体均诱导MDSC细胞死亡增加约30％(图18，中间行)。

[0917] 总之，上述研究表明抗Siglec-7抗体10B5和4E3能够在表型上改变MDSC(例如通过减少抑制性配体和受体的表达)、影响下游MDSC功能(例如，减少T细胞增殖的MDSC依赖性抑制)并诱导MDSC子集的细胞死亡。

序列表

<110> MONROE, Kate

LAM, Helen

ROSENTHAL, Arnon

LEE, Seung-Joo

AVOGADRI-CONNORS, Francesca

MONTEITH, William

<120> 抗SIGLEC-7抗体及其使用方法

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<151> 2015-08-28

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Thr Trp Arg Ser Leu Thr Leu Tyr Pro Ser Gln Pro Ser Asn Pro Leu
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Trp Thr Trp Arg Ser Leu Thr Leu Tyr Pro Ser Gln Pro Ser Asn Pro
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305 310 315 320
Cys Arg Ala Gln Asn Ser Leu Gly Ser Gln His Val Ser Leu Asn Leu
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Ser Leu Gln His Glu Tyr Thr Gly Lys Met Arg Pro Val Ser Gly Val
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Leu Leu Gly Ala Val Gly Gly Ala Gly Ala Thr Ala Leu Val Phe Leu
355 360 365
Ser Phe Cys Val Ile Phe Ile Val Val Arg Ser Cys Arg Lys Lys Ser
370 375 380
Ala Arg Pro Ala Ala Asp Val Gly Asp Thr Gly Met Glu Asp Ala Asn
385 390 395 400
Thr Ile Arg Gly Ser Ala Ser Gln Gly Thr Leu Thr Glu Ser Trp Ala
405 410 415
Tyr Asp Asn Pro Arg His His Gly Leu Ala Ala Pro Ser Ser Gly Glu
420 425 430
Glu Arg Glu Val Gln Tyr Ala Pro Leu Ser Phe His Lys Gly Glu Pro
435 440 445
Gln Asp Leu Ser Gly Gln Glu Ala Thr Asn Asn Glu Tyr Ser Glu Ile
450 455 460

Xaa Ile Pro Lys Xaa Glu Asn Ala Glu Ala Arg Ala Cys Leu Arg Val
465 470 475 480
His Asp Pro Ser Ser Lys Gly Val Arg Gly
485 490

<210> 4
<211> 599
<212> PRT
<213> 苏门答腊猩猩
<220>
<221> 变体
<222> 179, 257, 337, 378
<223> Xaa = 任何氨基酸
<400> 4

Met Leu Leu Leu Leu Leu Leu Phe Leu Pro Leu Leu Trp Gly Arg Glu
1 5 10 15
Arg Val Glu Gly Gln Lys Asn Asn Arg Lys Asp Tyr Ser Leu Met Met
20 25 30
Gln Ser Ser Val Thr Val Gln Glu Gly Leu Cys Val His Val Gln Cys
35 40 45
Ser Phe Ser Tyr Pro Val Asp Ser Gln Thr Asp Ser Asp Pro Val His
50 55 60
Gly Tyr Trp Phe Arg Ala Gly Asp Asp Ile Ser Trp Lys Ala Pro Val
65 70 75 80
Ala Thr Asn Asn Pro Ala Gln Ala Val Arg Glu Glu Thr Arg Asp Arg
85 90 95
Phe His Leu Leu Gly Asp Pro Gln Thr Lys Asn Cys Thr Leu Ser Ile
100 105 110
Arg Asp Ala Arg Met Ser Asp Ala Gly Arg Tyr Phe Phe Arg Met Glu
115 120 125
Arg Gly Asn Ile Lys Trp Asn Tyr Lys Tyr Asp Arg Leu Ser Val Asn
130 135 140
Val Thr Ala Ser Gln Ala Pro Pro Ser Arg Tyr Arg Leu Glu Val Pro
145 150 155 160
Glu Ser Val Thr Val Gln Glu Gly Leu Cys Val Ser Val Pro Cys Ser
165 170 175
Val Leu Xaa Pro Tyr Tyr Asn Trp Thr Asp Ser Ser Pro Val His Gly
180 185 190
Cys Trp Phe Lys Lys Gly Ile Asn Ile Gln Trp Asn Asn Pro Val Ala
195 200 205

Thr Asn Ile Pro Asn Gly Lys Val Glu Glu Thr Arg Gly Arg Phe His
210 215 220
Leu Leu Gly Asp Leu Lys Thr Asn Asn Cys Ser Leu Ser Ile Arg Asp
225 230 235 240
Ala Arg Lys Gly Asp Leu Gly Asn Tyr Tyr Phe Gln Val Glu Arg Gly
245 250 255
Xaa Ile Arg Trp Asn Tyr Lys Met Lys Gln Leu Ser Val Asn Val Thr
260 265 270
Ala Leu Thr His Arg Pro Asn Ile Leu Ile Pro Gly Thr Leu Glu Ser
275 280 285
Gly Cys Phe Gln Asn Leu Thr Cys Ser Val Pro Trp Ala Cys Glu Gln
290 295 300
Gly Thr Pro Pro Met Ile Ser Trp Met Gly Thr Ser Val Ser Thr His
305 310 315 320
Leu His Pro Ser Thr Thr Arg Ser Ser Val Leu Thr Leu Ile Pro Gln
325 330 335
Xaa Glu Asp His Gly Thr Asn Phe Thr Leu Gln Tyr Val Leu Thr Pro
340 345 350
Ala Tyr Val Thr Val Cys Ser Ile Pro Gln Ser His Ser Val Ser Phe
355 360 365
Leu Pro Val Ser Ile Thr Leu Ser Leu Xaa Pro Phe Asn Phe Phe Ser
370 375 380
Thr Ala Ser Thr Ala Leu Gly Asn Ser Ser Ser Leu Ser Val Leu Glu
385 390 395 400
Gly Gln Ser Leu Arg Leu Val Cys Ala Val Asp Ser Asn Pro Pro Ala
405 410 415
Arg Leu Ser Trp Thr Trp Arg Ser Leu Thr Leu Tyr Pro Ser Gln Pro
420 425 430
Ser Asn Pro Leu Val Leu Glu Leu Arg Val His Leu Gly Asp Glu Gly
435 440 445
Glu Cys Ile Cys Arg Ala Gln Asn Ser Leu Gly Ser Gln His Val Ser
450 455 460
Leu Asn Leu Ser Leu Gln His Glu Tyr Thr Gly Lys Met Arg Pro Val
465 470 475 480
Ser Gly Val Met Leu Gly Ala Val Gly Gly Ala Gly Ala Thr Ala Leu
485 490 495
Val Phe Leu Ser Phe Cys Val Ile Phe Ile Val Val Arg Ser Cys Arg
500 505 510
Lys Lys Ser Ala Arg Pro Ala Ala Asp Val Gly Asp Thr Gly Met Glu

515 520 525

Asp Ala Asn Thr Val Arg Gly Ser Ala Ser Gln Gly Thr Leu Ile Glu
530 535 540

Ser Trp Ala Asp Asp Asn Pro Arg His Leu Gly Leu Ala Ala Pro Ser
545 550 555 560

Ser Gly Glu Glu Arg Glu Ile Gln Tyr Ala Ser Leu Ser Phe His Lys
565 570 575

Gly Glu Pro Gln Asp Leu Ser Arg Gln Glu Ala Thr Asn Asn Glu Tyr
580 585 590

Ser Glu Ile Lys Ile Pro Lys
595

<210> 5

<211> 468

<212> PRT

<213> 西部低地大猩猩

<400> 5

Met Leu Leu Leu Leu Leu Leu Leu Pro Leu Leu Trp Gly Arg Glu Arg
1 5 10 15

Val Glu Gly Gln Lys Ser Lys Arg Lys Asp Tyr Ser Leu Thr Met Gln
20 25 30

Ser Ser Val Thr Val Gln Glu Gly Met Cys Val His Val Arg Cys Ser
35 40 45

Phe Ser Tyr Pro Val Asp Ser Gln Thr Asp Ser Asp Pro Val His Gly
50 55 60

Tyr Trp Phe Arg Ala Glu Asn Asp Ile Ser Trp Lys Ala Pro Val Ala
65 70 75 80

Thr Asn Asp Pro Ala Arg Ala Val Arg Glu Glu Thr Arg Asp Arg Phe
85 90 95

His Leu Leu Gly Asp Pro Gln Thr Lys Asn Cys Thr Leu Ser Ile Arg
100 105 110

Asp Ala Arg Met Ser Asp Ala Gly Arg Tyr Phe Phe Arg Met Glu Lys
115 120 125

Gly Asn Ile Lys Trp Asn Tyr Lys Tyr Asp Gln Leu Ser Val Asn Val
130 135 140

Thr Ala Leu Thr His Arg Pro Asn Ile Leu Ile Pro Ser Thr Leu Glu
145 150 155 160

Ser Gly Cys Phe Gln Asn Leu Thr Cys Ser Val Pro Trp Ala Cys Glu
165 170 175

Gln Gly Thr Pro Pro Met Ile Ser Trp Met Gly Thr Ser Val Ser Pro

180 185 190

Leu His Pro Ser Thr Thr Arg Ser Ser Val Leu Thr Leu Ile Pro Gln

195 200 205

Pro Gln His His Gly Thr Ser Leu Thr Cys Gln Val Thr Leu Pro Gly

210 215 220

Ala Gly Val Thr Thr Asn Arg Thr Ile Gln Leu Asn Val Ser Tyr Pro

225 230 235 240

Pro Gln Asn Leu Thr Val Thr Ile Phe Gln Gly Glu Gly Thr Ala Ser

245 250 255

Thr Ala Leu Gly Asn Ser Ser Ser Leu Ser Val Leu Glu Gly Gln Ser

260 265 270

Leu Arg Leu Val Cys Ala Val Asp Ser Asn Pro Pro Ala Arg Leu Ser

275 280 285

Trp Thr Trp Arg Ser Leu Thr Leu Tyr Pro Ser Gln Pro Ser Asn Pro

290 295 300

Leu Val Leu Glu Leu Gln Val His Leu Gly Asp Glu Gly Glu Phe Thr

305 310 315 320

Cys Arg Ala Gln Asn Ser Leu Gly Ser Gln His Val Ser Leu Asn Leu

325 330 335

Ser Leu Gln His Glu Tyr Thr Gly Lys Met Arg Pro Val Ser Gly Val

340 345 350

Leu Leu Gly Ala Val Gly Gly Ala Gly Ala Thr Ala Leu Val Phe Leu

355 360 365

Ser Phe Cys Val Ile Phe Ile Val Val Arg Ser Cys Arg Lys Lys Ser

370 375 380

Ala Arg Pro Ala Ala Asp Val Gly Asp Thr Gly Met Glu Asp Ala Asn

385 390 395 400

Thr Ile Arg Gly Ser Ala Ser Gln Gly Thr Leu Thr Glu Ser Trp Ala

405 410 415

Asp Asp Asn Pro Arg His Tyr Gly Leu Ala Ala Pro Ser Ser Gly Glu

420 425 430

Glu Arg Glu Val Gln Tyr Ala Pro Leu Ser Phe His Lys Gly Glu Pro

435 440 445

Gln Asp Leu Ser Gly Gln Glu Ala Thr Asn Asn Glu Tyr Ser Glu Ile

450 455 460

Lys Ile Pro Lys

465

<210> 6

<211> 468

<212> PRT

<213> 白颊长臂猿

<400> 6

Met Leu Leu Leu Leu Leu Leu Leu Pro Leu Leu Trp Gly Arg Glu Arg
1 5 10 15
Val Glu Gly Gln Lys Ser Asn Gln Lys Asn Tyr Pro Leu Met Met Gln
20 25 30
Ser Ser Val Thr Val Gln Glu Gly Leu Cys Val His Val Arg Cys Ser
35 40 45
Phe Ser Tyr Pro Val Asp Ser Gln Thr Asp Ser Asp Pro Val His Gly
50 55 60
Tyr Trp Phe Arg Ala Gly Asp Asp Ile Ser Trp Lys Thr Pro Val Ala
65 70 75 80
Thr Asn Asn Arg Ala Arg Ala Val Arg Glu Glu Thr Arg Asp Arg Phe
85 90 95
His Leu Leu Gly Asp Pro Gln Thr Lys Asn Cys Thr Leu Ser Ile Arg
100 105 110
Asp Ala Arg Met Ser Asp Ala Gly Thr Tyr Phe Tyr Arg Met Glu Arg
115 120 125
Gly Lys Ile Lys Trp Asn Tyr Lys Tyr His Gln Leu Ser Val His Val
130 135 140
Thr Ala Leu Thr His Arg Pro Asn Ile Val Ile Pro Gly Thr Leu Glu
145 150 155 160
Ser Gly Cys Phe Gln Asn Leu Thr Cys Ser Val Pro Trp Ala Cys Glu
165 170 175
Gln Gly Thr Pro Pro Met Ile Ser Trp Met Gly Thr Ser Leu Ser Pro
180 185 190
Leu His Pro Ser Thr Thr Arg Ser Ser Val Leu Thr Leu Ile Pro Gln
195 200 205
Pro Gln Asp His Gly Thr Ser Leu Thr Cys Gln Val Thr Leu Pro Gly
210 215 220
Ala Gly Val Thr Thr Asn Arg Thr Ile Arg Leu Asn Val Ser Tyr Pro
225 230 235 240
Pro Gln Asn Leu Thr Val Thr Val Phe Gln Gly Glu Gly Thr Ala Ser
245 250 255
Thr Ala Leu Gly Asn Ser Ser Ser Leu Ser Val Leu Glu Gly Gln Ser
260 265 270
Leu Arg Leu Val Cys Ala Val Asp Ser Asn Pro Pro Ala Arg Leu Ser
275 280 285

Trp Thr Trp Arg Ser Leu Thr Leu Tyr Pro Ser Gln Pro Ser Asn Pro
290 295 300
Leu Val Leu Glu Leu Arg Val His Leu Gly Asp Glu Gly Glu Phe Thr
305 310 315 320
Cys Arg Ala Arg Asn Ser Leu Gly Ser Gln His Phe Ser Leu Asn Leu
325 330 335
Ser Leu Gln His Glu Tyr Thr Gly Lys Met Arg Pro Val Ser Gly Val
340 345 350
Thr Leu Gly Ala Val Gly Gly Ala Gly Ala Thr Ala Leu Val Phe Leu
355 360 365
Ser Phe Cys Val Ile Phe Ile Val Val Arg Ser Tyr Arg Lys Lys Ser
370 375 380
Ala Arg Pro Ala Ala Gly Val Gly Asp Thr Gly Met Glu Asp Ala Asn
385 390 395 400
Ala Ile Arg Gly Ser Ala Ser Gln Gly Thr Met Ile Glu Ser Trp Ala
405 410 415
Asp Asp Asn Pro Arg His His Gly Leu Ala Ala Pro Ser Ser Gly Glu
420 425 430
Glu Gly Glu Ile Gln Tyr Ala Ser Val Ser Phe His Lys Val Glu Pro
435 440 445
Gln Asp Leu Ser Gly Gln Glu Ala Thr Asn Asn Glu Tyr Ser Glu Ile
450 455 460
Lys Ile Pro Lys
465

<210> 7
<211> 16
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 7
Arg Ser Ser Gln Ser Leu Val His Ser Thr Gly Asn Thr Tyr Leu His
1 5 10 15

<210> 8
<211> 11
<212> PRT
<213> 人工序列
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<223> 合成构建体

<400> 8
Arg Ala Ser Gln Ser Ile Ser Asp Tyr Leu His
1 5 10
<210> 9
<211> 10
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 9
Ser Ala Asn Ser Ser Phe Ile Tyr Met Tyr
1 5 10
<210> 10
<211> 11
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 10
Lys Ala Ser Asp His Ile Asn Asn Trp Leu Ala
1 5 10
<210> 11
<211> 16
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 11
Arg Ser Ser Gln Ser Leu Val His Ser Thr Gly Asn Thr Tyr Leu His
1 5 10 15
<210> 12
<211> 16
<212> PRT
<213> 人工序列
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<400> 12
Arg Ser Ser Gln Ser Leu Val His Ser Thr Gly Asn Ile Tyr Leu His
1 5 10 15

<210> 13
<211> 11
<212> PRT
<213> 人工序列
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<400> 13
Lys Ala Ser Gln Lys Val Gly Thr Asn Val Ala
1 5 10
<210> 14
<211> 10
<212> PRT
<213> 人工序列
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<400> 14
Ser Ala Asn Ser Ser Phe Thr Tyr Met Tyr
1 5 10
<210> 15
<211> 11
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<400> 15
Arg Ala Ser Gln Ser Ile Ser Glu Tyr Leu His
1 5 10
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<211> 11
<212> PRT
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<400> 16
Leu Ala Ser Gln Thr Ile Gly Thr Trp Leu Ala
1 5 10
<210> 17
<211> 16
<212> PRT

<213> 人工序列
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<400> 17
Arg Ser Ser Gln Ser Leu Val His Ser Thr Gly Asn Thr Tyr Leu His
1 5 10 15
<210> 18
<211> 11
<212> PRT
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<400> 18
Arg Ala Ser Gln Asp Ile Ser Glx Tyr Leu Asn
1 5 10
<210> 19
<211> 11
<212> PRT
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<400> 19
Arg Ala Ser Gln Ser Ile Arg Glu Tyr Leu His
1 5 10
<210> 20
<211> 7
<212> PRT
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<400> 20
Lys Val Ser Asn Arg Phe Ser
1 5
<210> 21
<211> 7
<212> PRT
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<400> 21
Tyr Ala Ser Gln Ser Ile Ser
1 5
<210> 22
<211> 7
<212> PRT
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<400> 22
Asp Thr Ser Asn Leu Ala Ser
1 5
<210> 23
<211> 7
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 23
Gly Ala Thr Ser Leu Glu Thr
1 5
<210> 24
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 24
Lys Val Ser Asn Arg Phe Cys
1 5
<210> 25
<211> 7
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 25
Lys Val Ser Asn Arg Phe Glx
1 5

<210> 26
<211> 7
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 26
Ser Ala Ser Thr Arg His Arg
1 5
<210> 27
<211> 7
<212> PRT
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<223> 合成构建体
<400> 27
Asp Thr Ser Asn Leu Ala Ser
1 5
<210> 28
<211> 7
<212> PRT
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<400> 28
Phe Ala Ser Gln Ser Ile Cys
1 5
<210> 29
<211> 7
<212> PRT
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<400> 29
Ala Ala Thr Ser Leu Ala Asp
1 5
<210> 30
<211> 7
<212> PRT

<213> 人工序列
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<400> 30
Lys Val Ser Asn Arg Phe Ser
1 5
<210> 31
<211> 7
<212> PRT
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<400> 31
Leu Ser Ser Arg Leu His Ser
1 5
<210> 32
<211> 7
<212> PRT
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<400> 32
Phe Ala Ser Gln Ser Ile Cys
1 5
<210> 33
<211> 9
<212> PRT
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<400> 33
Ser Gln Asn Thr His Val Pro Tyr Thr
1 5
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<211> 9
<212> PRT
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<400> 34
Gln Lys Gly Leu Asn Phe Pro Leu Thr
1 5
<210> 35
<211> 9
<212> PRT
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<400> 35
Gln Gln Trp Ser Ser Ser Pro Leu Thr
1 5
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<400> 36
His Gln Tyr Trp Asn Thr Pro Tyr Thr
1 5
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<211> 9
<212> PRT
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<400> 37
Ser Gln Asn Thr His Val Pro Tyr Thr
1 5
<210> 38
<211> 9
<212> PRT
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<400> 38
Ser Gln Asn Thr His Val Pro Tyr Thr
1 5

<210> 39
<211> 9
<212> PRT
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<400> 39
His Gln Gly Asn Ser Val Gln Tyr Thr
1 5
<210> 40
<211> 9
<212> PRT
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<400> 40
Gln Gln Trp Ser Ser Ser Pro Leu Thr
1 5
<210> 41
<211> 9
<212> PRT
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<400> 41
Gln Asn Gly His Asn Phe Pro Tyr Thr
1 5
<210> 42
<211> 9
<212> PRT
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<400> 42
Gln Gln Leu Tyr Ser Thr Pro Tyr Thr
1 5
<210> 43
<211> 9
<212> PRT

<213> 人工序列
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<400> 43
Ser Gln Asn Thr His Val Pro Tyr Thr
1 5
<210> 44
<211> 9
<212> PRT
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<400> 44
Gln Gln Gly His Thr Gly Ala Trp Thr
1 5
<210> 45
<211> 9
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 45
Gln Lys Ala His Asn Phe Pro Tyr Thr
1 5
<210> 46
<211> 10
<212> PRT
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<400> 46
Ser Glu Val Phe Pro Ile Thr Tyr Met Asn
1 5 10
<210> 47
<211> 9
<212> PRT
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<400> 47
Phe Asn Ile Lys Gly Ser Leu Leu His
1 5
<210> 48
<211> 9
<212> PRT
<213> 人工序列
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<400> 48
Phe Thr Phe Ser Asn Tyr Asp Met Ser
1 5
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<211> 10
<212> PRT
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<400> 49
Ser Glu Val Phe Pro Ile Thr Tyr Met Asn
1 5 10
<210> 50
<211> 9
<212> PRT
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Tyr Ile Phe Thr Asp Tyr Gly Ile Thr
1 5
<210> 51
<211> 10
<212> PRT
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<400> 51
Ser Glu Val Phe Pro Ile Thr Tyr Met Asn
1 5 10

<210> 52
<211> 9
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<400> 52
Tyr Thr Phe Thr Asn Tyr Trp Ile Asn
1 5
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<211> 9
<212> PRT
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<400> 53
Phe Ile Phe Ser Asn Tyr Asp Met Ser
1 5
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<211> 9
<212> PRT
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<400> 54
Phe Thr Phe Ser Asn Tyr Ala Met Ser
1 5
<210> 55
<211> 9
<212> PRT
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<400> 55
Phe Ser Leu Ser Asn Tyr Gly Val His
1 5
<210> 56
<211> 10
<212> PRT

<213> 人工序列
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<400> 56
Ser Glu Val Phe Pro Ile Thr Tyr Met Asn
1 5 10
<210> 57
<211> 9
<212> PRT
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<400> 57
Tyr Ala Phe Thr Asn Cys Trp Met Asn
1 5
<210> 58
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 58
Phe Thr Phe Ser Thr Tyr Ala Met Phe
1 5
<210> 59
<211> 14
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 59
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly
1 5 10
<210> 60
<211> 14
<212> PRT
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<400> 60
Ile Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp
1 5 10
<210> 61
<211> 14
<212> PRT
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<400> 61
Val Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro
1 5 10
<210> 62
<211> 14
<212> PRT
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<400> 62
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly
1 5 10
<210> 63
<211> 14
<212> PRT
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<400> 63
Ile Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn
1 5 10
<210> 64
<211> 14
<212> PRT
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<400> 64
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly
1 5 10

<210> 65
<211> 14
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<400> 65
Ile Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn
1 5 10
<210> 66
<211> 14
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<400> 66
Val Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro
1 5 10
<210> 67
<211> 14
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<400> 67
Val Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro
1 5 10
<210> 68
<211> 13
<212> PRT
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<400> 68
Leu Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn
1 5 10
<210> 69
<211> 14
<212> PRT

<213> 人工序列
<220>
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<400> 69
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly
1 5 10
<210> 70
<211> 14
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 70
Ile Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser
1 5 10
<210> 71
<211> 14
<212> PRT
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<223> 合成构建体
<400> 71
Val Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro
1 5 10
<210> 72
<211> 10
<212> PRT
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<223> 合成构建体
<400> 72
Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr
1 5 10
<210> 73
<211> 13
<212> PRT
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<400> 73
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr
1 5 10
<210> 74
<211> 14
<212> PRT
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<223> 合成构建体
<400> 74
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val
1 5 10
<210> 75
<211> 10
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 75
Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr
1 5 10
<210> 76
<211> 9
<212> PRT
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<220>
<223> 合成构建体
<400> 76
Ala Arg Glu Gly Asn Pro Phe Thr Tyr
1 5
<210> 77
<211> 10
<212> PRT
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Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val
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Ala Lys Gln Gly Gly Thr Ser Phe Ser Tyr
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Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val
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1 5 10 15
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1 5 10 15
Asp Arg Val Ser Leu Ser Cys
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Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys
1 5 10 15
Val Thr Met Thr Cys
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1 5 10 15
Gly Arg Val Thr Ile Thr Cys
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1 5 10 15
Asp Gln Ala Ser Ile Ser Cys

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1 5 10 15
Asp Gln Ala Ser Ile Ser Cys
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Asn Glx Met Thr Gln Phe Gln Lys Phe Met Ser Thr Ser Val Gly Asp
1 5 10 15
Arg Val Ser Leu Thr Cys
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1 5 10 15
Pro Gly Glu Lys Val Thr Met Thr Cys
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1 5 10 15
Glu Ser Val Thr Ile Thr Cys
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Val Thr Ile Ser His
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Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr
1 5 10 15
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<400> 104
Gly Phe Gln Gln Lys Pro Gly His Ser Pro Lys Ala Gly Ile Tyr
1 5 10 15
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Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu Ile Phe
1 5 10 15
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Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile Tyr
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Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr
1 5 10 15
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Trp Tyr Glu Gln Lys Ala Asp Gly Thr Ala Asn Leu Ile Ile Tyr
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Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Trp Asp Phe Thr
1 5 10 15
Leu Ser Ile Asn Ser Val Glu Pro Glu Asp Val Gly Ile Tyr Tyr Cys
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<400> 113
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1 5 10 15
Leu Thr Ile Ser Arg Met Glu Ala Glu Asp Thr Ala Thr Tyr Tyr Cys
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Leu Ser Ile Thr Ser Leu Gln Thr Glu Asp Val Ala Thr Tyr Tyr Cys
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Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr
1 5 10 15
Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
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Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
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Leu Pro Ile Thr Thr Glx Gln Leu Glu Asp Leu Ala Glu Tyr Glx Cys
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Leu Thr Ile Ser Arg Met Glu Ala Glu Asp Thr Ala Thr Tyr Tyr Cys
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Leu Thr Ile Asn Ser Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys
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Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Lys Phe Ser
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Phe Lys Ile Ser Ser Leu Gln Ala Glu Asp Phe Val Ser Tyr Tyr Cys
20 25 30

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Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr
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Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
20 25 30

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Gly Glx Pro Ser Arg Leu Ser Gly Glx Gly Trp Val Thr Asp Tyr Phe
1 5 10 15
Leu Pro Ile His Thr Ser Glu Gln Glu Asp Arg Gly Ser Tyr Phe Cys
20 25 30

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Leu Ser Ile Asn Thr Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys
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Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
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1 5 10
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1 5 10

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<400> 134

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<400> 135

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

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<400> 136

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

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Ser Val Lys Leu Ser Cys Lys Asp Phe Asp
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Ser Val Lys Leu Ser Cys Ser Ala Ser Gly
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Glu Val Lys Leu Val Glu Ser Gly Gly Thr Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Lys Ile Ser Cys Ala Ala Ser Gly
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1 5 10 15
Ser Val Lys Leu Ser Cys Lys Asp Phe Asp
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1 5 10 15
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly
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Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Arg Ser Pro Gly Ser
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Asp Phe Asp
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1 5 10 15
Ser Val Lys Leu Ser Cys Lys Thr Ser Gly
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Glu Val Lys Leu Ala Asp Ser Gly Gly Ala Leu Val Asn Pro Gly Gly
1 5 10 15
Ser Leu Lys Ile Ser Cys Ala Val Ser Gly
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Leu Ser Cys Ala Ala Ser Gly
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Gln Val Gln Leu Lys Gln Ser Gly Pro Val Leu Val Ala Pro Ser Gln
1 5 10 15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
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Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Arg Ser Pro Gly Ser
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Asp Phe Asp
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Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
20 25

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Ser Leu Lys Leu Ser Cys Ala Ala Leu Gly
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Trp Val Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
1 5 10
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Trp Val Arg Gln Arg Pro Gly Lys Gly Leu Asp Trp
1 5 10
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Arg Val Arg Gln Thr Pro Glu Lys Arg Glu Glu Gly
1 5 10
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<400> 163
Glu Lys Phe Glu Asp Lys Ala Thr Leu Asp Ala Asp Thr Val Ser Asn
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Thr Ala Tyr Leu Glu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Ile
20 25 30
Tyr Tyr Cys
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Pro Lys Phe Gln Asp Lys Ala Phe Leu Thr Ala Asp Thr Ser Ser Thr
1 5 10 15
Thr Ala Tyr Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Ile
20 25 30
Tyr Tyr Cys
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Asp Ile Phe Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn
1 5 10 15
Ala Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu
20 25 30
Tyr Tyr Cys
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<210> 166
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<400> 166
Glu Lys Phe Glu Asp Lys Ala Thr Leu Asp Ala Asp Thr Val Ser Asn
1 5 10 15
Thr Ala Tyr Leu Glu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Ile
20 25 30
Tyr Tyr Cys
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<210> 167
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<212> PRT
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Glu Asn Tyr Arg Val Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser
1 5 10 15
Thr Ala Tyr Met Gln Leu Phe Ser Leu Thr Ser Glu Asp Ser Ala Val
20 25 30
Tyr Phe Cys
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<210> 168
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Glu Lys Phe Glu Asp Lys Ala Thr Leu Asp Ala Asp Thr Val Ser Asn
1 5 10 15
Thr Ala Tyr Leu Glu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Ile
20 25 30
Tyr Tyr Cys
35
<210> 169
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<400> 169
Glu Lys Phe Lys Ser Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser
1 5 10 15
Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val
20 25 30
Tyr Tyr Cys
35
<210> 170
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<212> PRT
<213> 人工序列
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<400> 170
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
1 5 10 15
Ala Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu
20 25 30
Tyr Tyr Cys
35
<210> 171
<211> 35
<212> PRT
<213> 人工序列
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<400> 171
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn
1 5 10 15
Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Lys Asp Thr Ala Met
20 25 30
Tyr Tyr Cys
35
<210> 172
<211> 35
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 172
Ser Val Leu Met Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser
1 5 10 15
Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met
20 25 30
Tyr Tyr Cys
35
<210> 173
<211> 35

<212> PRT
<213> 人工序列
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<400> 173
Glu Lys Phe Glu Asp Lys Ala Thr Leu Asp Ala Asp Thr Val Ser Asn
1 5 10 15
Thr Ala Tyr Leu Glu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Ile
20 25 30
Tyr Tyr Cys
35
<210> 174
<211> 35
<212> PRT
<213> 人工序列
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<400> 174
Gly Lys Phe Lys Asp Lys Ala Thr Leu Thr Glu Asp Lys Ser Ser Ser
1 5 10 15
Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
20 25 30
Tyr Phe Cys
35
<210> 175
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<212> PRT
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<400> 175
Asp Ser Ala Lys Asp Arg His Pro Ile Phe Arg Asp Asn Ala Arg Asn
1 5 10 15
Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Lys Asp Thr Ala Met
20 25 30
Tyr Tyr Cys
35
<210> 176
<211> 11

<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 176
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
1 5 10
<210> 177
<211> 11
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 177
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
1 5 10
<210> 178
<211> 11
<212> PRT
<213> 人工序列
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<400> 178
Trp Gly Ala Gly Ala Thr Val Thr Val Ser Ser
1 5 10
<210> 179
<211> 11
<212> PRT
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<400> 179
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
1 5 10
<210> 180
<211> 11
<212> PRT
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<223> 合成构建体
<400> 180
Trp Gly His Gly Thr Leu Val Thr Val Ser Ala
1 5 10
<210> 181
<211> 11
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<223> 合成构建体
<400> 181
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
1 5 10
<210> 182
<211> 11
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 182
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
1 5 10
<210> 183
<211> 11
<212> PRT
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<400> 183
Trp Gly Ala Gly Ala Thr Val Thr Val Ser Ser
1 5 10
<210> 184
<211> 11
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<400> 184
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser

1 5 10

<210> 185

<211> 11

<212> PRT

<213> 人工序列

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<223> 合成构建体

<400> 185

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala

1 5 10

<210> 186

<211> 11

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 186

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala

1 5 10

<210> 187

<211> 11

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 187

Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser

1 5 10

<210> 188

<211> 11

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 188

Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser

1 5 10

<210> 189

<211> 112

<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 189

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 190
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 190

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105 110

<210> 191
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 191

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Pro
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 192
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 192

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Pro
50 55 60
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80

Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 193
<211> 112
<212> PRT
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<400> 193

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 194
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<212> PRT
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<400> 194

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Pro

50 55 60
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 195
<211> 112
<212> PRT
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<400> 195
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 196
<211> 112
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 196
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 197
<211> 112
<212> PRT
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<400> 197

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 198
<211> 112
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 198

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly

1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 199
<211> 107
<212> PRT
<213> 人工序列
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<400> 199
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 200
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 200

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 201
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 201

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 202
<211> 107

<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 202

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 203
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 203

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 204
<211> 107
<212> PRT
<213> 人工序列
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<400> 204

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 205
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 205

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 206
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 206

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 207
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 207

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Asp Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 208
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 208

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80
Glu Asp Val Ala Val Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 209
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 209

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 210
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 210
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 211
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 211
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly

1 5 10 15
Asp Arg Val Thr Ile Thr Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65 70 75 80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 212
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 212
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80
Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 213
<211> 106
<212> PRT
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<223> 合成构建体

<400> 213

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 214

<211> 106

<212> PRT

<213> 人工序列

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<223> 合成构建体

<400> 214

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 215

<211> 106

<212> PRT
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<400> 215

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 216
<211> 106
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 216

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30
Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu
65 70 75 80
Asp Val Gly Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 217
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 217

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30
Tyr Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu
65 70 75 80
Asp Val Gly Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 218
<211> 106
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 218

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu
65 70 75 80

Asp Val Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 219
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 219

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 220
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 220

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ile Ala Thr Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 221
<211> 107
<212> PRT
<213> 人工序列
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<400> 221

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 222
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 222

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 223
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 223
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 224
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 224
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 225
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 225
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 226
<211> 107
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体
<400> 226

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Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                  10                  15
Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Asp His Ile Asn Asn Trp
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65                  70                  75                  80
Glu Asp Val Ala Val Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 227
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 227

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Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                  10                  15
Gln Pro Ala Ser Ile Ser Cys Lys Ala Ser Asp His Ile Asn Asn Trp
            20                  25                  30
Leu Ala Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile
        35                  40                  45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65                  70                  75                  80
Glu Asp Val Gly Val Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 228
<211> 107

<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 228

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45
Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 229
<211> 112
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 229

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105 110

<210> 230
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 230

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 231
<211> 112
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 231

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Pro
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80

Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 232
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 232

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Ile Pro
50 55 60
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 233
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 233

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Val Pro

50 55 60

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 234
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 234

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Ile Pro
50 55 60
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 235
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 235

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Ile Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 236
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 236

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 237
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 237

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 238
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 238
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 239
<211> 112
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体

<400> 239

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 240

<211> 112

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 240

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 241

<211> 112

<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 241

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Pro
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 242
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 242

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Ile Pro
50 55 60
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105 110

<210> 243
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 243

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 244
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 244

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Ile Pro
50 55 60
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80

Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 245
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 245

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Ile Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 246
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 246

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Val Pro

50 55 60

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 247
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 247

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 248
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 248

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Thr Gly Asn Ile Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 249
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 249

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Thr Arg His Arg Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 250
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 250

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Thr Arg His Arg Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 251
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 251
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Thr Arg His Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 252
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 252

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Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
            20                  25                  30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ser Ala Ser Thr Arg His Arg Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Asp Asp Phe Ala Thr Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 253
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 253

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
            20                  25                  30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ser Ala Ser Thr Arg His Arg Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 254
<211> 107

<212> PRT
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<400> 254

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Thr Arg His Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ile Ala Thr Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

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<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 255

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Thr Arg His Arg Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

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<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 256

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Thr Arg His Arg Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80
Glu Asp Val Ala Val Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 257
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 257

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Thr Arg His Arg Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80

Glu Asp Val Gly Val Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 258
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 258
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Lys Ala Ser Gln Lys Val Gly Thr Asn
20 25 30
Val Ala Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile
35 40 45
Tyr Ser Ala Ser Thr Arg His Arg Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys His Gln Gly Asn Ser Val Gln Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 259
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 259
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser

50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
65 70 75 80

Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 260
<211> 106
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 260

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80

Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

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<211> 106
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 261

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

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<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 262
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65 70 75 80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 263
<211> 106
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 263
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly

1 5 10 15
Asp Arg Val Thr Ile Thr Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 264
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<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 264
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 265
<211> 106
<212> PRT
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<223> 合成构建体

<400> 265

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 266

<211> 106

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 266

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu
65 70 75 80
Asp Val Gly Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 267

<211> 106

<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 267

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu
65 70 75 80
Asp Val Gly Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 268
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 268

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu
65 70 75 80
Asp Val Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 269
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 269

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 270
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 270

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 271
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 271

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 272
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<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 272

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 273
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 273

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 274
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 274

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30

Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 275
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 275
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 276
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 276
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly

1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 277
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 277
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 278
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 278

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80
Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 279
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 279

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 280
<211> 107

<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 280

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 281
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 281

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 282
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 282

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 283
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 283

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 284
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 284
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 285
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 285
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Ile Pro Asp Arg Phe Ser Gly

50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 286
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 286
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 287
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 287
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80
Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 288
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 288
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 289
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 289
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly

1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 290
<211> 112
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 290
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 291
<211> 112
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体
<400> 291

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Pro
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 292
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 292

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Pro
50 55 60
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 293
<211> 112

<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 293

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 294
<211> 112
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 294

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Pro
50 55 60
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105 110

<210> 295
<211> 112
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 295

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 296
<211> 112
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 296

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 297
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 297

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 298
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 298

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Pro

50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 299
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 299

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 300
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 300

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 301
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 301
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 302
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 302
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly

1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 303
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 303
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 304
<211> 107
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体
<400> 304

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 305
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 305

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 306
<211> 107

<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 306

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30
Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 307
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 307

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30
Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 308
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 308

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Gln Asp Ile Ser Glx Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45
Tyr Leu Ser Ser Arg Leu His Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80
Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Gly His Thr Gly Ala Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 309
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 309

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 310
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 310

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 311
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 311

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 312
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 312

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 313
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 313

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30

Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 314
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 314
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 315
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 315
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly

1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 316
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 316
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80
Glu Asp Val Ala Val Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 317
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 317

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 318
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 318

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45
Tyr Phe Ala Ser Gln Ser Ile Cys Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 319
<211> 118

<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 319

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Gln Lys
50 55 60
Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val
65 70 75 80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 320
<211> 118
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 320

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr

85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115
<210> 321
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 321
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Gln Lys
50 55 60
Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala
65 70 75 80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115
<210> 322
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 322
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Ser Glu Val Phe Pro Ile
20 25 30

Thr Tyr Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala
65 70 75 80
Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 323
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 323

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 324
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体
<400> 324

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 325
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 325

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr

100 105 110

Leu Val Thr Val Ser Ser
115

<210> 326
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 326

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 327
<211> 118
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 327

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 328
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 328
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 329
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 329

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 330

<211> 120

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 330

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser

115 120

<210> 331
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 331

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 332
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 332

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 333
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 333
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 334
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 334
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 335
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 335
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 336

<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 336

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 337
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 337

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Ala Pro Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 338
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 338

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 339
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 339

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr

20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 340
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 340
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 341
<211> 121
<212> PRT

<213> 人工序列
<220>
<223> 合成构建体
<400> 341

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 342
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 342

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 343
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 343

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 344
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 344

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val

35 40 45

Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 345
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 345

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 346
<211> 121
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体

<400> 346

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 347

<211> 121

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 347

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Ala Pro Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 348
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 348

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 349
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 349

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Gln Lys

50 55 60

Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val
65 70 75 80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 350
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 350

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 351
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 351

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Gln Lys
50 55 60
Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala
65 70 75 80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 352
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 352

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala
65 70 75 80
Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 353
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 353

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 354
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 354

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu

65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 355
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 355
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 356
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 356
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 357
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 357

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 358
<211> 118

<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 358

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 359
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 359

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115
<210> 360
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 360
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115
<210> 361
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 361
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 362
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 362

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 363
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体
<400> 363

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 364
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 364

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

Thr Val Ser Ser
115

<210> 365
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 365

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 366
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 366

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 367
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 367
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Ala Pro Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 368
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 368

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 369

<211> 118

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 369

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Gln Lys
50 55 60
Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val
65 70 75 80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser

115

<210> 370
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 370

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 371
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 371

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Gln Lys
50 55 60

Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala
65 70 75 80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 372
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 372

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala
65 70 75 80
Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 373
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 373

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 374
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 374

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 375

<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 375

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 376
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 376

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 377
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 377

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 378
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 378

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile

20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 379
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 379
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 380
<211> 117
<212> PRT

<213> 人工序列
<220>
<223> 合成构建体
<400> 380

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 381
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 381

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 382
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 382

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 383
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 383

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 384
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 384
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 385
<211> 117
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体
<400> 385

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 386
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 386

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 387
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 387

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Ala Pro Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 388
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 388

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Pro Ser Leu

50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 389
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 389

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 390
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 390

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 391
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 391

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 392
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 392

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 393
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 393

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr

65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 394
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 394
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 395
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 395
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 396
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 396

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 397
<211> 121

<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 397

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Ala Pro Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 398
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 398

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys

85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 399
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 399
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 400
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 400
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 401
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 401

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 402
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体
<400> 402

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 403
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 403

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 404
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 404

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 405
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 405

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 406
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 406
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 407
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 407

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Ala Pro Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 408

<211> 121

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 408

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Gln Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser

115 120

<210> 409
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 409

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 410
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 410

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 411
<211> 116
<212> PRT
<213> 人工序列
<220>
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<400> 411

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 412
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 412

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 413
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 413

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 414

<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 414

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Pro Ser Phe Gln
50 55 60
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 415
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 415

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Gln Lys Phe Gln
50 55 60
Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr Met
65 70 75 80

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 416
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 416

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Gln Lys Phe Gln
50 55 60
Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met
65 70 75 80
Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 417
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 417

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Tyr

20 25 30
Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 418
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 418
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 419
<211> 118
<212> PRT

<213> 人工序列
<220>
<223> 合成构建体
<400> 419

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Gln Lys
50 55 60
Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val
65 70 75 80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 420
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 420

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 421
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 421

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Gln Lys
50 55 60
Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala
65 70 75 80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 422
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 422

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp

35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala
65 70 75 80
Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 423
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 423
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 424
<211> 118
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体

<400> 424

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 425

<211> 118

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 425

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 426
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 426

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 427
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 427

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser

50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 428
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 428

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 429
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 429

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 430
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 430

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 431
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 431

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 432
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 432

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 433
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 433
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 434
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 434
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 435
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 435

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 436
<211> 118

<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 436

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 437
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 437

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Ala Pro Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 438
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 438
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 439
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 439
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Ala Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 440
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 440

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 441
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体
<400> 441

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 442
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 442

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 443
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 443

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 444
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 444

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 445
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 445
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 446
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 446

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 447

<211> 121

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 447

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Ala Pro Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser

115 120

<210> 448
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 448

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 449
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 449

Asp Val Glx Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 450
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 450

Asp Ile Gln Met Thr Gln Phe Pro Ala Thr Leu Ser Val Thr Pro Gly
1 5 10 15
Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln His Lys Ser His Glu Ser Pro Arg Leu Leu Ile
35 40 45
Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Trp Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Pro
65 70 75 80
Glu Asp Val Gly Ile Tyr Tyr Cys Gln Lys Gly Leu Asn Phe Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Met Lys
100 105

<210> 451
<211> 104
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 451

Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys
1 5 10 15
Val Thr Met Thr Cys Ser Ala Asn Ser Ser Phe Ile Tyr Met Tyr Trp
20 25 30
Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu Ile Phe Asp Thr

35 40 45

Ser Asn Leu Ala Ser Gly Val Pro Ile Arg Phe Ser Gly Ser Gly Ser
50 55 60

Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu Asp Thr
65 70 75 80

Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr Phe Gly
85 90 95

Gly Gly Thr Lys Leu Glu Leu Lys
100

<210> 452
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 452

Asp Ile Gln Met Thr Gln Ser Leu Ser Tyr Leu Ser Val Ser Leu Gly
1 5 10 15

Gly Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile
35 40 45

Ser Gly Ala Thr Ser Leu Glu Thr Gly Phe Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys His Gln Tyr Trp Asn Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 453
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 453

Asp Val Glx Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Cys Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 454
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 454

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Ile Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Glx Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 455
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 455

Asn Glx Met Thr Gln Phe Gln Lys Phe Met Ser Thr Ser Val Gly Asp
1 5 10 15
Arg Val Ser Leu Thr Cys Lys Ala Ser Gln Lys Val Gly Thr Asn Val
20 25 30
Ala Gly Phe Gln Gln Lys Pro Gly His Ser Pro Lys Ala Gly Ile Tyr
35 40 45
Ser Ala Ser Thr Arg His Arg Gly Val Gln Asp Arg Phe Thr Ala Arg
50 55 60
Gly Leu Gly Ser Asp Phe Ile Leu Pro Ile Thr Thr Glx Gln Leu Glu
65 70 75 80
Asp Leu Ala Glu Tyr Glx Cys His Gln Gly Asn Ser Val Gln Tyr Thr
85 90 95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 456
<211> 108
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 456

Gly Glx Gln Asn Val Leu Thr Gln Ser Pro Ala Ile Leu Ser Ala Ser
1 5 10 15
Pro Gly Glu Lys Val Thr Met Thr Cys Ser Ala Asn Ser Ser Phe Thr
20 25 30
Tyr Met Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu
35 40 45
Ile Phe Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ile Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu
65 70 75 80
Ala Glu Asp Thr Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro
85 90 95
Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 457
<211> 107
<212> PRT

<213> 人工序列
<220>
<223> 合成构建体
<400> 457

Asp Ile Gln Met Thr Gln Glx Pro Ala Thr Leu Ser Val Thr Pro Gly
1 5 10 15
Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30
Leu His Trp Tyr His Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
35 40 45
Lys Phe Ala Ser Gln Ser Ile Cys Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Ser Asp Phe Thr Leu Thr Ile Asn Ser Val Glu Pro
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Asn Gly His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 458
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 458

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly
1 5 10 15
Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Ser Ser Leu Gln Ala
65 70 75 80
Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 459
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 459

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Asn
85 90 95
Thr His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 460
<211> 105
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 460

Glx Met Thr Gln Phe Thr Ser Ser Met Ser Gly Ser Glu Gly Asp Arg
1 5 10 15
Val Thr Ile Ser His Arg Ala Ser Gln Asp Ile Ser Glx Tyr Leu Asn
20 25 30
Trp Tyr Glu Gln Lys Ala Asp Gly Thr Ala Asn Leu Ile Ile Tyr Leu
35 40 45
Ser Ser Arg Leu His Ser Gly Glx Pro Ser Arg Leu Ser Gly Glx Gly
50 55 60
Trp Val Thr Asp Tyr Phe Leu Pro Ile His Thr Ser Glu Gln Glu Asp
65 70 75 80
Arg Gly Ser Tyr Phe Cys Gln Gln Gly His Thr Gly Ala Trp Thr Phe

85 90 95

Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 461
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 461

Asp Ile Gln Met Thr Gln Phe Pro Ala Thr Leu Ser Gly Thr Pro Gly
1 5 10 15
Asp Arg Val Glx Leu Ser Arg Arg Ala Ser Gln Ser Ile Arg Glu Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Glx Ile
35 40 45
Lys Phe Ala Ser Gln Ser Ile Cys Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Ser Asp Phe Thr Leu Ser Ile Asn Thr Val Glu Pro
65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Lys Ala His Asn Phe Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 462
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 462

Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Arg Ser Pro Gly Ser
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Asp Phe Asp Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Lys Pro Gly His Gly Phe Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Glu Lys
50 55 60

Phe Glu Asp Lys Ala Thr Leu Asp Ala Asp Thr Val Ser Asn Thr Ala
65 70 75 80
Tyr Leu Glu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ala
115

<210> 463
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 463

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15
Ser Val Lys Leu Ser Cys Ser Ala Ser Gly Phe Asn Ile Lys Gly Ser
20 25 30
Leu Leu His Trp Ile Lys Gln Arg Pro Leu Gln Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Arg Phe Asp Pro Lys Phe
50 55 60
Gln Asp Lys Ala Phe Leu Thr Ala Asp Thr Ser Ser Thr Thr Ala Tyr
65 70 75 80
Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95
Ala Arg Thr Glu Tyr Ser Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 464
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 464

Glu Val Lys Leu Val Glu Ser Gly Gly Thr Leu Val Lys Pro Gly Gly

1 5 10 15
Ser Leu Lys Ile Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Asn Pro Glu Lys Arg Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Asp Tyr Thr Tyr Tyr Pro Asp Ile Phe
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn Ala Leu Tyr
65 70 75 80
Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Ala Gly Ala Thr Val Thr Val Ser Ser
115 120

<210> 465
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 465

Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Arg Ser Pro Gly Ser
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Asp Phe Asp Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Lys Pro Gly His Gly Phe Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Glu Lys
50 55 60
Phe Glu Asp Lys Ala Thr Leu Asp Ala Asp Thr Val Ser Asn Thr Ala
65 70 75 80
Tyr Leu Glu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ala
115

<210> 466

<211> 116
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 466

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30
Gly Ile Thr Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ser Pro Arg Ser Gly Glu Thr Tyr Phe Asn Glu Asn Tyr
50 55 60
Arg Val Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Phe Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95
Ala Arg Glu Gly Asn Pro Phe Thr Tyr Trp Gly His Gly Thr Leu Val
100 105 110
Thr Val Ser Ala
115

<210> 467
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 467

Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Arg Ser Pro Gly Ser
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Asp Phe Asp Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Lys Pro Gly His Gly Phe Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Glu Lys
50 55 60
Phe Glu Asp Lys Ala Thr Leu Asp Ala Asp Thr Val Ser Asn Thr Ala
65 70 75 80

Tyr Leu Glu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr
85 90 95
Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ala
115

<210> 468
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 468
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Trp Ile Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Asn Ile Tyr Ser Gly Ser Ser Arg Thr Asn Tyr Asn Glu Lys Phe
50 55 60
Lys Ser Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Gly Leu Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110
Val Thr Val Ser Ser
115

<210> 469
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 469
Glu Val Lys Leu Ala Asp Ser Gly Gly Ala Leu Val Asn Pro Gly Gly
1 5 10 15
Ser Leu Lys Ile Ser Cys Ala Val Ser Gly Phe Ile Phe Ser Asn Tyr

20 25 30
Asp Met Ser Trp Val Arg Gln Asn Pro Glu Lys Arg Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Leu Tyr
65 70 75 80
Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Ala Gly Ala Thr Val Thr Val Ser Ser
115 120

<210> 470
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 470
Leu Val Glx Ser Gly Gly Ala Leu Val Lys Pro Gly Gly Ser Leu Lys
1 5 10 15
Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser
20 25 30
Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val Ala Ser Ile
35 40 45
Ser Ser Gly Gly Ser Tyr Asn Tyr Tyr Pro Asp Ser Val Lys Gly Arg
50 55 60
Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr Leu Gln Met
65 70 75 80
Ser Ser Leu Arg Ser Lys Asp Thr Ala Met Tyr Tyr Cys Ala Ser Gln
85 90 95
Ser Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr
100 105 110
Thr Val Thr Val Ser Ser
115

<210> 471
<211> 116
<212> PRT

<213> 人工序列
<220>
<223> 合成构建体
<400> 471

Gln Val Gln Leu Lys Gln Ser Gly Pro Val Leu Val Ala Pro Ser Gln
1 5 10 15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Val Leu Met
50 55 60
Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80
Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95
Lys Gln Gly Gly Thr Ser Phe Ser Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ala
115

<210> 472
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 472

Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Arg Ser Pro Gly Ser
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Asp Phe Asp Ser Glu Val Phe Pro Ile
20 25 30
Thr Tyr Met Asn Trp Val Arg Gln Lys Pro Gly His Gly Phe Glu Trp
35 40 45
Ile Gly Asp Ile Leu Pro Ser Ile Gly Arg Thr Met Tyr Gly Glu Lys
50 55 60
Phe Glu Asp Lys Ala Thr Leu Asp Ala Asp Thr Val Ser Asn Thr Ala
65 70 75 80
Tyr Leu Glu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr
85 90 95

Cys Ala Arg Ser Glu Gly Tyr Leu Leu Ala Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ala
115

<210> 473
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 473

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Arg Pro Gly Lys Gly Leu Asp Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Gly Lys Phe
50 55 60
Lys Asp Lys Ala Thr Leu Thr Glu Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Thr Leu Thr Val Ser Ser
115

<210> 474
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 474

Glu Val Lys Leu Val Glu Phe Gly Gly Ala Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Lys Leu Ser Cys Ala Ala Leu Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Phe Arg Val Arg Gln Thr Pro Glu Lys Arg Glu Glu Gly Val

35 40 45

Ala Ser Ile Ser Ser Gly Gly Arg Tyr Thr Tyr Tyr Pro Asp Ser Ala
50 55 60

Lys Asp Arg His Pro Ile Phe Arg Asp Asn Ala Arg Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Lys Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Val Arg His Ser Tyr Gly Ser Ser Tyr Trp Tyr Leu Asp Val Trp Gly
100 105 110

Ala Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 475
<211> 110
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<400> 475

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
100 105 110

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<400> 476

Arg Ala Ser Gln Asp Ile Asn Thr Tyr Leu Asn
1 5 10

<210> 477
<211> 7
<212> PRT
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<400> 477
Tyr Thr Ser Arg Leu His Ser
1 5

<210> 478
<211> 9
<212> PRT
<213> 人工序列
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<400> 478
Gln Gln Gly Asn Thr Leu Pro Trp Thr
1 5

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<211> 10
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<400> 479
Gly Tyr Ala Phe Thr Asn Cys Trp Met Asn
1 5 10

<210> 480
<211> 14
<212> PRT
<213> 人工序列
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<400> 480
Val Ser Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Ala
1 5 10

<210> 481

<211> 14
<212> PRT
<213> 人工序列
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<400> 481
Val Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Ala
1 5 10
<210> 482
<211> 10
<212> PRT
<213> 人工序列
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<400> 482
Arg Ile Phe Pro Gly Asn Gly His Thr Asn
1 5 10
<210> 483
<211> 9
<212> PRT
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<400> 483
Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr
1 5
<210> 484
<211> 106
<212> PRT
<213> 人工序列
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<400> 484
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 485
<211> 106
<212> PRT
<213> 人工序列
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<400> 485

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Val Thr Met Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Met Glu Pro Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 486
<211> 106
<212> PRT
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<400> 486

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Val Thr Met Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met

20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Phe
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Met Glu Pro Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 487
<211> 107
<212> PRT
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<400> 487
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn Thr Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 488
<211> 107
<212> PRT
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<400> 488

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn Thr Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 489
<211> 107
<212> PRT
<213> 人工序列
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<400> 489
Asp Val Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn Thr Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 490
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体
<400> 490

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 491
<211> 121
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 491

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 492
<211> 121
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 492

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Ile Ser Cys Ala Val Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Ala Leu Val Thr Val Ser Ser
115 120

<210> 493
<211> 118
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 493

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 494
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 494
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 495
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 495

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Ala Thr Leu Thr Glu Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Leu Thr Val Ser Ser
115

<210> 496

<211> 118

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 496

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Cys
20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Ala Thr Leu Thr Glu Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Leu Thr Val Ser Ser

115

<210> 497
<211> 95
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 497

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro
85 90 95

<210> 498
<211> 12
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 498

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
1 5 10

<210> 499
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 499

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15
Glu Lys Val Thr Met Thr Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met

20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu Ile Phe
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ile Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80
Asp Thr Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 500
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 500
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 501
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 501

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 502
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 502

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Val Thr Met Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Met Glu Pro Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 503
<211> 106
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体
<400> 503

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Val Thr Met Ser Cys Ser Ala Asn Ser Ser Phe Thr Tyr Met
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Phe
35 40 45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60
Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Met Glu Pro Glu
65 70 75 80
Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Pro Leu Thr
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 504
<211> 95
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 504

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Ser Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95

<210> 505
<211> 15
<212> PRT

<213> 人工序列
<220>
<223> 合成构建体
<400> 505
Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10 15
<210> 506
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 506
Glu Val Gln Leu Val Glu Ser Gly Gly Ala Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Lys Ile Ser Cys Ala Val Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Asn Pro Glu Lys Arg Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Leu Tyr
65 70 75 80
Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Ala Gly Ala Thr Val Thr Val Ser Ser
115 120
<210> 507
<211> 109
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 507
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

20 25 30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 508
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 508
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 509
<211> 121
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体
<400> 509

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 510
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 510

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Ile Ser Cys Ala Val Ser Gly Phe Ile Phe Ser Asn Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg His Gly Tyr Gly Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly
100 105 110

Gln Gly Ala Leu Val Thr Val Ser Ser
115 120

<210> 511
<211> 94
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 511

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
85 90

<210> 512
<211> 12
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 512

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
1 5 10

<210> 513
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 513

Asp Val Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Asn Thr Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45
Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 514
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 514
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 515
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 515

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn Thr Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
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35 40 45
Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Trp
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Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
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Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
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Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
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            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
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35 40 45
Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ser Gly Lys Phe
50 55 60
Lys Asp Lys Ala Thr Leu Thr Glu Asp Lys Ser Ser Ser Thr Ala Tyr
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35 40 45
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35 40 45
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50 55 60
Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Ser Thr Val Tyr
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Gly Arg Ile Phe Pro Gly Asn Gly His Thr Asn Tyr Ala Gln Lys Phe
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Xaa Xaa Xaa

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黑猩猩 Siglec-7 -MLLLLLLPPLLWGRERVEGQKSNRKDYSLTMQSSVTVQEGMCVHVRCSFSYPVDSQTDS 59
矮小黑猩猩 Siglec-7 -MLLLLLLLPLLWGRERVEGQKSNRKDYSLTMQSSVTVQEGMCVHVRCSFSYPVDSQTDS 59
猩猩 Siglec-7 MLLLLLLLFTLPLLWGRERVEGQKNNRKDYSLMMQSSVTVQEGLCVHVQCSFSYPVDSQTDS 60
大猩猩 Siglec-7 -MLLLLLLLLPLLWGRERVEGQKSKRKDYSLTMQSSVTVQEGMCVHVRCSFSYPVDSQTDS 59
长臂猿 Siglec-7 -MLLLLLLLPLLWGRERVEGQKSNQKNYPLMMQSSVTVQEGLCVHVRCSFSYPVDSQTDS 59
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矮小黑猩猩 Siglec-7 DPVHGYWFRAENDISWKAPVATNMPARAVREETRDRFHLLGDPQTKNCTLSIRDARMSDA 119
猩猩 Siglec-7 DPVHGYWFRAGDDISWKAPVATNMPAQAVREETRDRFHLLGDPQTKNCTLSIRDARMSDA 120
大猩猩 Siglec-7 DPVHGYWFRAENDISWKAPVATNDPARAVREETRDRFHLLGDPQTKNCTLSIRDARMSDA 119
长臂猿 Siglec-7 DPVHGYWFRAGDDISWKTPVATNNRARAVREETRDRFHLLGDPQTKNCTLSIRDARMSDA 119
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黑猩猩 Siglec-7 GRYFFRMEKGNIKWNYKHDQLSVNVTASQAPLSRYRLEVLELVTVQEGXCVSVPCSVLXP 179
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猩猩 Siglec-7 GRYFFRMERGNIKWNYKYDRLSVNVTASQAPPSRYRLEVPESVTVQEGLCVSVPCSVLXP 180
大猩猩 Siglec-7 GRYFFRMEKGNIKWNYKYDQLS---------- 141
长臂猿 Siglec-7 GTYFYRMERGKIKWNYKYHQLS---------- 141
* **;***:*;*******;.:**
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矮小黑猩猩 Siglec-7 -- 141
猩猩 Siglec-7 YYNWTDSSPVHGCWFKKGINIQWNNPVATNIPNGKVEETRGRFHLLGDLKTNNCSLSIRD 240
大猩猩 Siglec-7 -- 141
长臂猿 Siglec-7 -- 141
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黑猩猩 Siglec-7 ARKGDLGNYYFQVERGQIRWNYKTKQLSVNVTALTHRPNILIPGTLESGCFQNLTCSVPW 299
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图1A

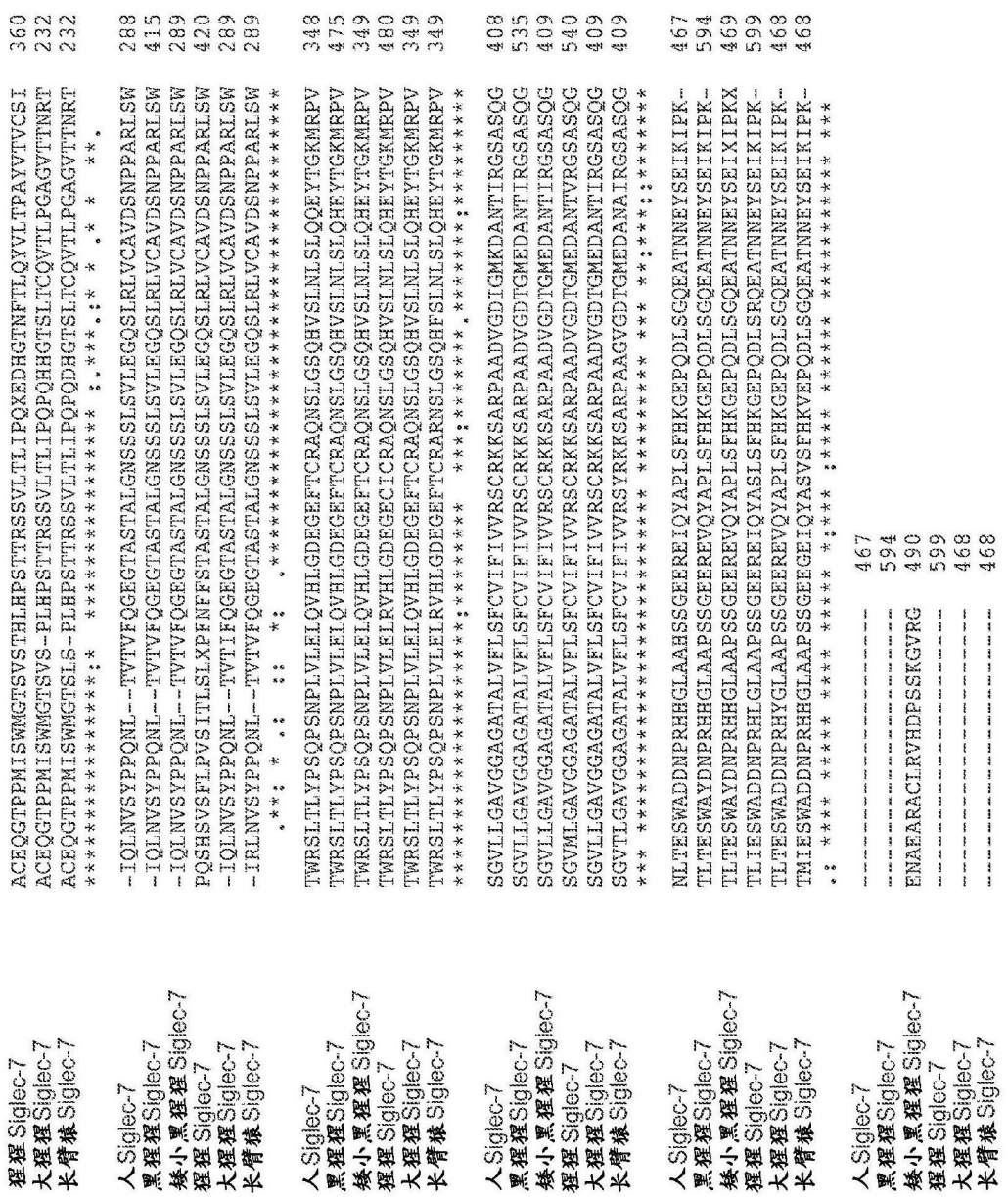

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猩猩 Siglec-7 PQSHSVSFLPVSITLSLXPFNFFSTASTALGNSSSLSVLEGQSLRLVCAVDSNPPARLSW 420
大猩猩Siglec-7 -IQLNVSYPPQNL--TVTIFQGEGTASTALGNSSSLSVLEGQSLRLVCAVDSNPPARLSW 289
长臂猿 Siglec-7 -IRLNVSYPPQNL--TVTVFQGEGTASTALGNSSSLSVLEGQSLRLVCAVDSNPPARLSW 289
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矮小黑猩猩 Siglec-7 TWRSLTLYPSQPSNPLVLELQVHLGDEGEFTCRAQNSLGSQHVSLNLSLQHEYTGKMRPV 349
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黑猩猩Siglec-7 SGVLLGAVGGAGATALVFLSFCVIFIVVRSCRKKSARPAADVGDTGMEDANTTRGSASQG 535
矮小黑猩猩 Siglec-7 SGVLLGAVGGAGATALVFLSFCVIFIVVRSCRKKSAEPAADVGDTGMEDANTIRGSASQG 409
猩猩 Siglec-7 SGVMLGAVGGAGATALVFLSFCVIFIVVRSCRKKSARPAADVGDTGMEDANTVRGSASQG 540
大猩猩Siglec-7 SGVLLGAVGGAGATALVFLSFCVIFIVVRSCRKKSARPAADVGDTGMEDANTTRGSASQG 409
长臂猿 Siglec-7 SGVTLGAVGGAGATALVFLSFCVIFIVVRSYRKKSARPAAGVGDTGMEDANAIRGSASQG 409
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大猩猩Siglec-7 TLTESWADDNPRHYGLAAPSSGEERREVQYAPLSFHKGEPQDLSGQEATNNEYSEIKIPK- 468
长臂猿 Siglec-7 TMIESWADDNPRHHGLAAPSSGEGEIQYASVSFHKVEPQDLSGQEATNNEYSEIKIPK- 468
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黑猩猩Siglec-7 ---------- 594
矮小黑猩猩 Siglec-7 ENAEARACLRVHDPSSKGVRG 490
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图1A(续)

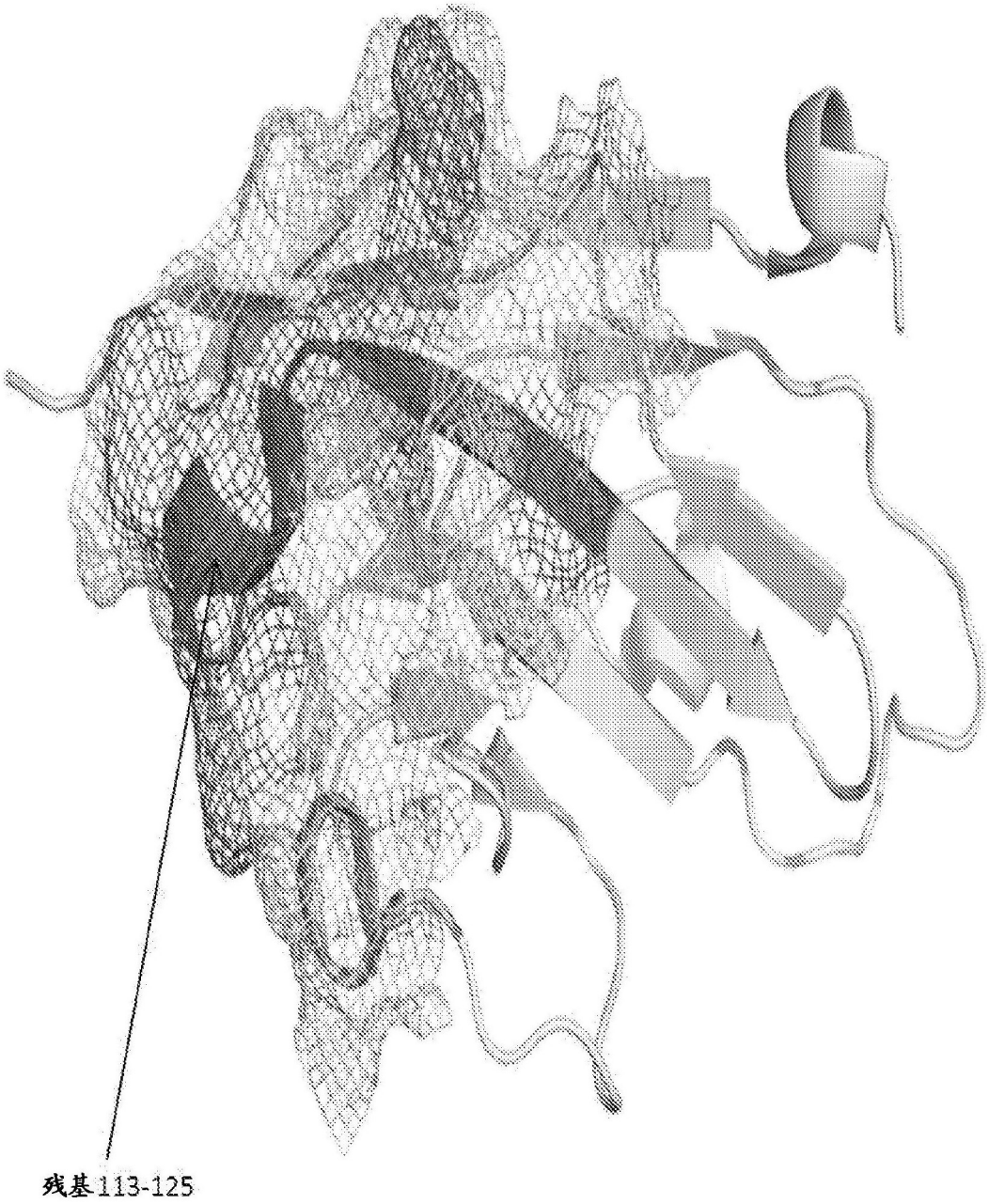


图1B

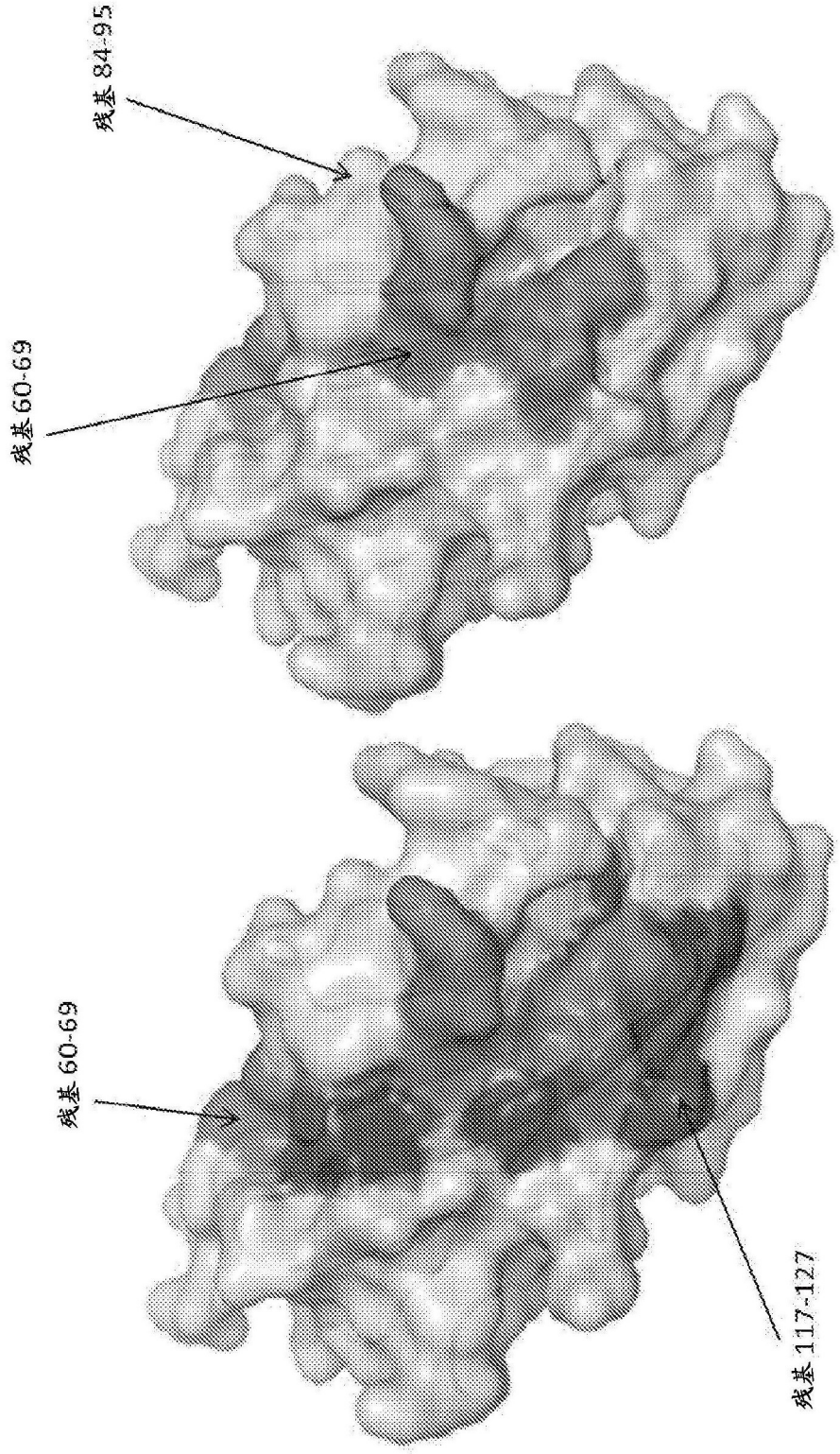


图 1D

图 1C

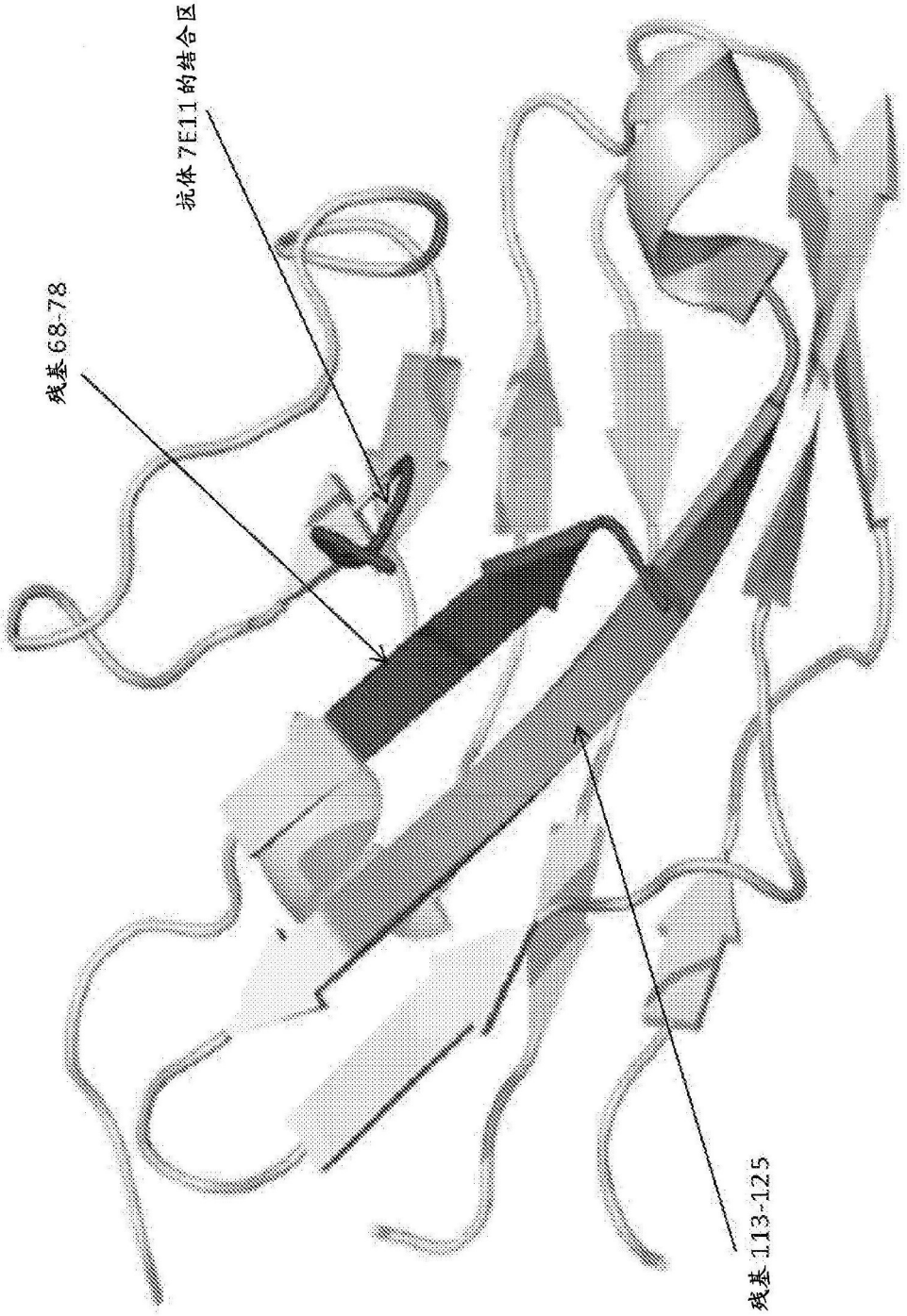
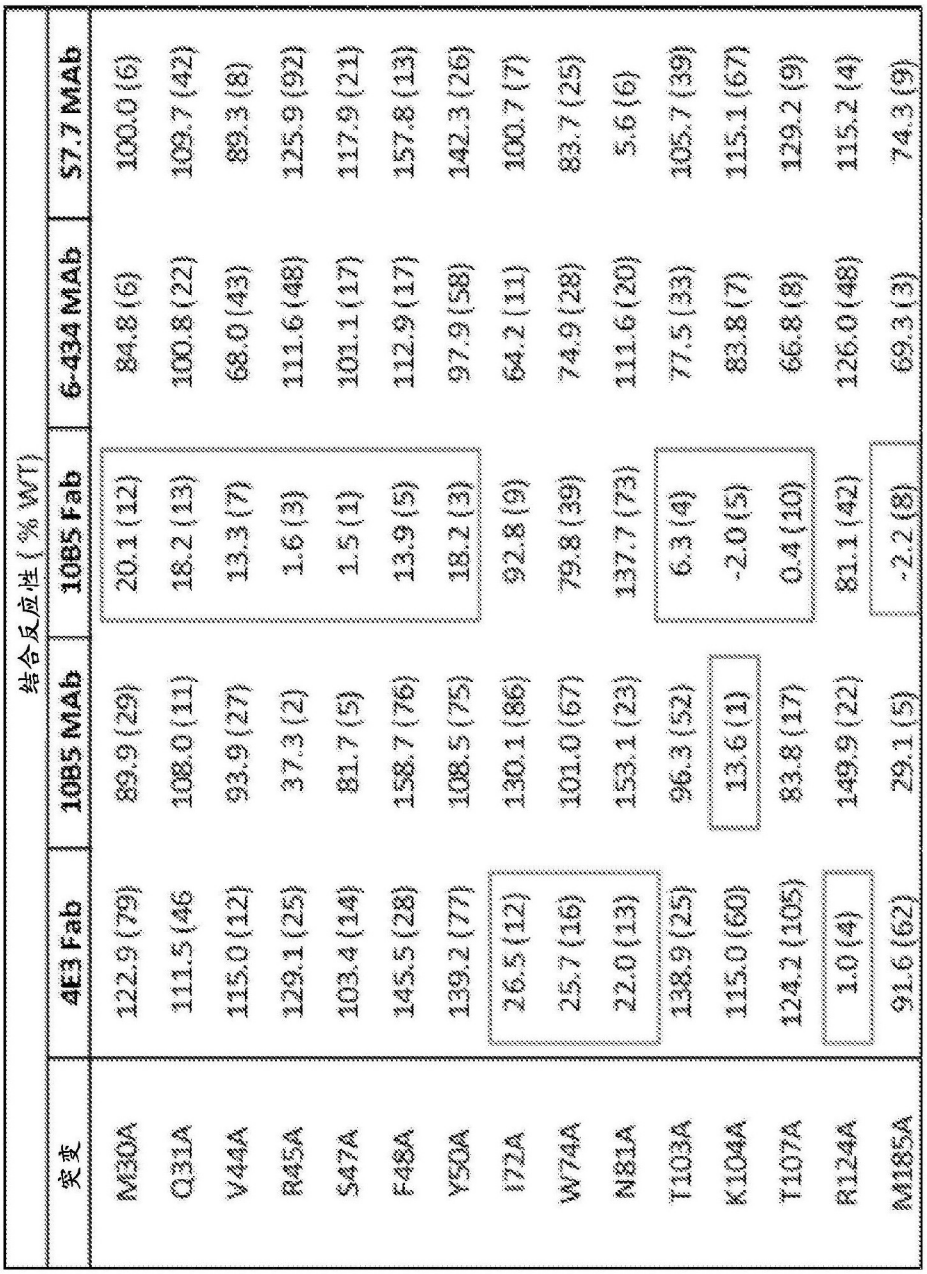


图1E



结合反应性(% WT)					
突变	4E3 Fab	1085 MAb	1085 Fab	6-434 MAb	S7.7 MAb
M30A	122.9 (79)	89.9 (29)	20.1 (12)	84.8 (6)	100.0 (6)
Q31A	111.5 (46	108.0 (11)	18.2 (13)	100.8 (22)	109.7 (42)
V44A	115.0 (12)	93.9 (27)	13.3 (7)	68.0 (43)	89.3 (8)
R45A	129.1 (25)	37.3 (2)	1.6 (3)	111.6 (48)	125.9 (92)
S47A	103.4 (14)	81.7 (5)	1.5 (1)	101.1 (17)	117.9 (21)
F48A	143.5 (28)	158.7 (76)	13.9 (5)	112.9 (17)	157.8 (13)
Y50A	139.2 (77)	108.5 (75)	18.2 (3)	97.9 (58)	142.3 (26)
I72A	26.5 (12)	130.1 (86)	92.8 (9)	64.2 (11)	100.7 (7)
W74A	25.7 (16)	101.0 (67)	79.8 (39)	74.9 (28)	83.7 (25)
N81A	22.0 (13)	153.1 (23)	137.7 (73)	111.6 (20)	5.6 (6)
T103A	138.9 (25)	96.3 (52)	6.3 (4)	77.5 (33)	105.7 (39)
K104A	115.0 (60)	13.6 (1)	-2.0 (5)	83.8 (7)	115.1 (67)
T107A	124.2 (105)	83.8 (17)	0.4 (10)	66.8 (8)	129.2 (9)
R124A	1.0 (4)	149.9 (22)	81.1 (42)	126.0 (48)	115.2 (4)
M185A	91.6 (62)	29.1 (5)	-2.2 (8)	69.3 (3)	74.3 (9)

图1F

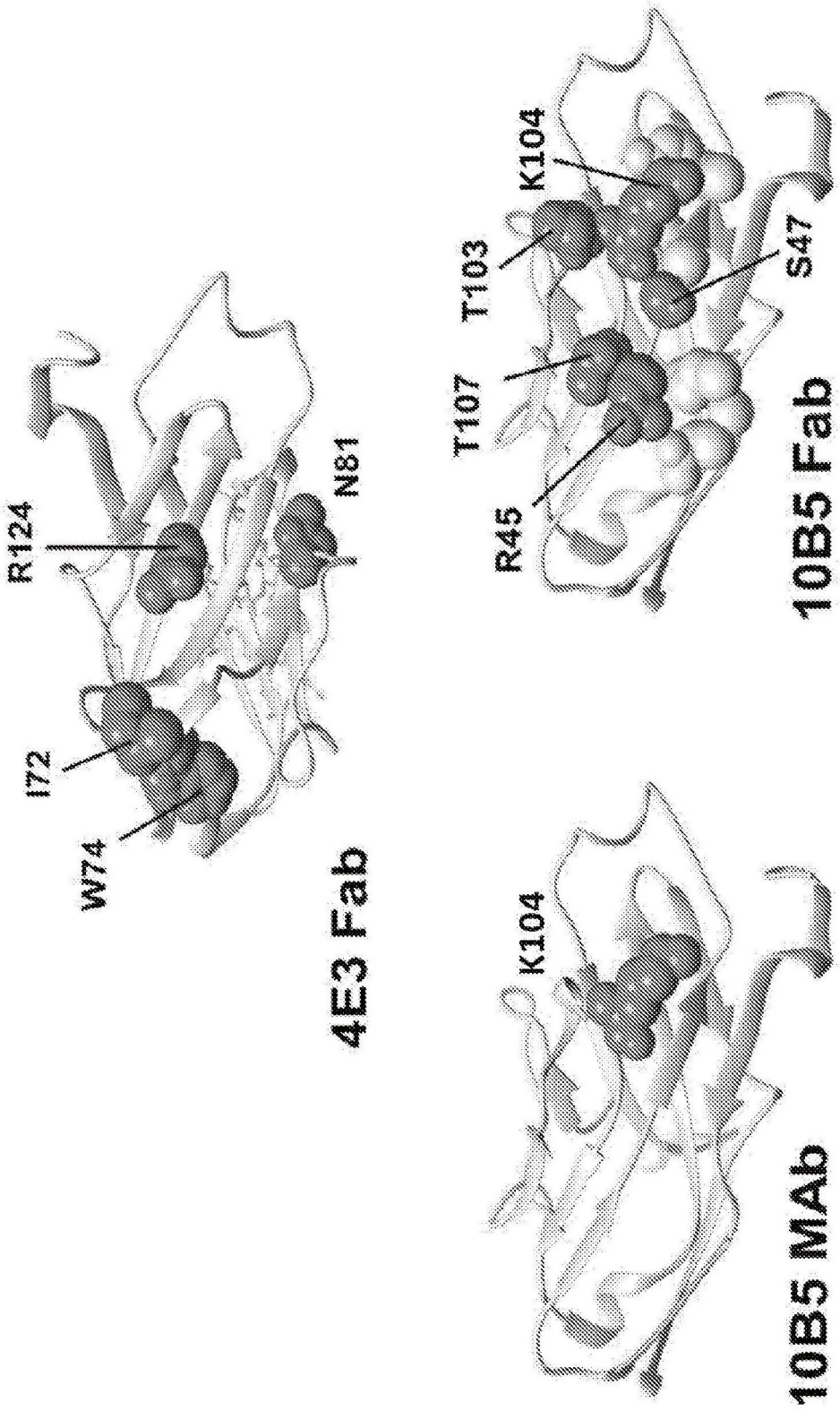

R124
N81
I72
W74
4E3 Fab
K104
T103
S47
T107
R45
10B5 Fab
K104
10B5 MAb

图1G

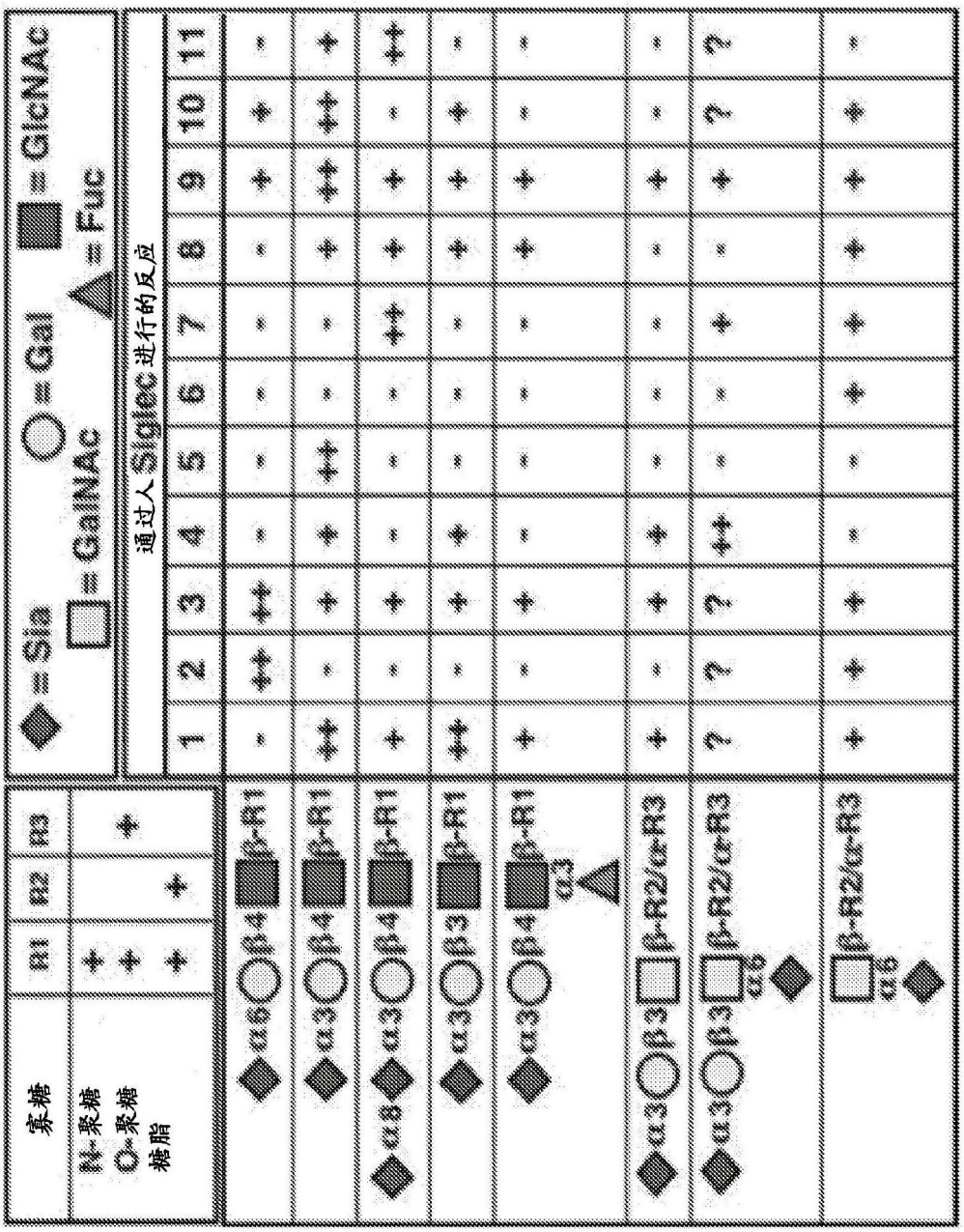

◆ = Sia
○ = Gal
■ = GlcNAc
□ = GalNAc
▲ = Fuc
通过人Siglec进行的反应
1 2 3 4 5 6 7 8 9 10 11
寡糖
N-聚糖
O-聚糖
糖脂
R1 R2 R3
◆α6○β4■β-R1
◆α3○β4■β-R1
◆α8◆α3○β4■β-R1
◆α3○β3■β-R1
◆α3○β4■β-R1 α3▲
◆α3○β3□β-R2/α-R3
◆α3○β3□β-R2/α-R3 α6◆
□α6◆β-R2/α-R3

图2

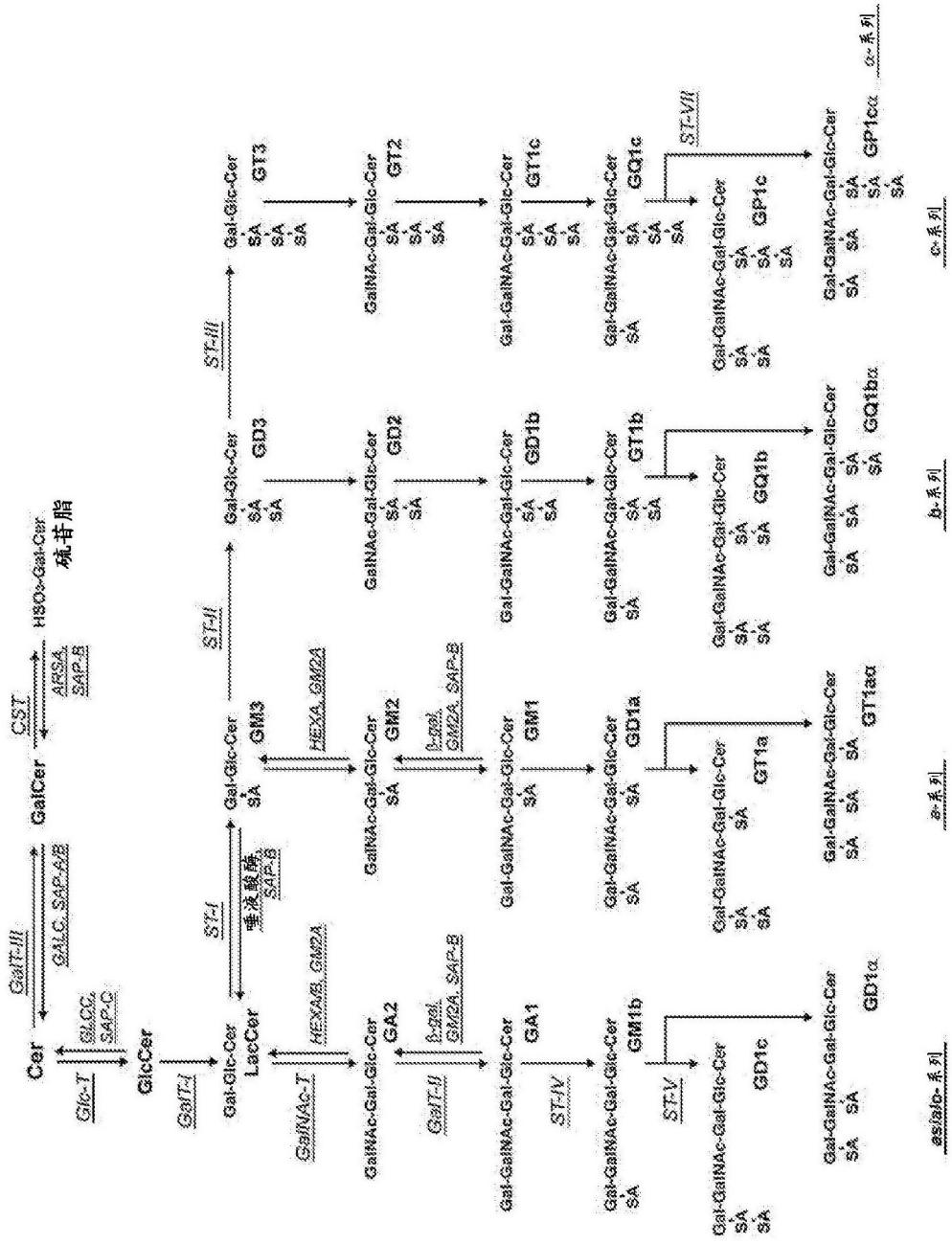

Cer
GalCer
HSO3-Gal-Cer
硫苷脂
GalT-III
GALC, SAP-A/B
CST
ARSA, SAP-B
Glc-T
GALC, SAP-C
GlcCer
GalT-I
Gal-Glc-Cer
LacCer
ST-I
唾液酸酶, SAP-B
ST-II
ST-III
GM3
GD3
GT3
HEXA, GM2A
GalNAc-T
GalNAc-Gal-Glc-Cer
GA2
GM2
GD2
GT2
β-gal, GM2A, SAP-B
GalT-II
Gal-GalNAc-Gal-Glc-Cer
GA1
GM1
GD1b
GT1c
ST-IV
GM1b
GD1a
GT1b
GQ1c
ST-V
GD1c
GT1a
GQ1b
GP1c
ST-VI
GT1aα
GQ1bα
GP1cα
ST-VII
asialo-系列
a-系列
b-系列
c-系列
α-系列

图3

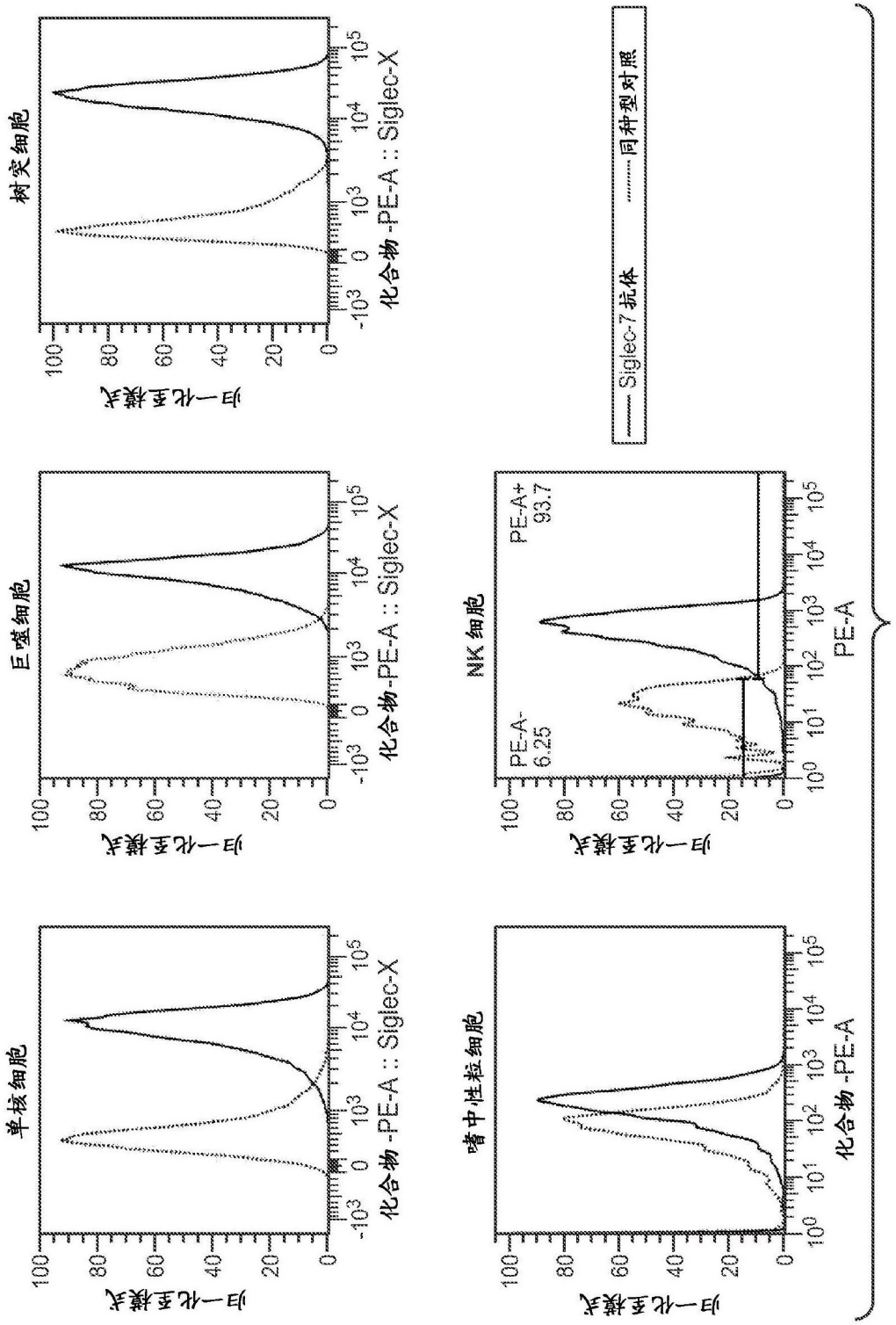

单核细胞
巨噬细胞
树突细胞
嗜中性粒细胞
NK 细胞
归一化至模式
化合物-PE-A :: Siglec-X
化合物-PE-A
PE-A
PE-A-
6.25
PE-A+
93.7
Siglec-7 抗体
同种型对照

图4

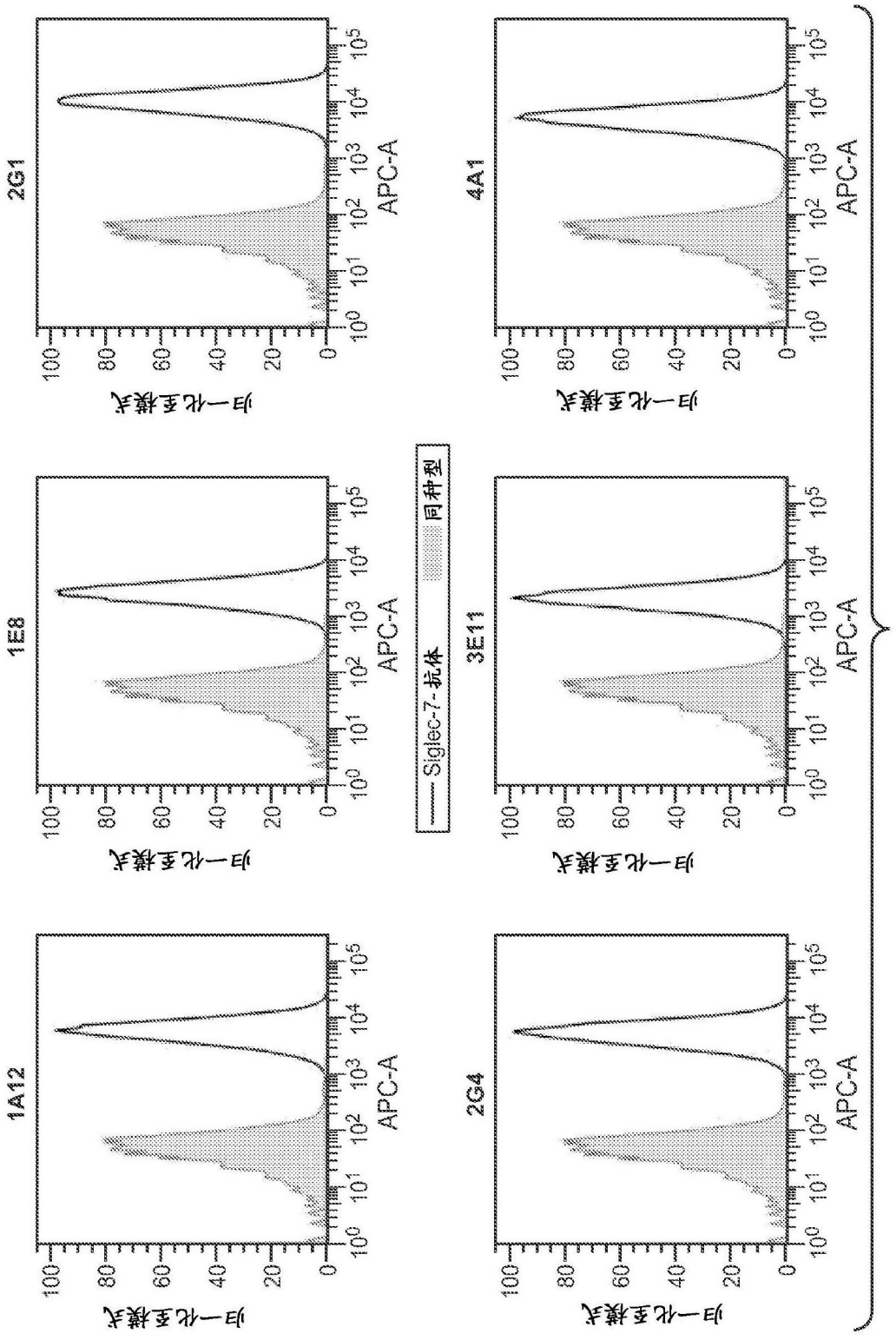


图5A

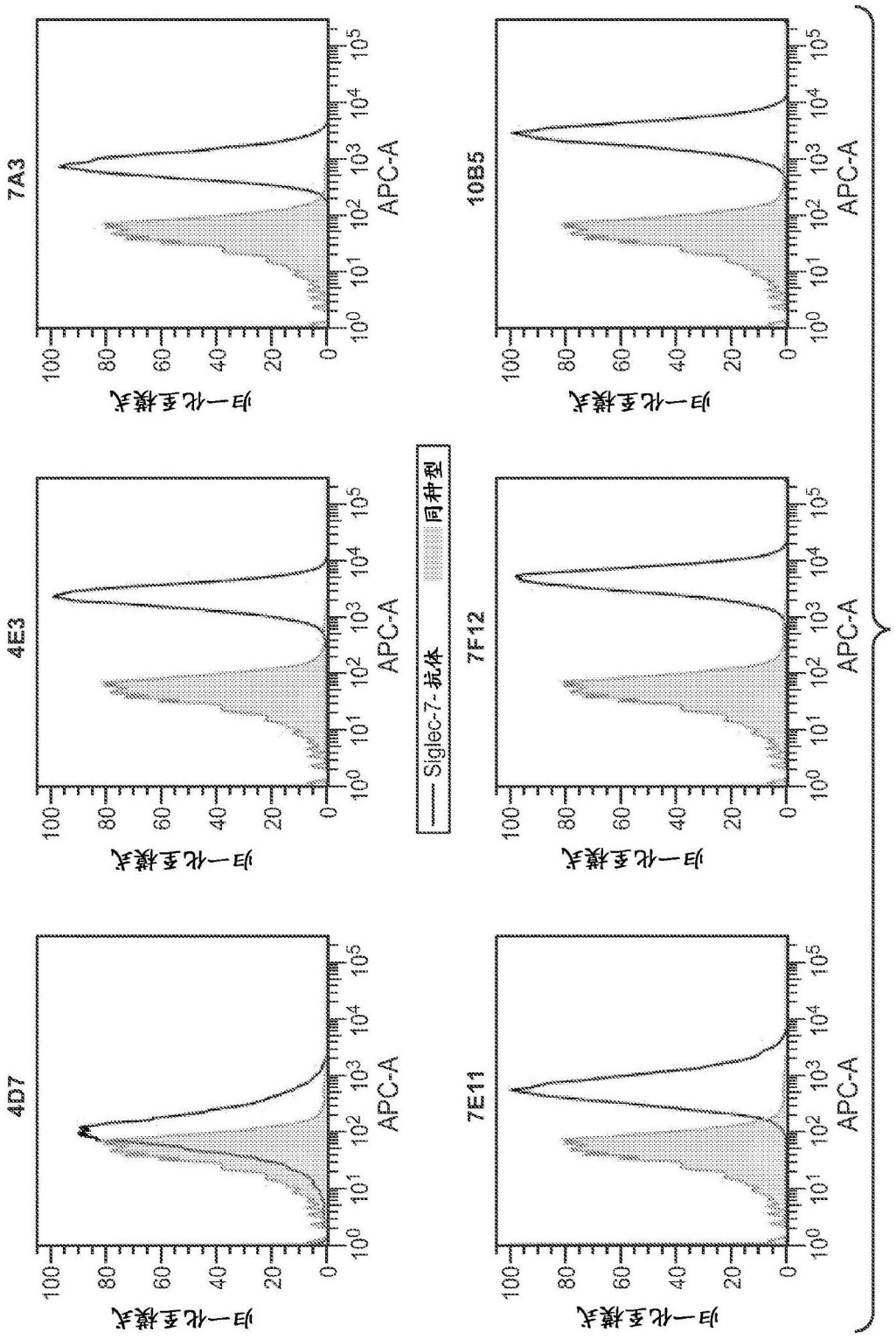


图5A(续)

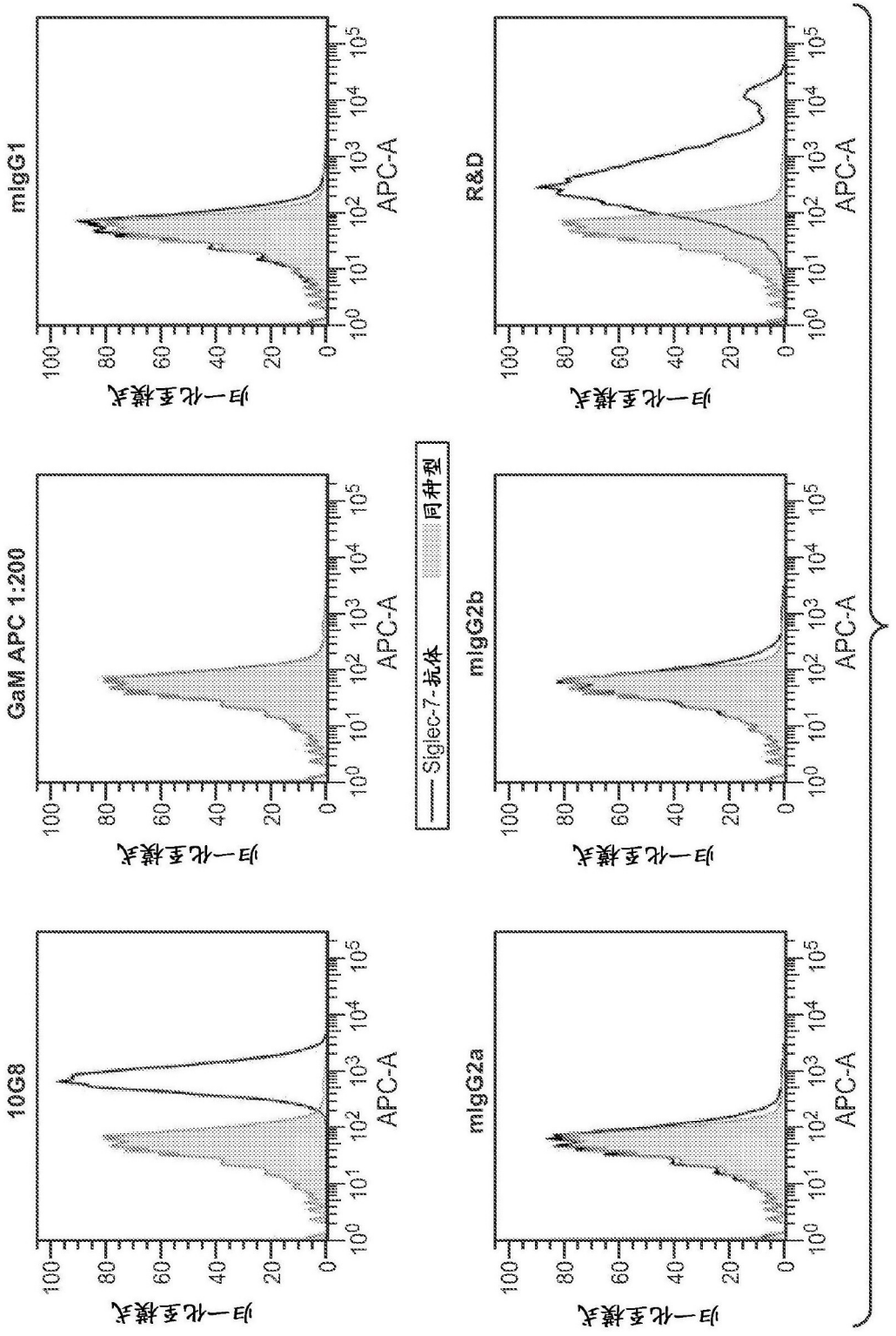

10G8
GaM APC 1:200
mIgG1
mIgG2a
mIgG2b
R&D
Siglec-7-抗体
同种型
归一化至模式
APC-A

图5A(续)

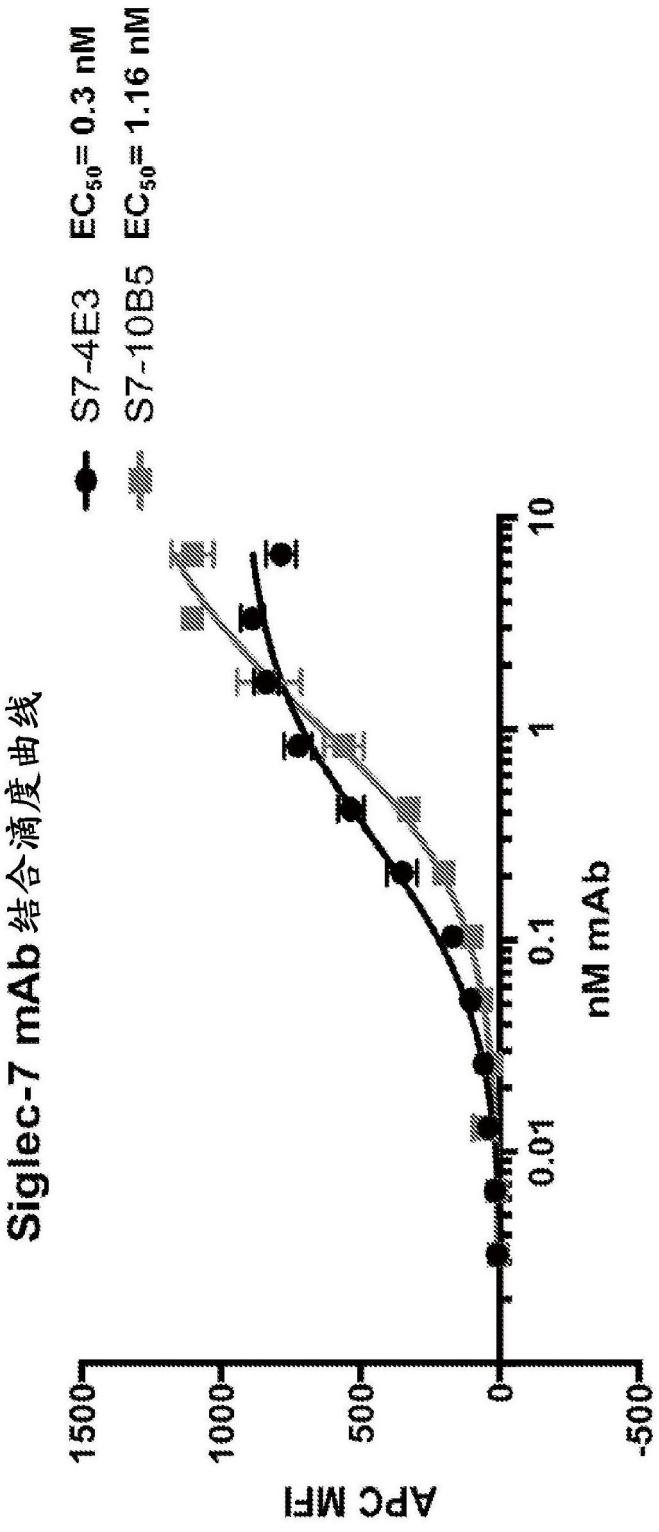

Siglec-7 mAb 结合滴度曲线
S7-4E3 EC50= 0.3 nM
S7-10B5 EC50= 1.16 nM
APC MFI
1500
1000
500
0
-500
0.01
0.1
1
10
nM mAb

图5B

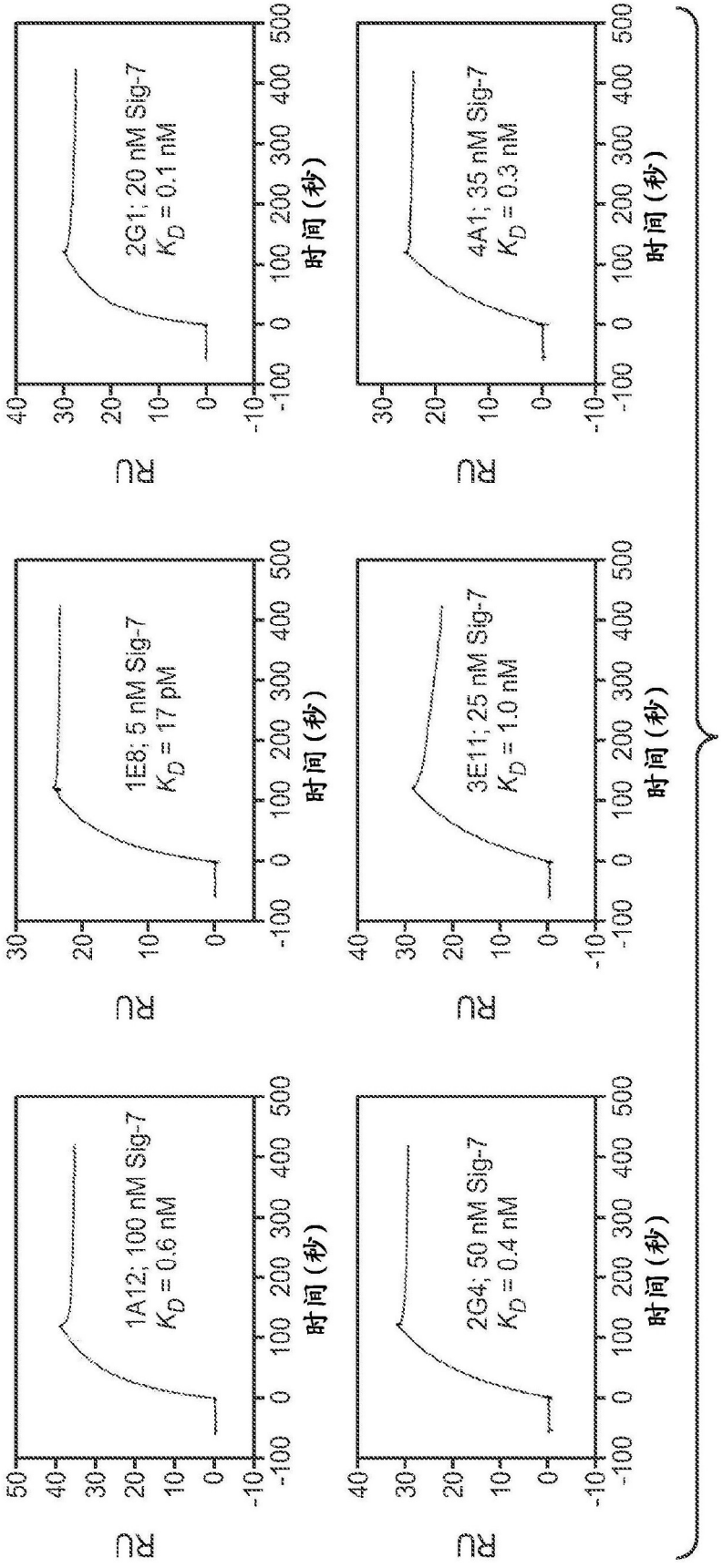

2G1; 20 nM Sig-7
K_D = 0.1 nM
4A1; 35 nM Sig-7
K_D = 0.3 nM
1E8; 5 nM Sig-7
K_D = 17 pM
3E11; 25 nM Sig-7
K_D = 1.0 nM
1A12; 100 nM Sig-7
K_D = 0.6 nM
2G4; 50 nM Sig-7
K_D = 0.4 nM
RU
时间 (秒)

图6A

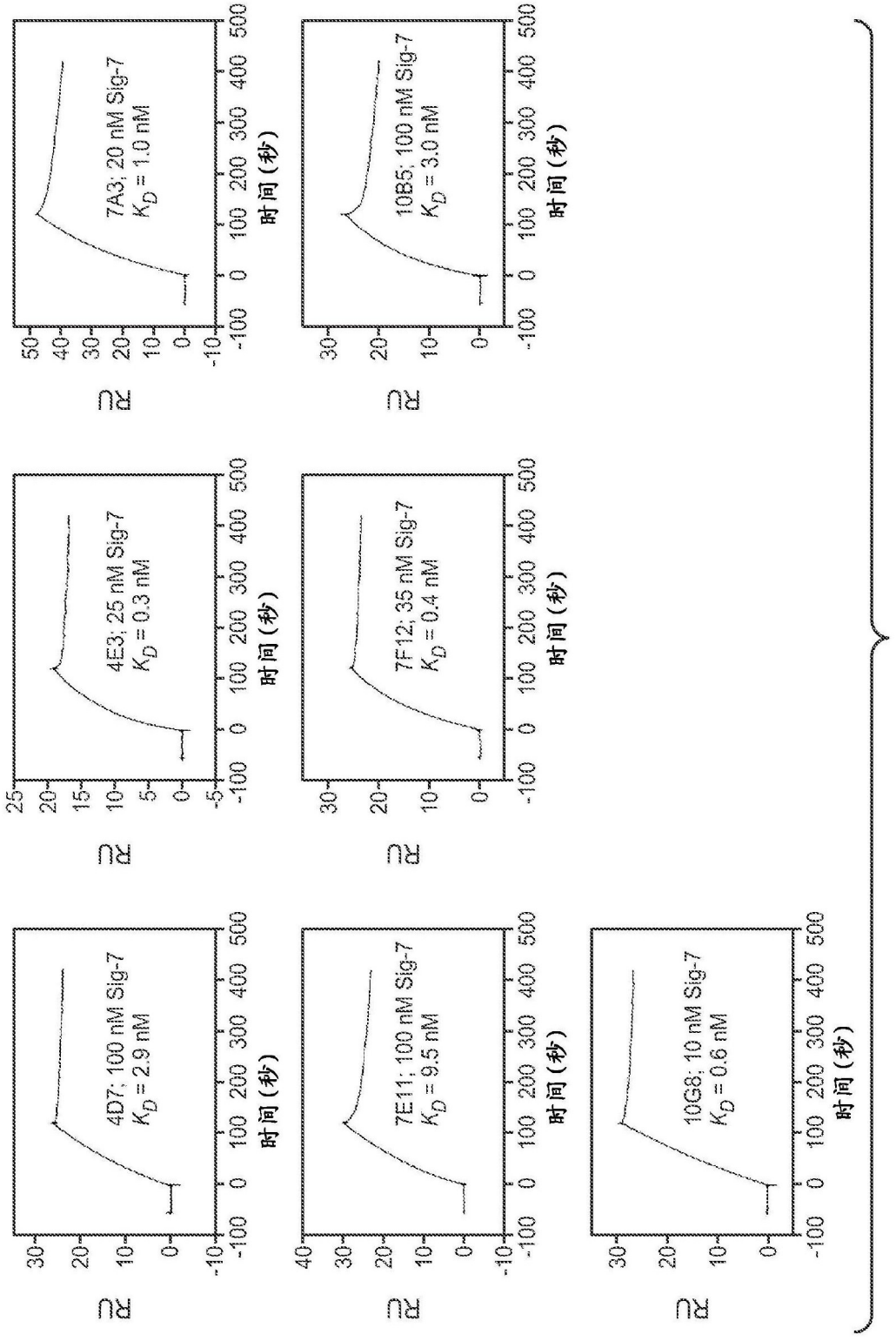

4D7; 100 nM Sig-7
K_D = 2.9 nM
7E11; 100 nM Sig-7
K_D = 9.5 nM
10G8; 10 nM Sig-7
K_D = 0.6 nM
4E3; 25 nM Sig-7
K_D = 0.3 nM
7F12; 35 nM Sig-7
K_D = 0.4 nM
7A3; 20 nM Sig-7
K_D = 1.0 nM
10B5; 100 nM Sig-7
K_D = 3.0 nM
RU
时间 (秒)

图6A(续)

基于 IMGT IGKV3-11*01 受体框架的潜在人源化序列（AbM CDR 定义）

```
IGKV3-11*01 EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRAT
                GIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPP
连接区                IMGT J00242|IGKJ2*01|YTFGQGTKLEIK

seq                10        20        30        40        50
AbM                10        20        30        40        50
                b b b   p p   b b b  b   b  bi bi i   ii ibbi    i
S7-4E3     QIVLTQSPAILSASPGEKVTMTC SAMSSFTYMY WYQQKPGSSPRLLIF DTSNLAS
                *   *   ** **                 **        *
3-11*01    EIVLTQSPATLSLSPGERATLSC RASQSVSSYLAWYQQKPGQAPRLLIY DASNRAT
h4E3-L1    EIVLTQSPATLSLSPGERATLSC SAMSSFTYMY WYQQKPGQAPRLLIV DTSNLAS
h4E3-L2    EIVLTQSPATLSLSPGERVTMSC SAMSSFTYMY WYQQKPGQAPRLLIY DTSNLAS
h4E3-L3    EIVLTQSPATLSLSPGERVTMSC SAMSSFTYMY WYQQKPGQAPRLLIF DTSNLAS
                                  A         #                 S       #

seq                60        70        80        90        100
AbM                60        70        80        90        100
                b   b       b b b  b   ib bib  ibi iib   i   b b b
S7-4E3     GVPIRFSGSGSGTSYSLTISRMEAEDTATYYC QQWSSSPLT FGAGTKLELK
                * *       ***    ** *  * * *            *       *
3-11*01    GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC QQRSNWPP   FGQGTKLEIK
h4E3-L1    GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC QQWSSSPLT FGQGTKLEIK
h4E3-L2    GVPARFSGSGSGTDYTLTISSMEPEDFAVYYC QQWSSSPLT FGQGTKLEIK
h4E3-L3    GVPARFSGSGSGTDYTLTISSMEPEDFAVYYC QQWSSSPLT FGQGTKLELK
                                          T         ^
```

脱酰胺取代：Q/S/A/D

^ 色氨酸氧化取代：H/Y/F

h4E3-L1 是对人框架无改变的 "CDR- 交换"。随后序列改变框架变化以红色示出（相较于其上方的序列）。

图6B

基于 IMGT IGHV3-21*01 受体框架的潜在人源化序列（AbM CDR 定义）

```
IGHV3-21*01 EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIY
                YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARX
连接区                IMGT J00256|IGHJ4*01||YFDYWGQGTLVTVSS

seq                  10        20        30        40        50
AbM                  10        20        30        40        50  a
                   b b b     p     b b b b   b b     b   bi i     i ibb  b
S7-4E3      EVQLVESGGALVKPGGSLKISCAVS GFTFSNYDMS WVRQNPEKRLEWVA TISSGGGYTY
                     *         **    *           * * *    *
3-21*01     EVQLVESGGGLVKPGGSLRLSCAAS GFTFSSYSMN WVRQAPGKGLEWVS SISSSSSYIY
h4E3-H1     EVQLVESGGGLVKPGGSLRLSCAAS GFTFSNYDMS WVRQAPGKGLEWVS TISSGGGYTY
h4E3-H2     EVQLVESGGGLVKPGGSLRLSCAVS GFTFSNYDMS WVRQAPGKGLEWVA TISSGGGYTY
h4E3-H3     EVQLVESGGGLVKPGGSLRISCAVS GFTFSNYDMS WVRQAPGKGLEWVA TISSGGGYTY
                                      #

seq         60        70        80        90        100       110       120
AbM         60        70        80  abc       90                      110
              i  b    b b b x    b b b  b     bibibb                i   b b b
S7-4E3      YPDSVKGRFTISRDNAKNALYLQMSSLRSEDTALYYCTR HGYGNYDWYFDV WGAGATVTVSS
              *         *         *    *    *    *                     * *
3-21*01     YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR                WGQGTLVTVSS
h4E3-H1     YADSVKGRFTISRDNAFNSLYLQMNSLRAEDTAVYYCAR HGYGNYDWYFDV WGQGTLVTVSS
h4E3-H2     YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCTR HGYGNYDWYFDV WGQGTLVTVSS
h4E3-H3     YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCTR HGYGNYDWYFDV WGQG&LVTVSS
              P                                     L          #  ^

#  脱酰胺取代：Q/S/A/D
^  色氨酸氧化取代：H/Y/F
```

h4E3-H1是对人框架无改变的"CDR-交换"。随后序列改变框架变化以红色示出（相较于其上方的序列）。

图6C

基于IMGT IGKV1-39*01受体框架的潜在人源化序列(AbM CDR定义)

```
IGKV1-39*01 DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS
                GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPP
连接区                IMGT J00242|IGKJ2*01|YTFGQGTKLEIK

seq                10        20        30        40        50
AbM                10        20        30        40        50
                b b b   p p   b b b   b   b  bi bi i   ii ibbi     i
S7-10B5.1 DVQMTQTTSSLSASLGDRVTISC RASQDIMTYLN WYQQKPDGTVKLLIY YTSRLHS
                 *   **    *                  ****
1-39*01   DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQQKPGKAPKLLIY AASSLQS
h10B5-L1  DIQMTQSPSSLSASVGDRVTITC RASQDIMTYLN WYQQKPGKAPKLLIY YTSRLHS
h10B5-L2  DIQMTQSPSSLSASVGDRVTITC RASQDIMTYLN WYQQKPGKAPKLLIY YTSRLHS
h10B5-L3  DVQMTQSPSSLSASVGDRVTITC RASQDIMTYLN WYQQKPGKAPKLLIY YTSRLHS
                                      #                  TW

seq                60        70        80        90        100
AbM                60        70        80        90        100
                 b   b       b b b   b    ib bib  ibi iib  i   b b b
S7-10B5.1 GVPSRFSGSGSGTDYSLTISNLEQEDIATYFC QQGNTLPWT FGGGTKLEIK
                        **    * **  *  *          *
1-39*01   GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYSTPP  FGQGTKLEIK
h10B5-L1  GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGNTLPWT FGQGTKLEIK
h10B5-L2  GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QQGNTLPWT FGQGTKLEIK
h10B5-L3  GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QQGNTLPWT FGQGTKLEIK
                                    I   F     #

#  脱酰胺取代：  Q/S/A/D
```

h10B5-L1是对人框架无改变的"CDR-交换"。 随后序列改变框架变化以红色示出(相较于其上方的序列)。

图6D

基于 IGHV1-46*01 受体框架的潜在人源化序列 (AbM CDR 定义)

```
IGHV1-46*01  QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTS
                 YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
连接区                IMGT J00256|IGHJ4*01|YFDYWGQGTLVTVSS

seq                10        20        30        40        50
AbM                10        20        30        40        50  a
                b b b     p     b b b b   b b     b   bi i     i ibb  b
S7-10B5.1  QVHLQQSGPELVKPGASVKISCKAS GYAFTNCWMN WVRQRPGKGLDWIG RIFPGNGHTN
                * *   * **      *                 *   *   * *
1-46*01    QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYYMH WVRQAPGQGLEWMG IINPSGGSTS
h10B5-H1   QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNCWMN WVRQAPGQGLEWMG RIFPGNGHTN
h10B5-H2   QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNCWMN WVRQAPGQGLEWIG RIFPGNGHTN
h10B5-H3   QVQLVQSGAEVKKPGASVKISCKAS GYAFTNCWMN WVRQAPGQGLEWIG RIFPGNGHTN
h10B5-H4   QVQLVQSGAEVKKPGASVKISCKAS GYAFTNCWMN WVRQAPGQGLEWIG RIFPGNGHTN
                          V                  #x^                @   #
seq        60        70        80        90        100       110
AbM        60        70        80  abc   90                  110
              i  b   b b b x     b b b  b     bibibb          i   b b b
S7-10B5.1  YSGKFKDKATLTEDKSSSTAYMQLSSLTSEDSAVYFCAR DYSDYYFDY WGQGTTLTVSS
              **  **** * * * *  *  *   *   *   *                 **
1-46*01    YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR             WGQGTLVTVSS
h10B5-H1   YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR DYSDYYFDY WGQGTLVTVSS
h10B5-H2   YAQKFQGRVTMTEDTSTSTVYMELSSLRSEDTAVYYCAR DYSDYYFDY WGQGTLVTVSS
h10B5-H3   YAQKFQGRATLTEDTSTSTAYMELSSLRSEDTAVYYCAR DYSDYYFDY WGQGTLLTVSS
h10B5-H4   YAQKFQGRATLTEDKSTSTAYMELSSLRSEDTAVYYCAR DYSDYYFDY WGQGTLLTVSS
              S                                      F
# 脱酰胺取代：Q/S/A
@ 异天冬氨酸取代：Q/S/A
^ 色氨酸氧化取代：H/Y/F
```

h10B5-H1是对人框架无改变的"CDR-交换"。随后序列改变框架变化以红色示出（相较于其上方的序列）。

图6E

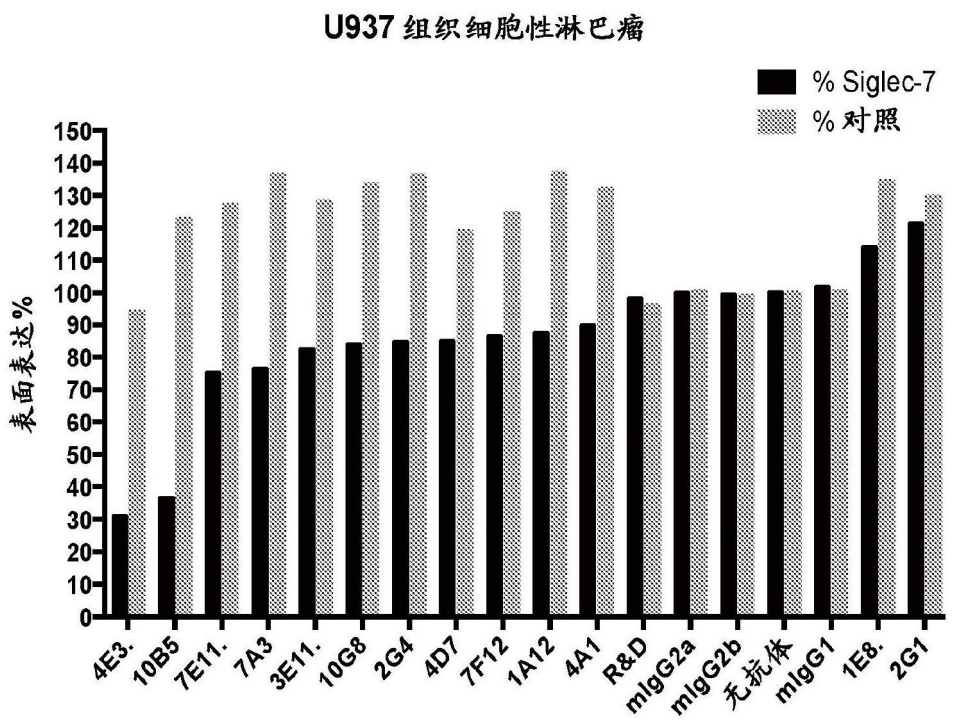

U937 组织细胞性淋巴瘤
% Siglec-7
% 对照
表面表达%
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
4E3.
10B5
7E11.
7A3
3E11.
10G8
2G4
4D7
7F12
1A12
4A1
R&D
mIgG2a
mIgG2b
无抗体
mIgG1
1E8.
2G1

图7A

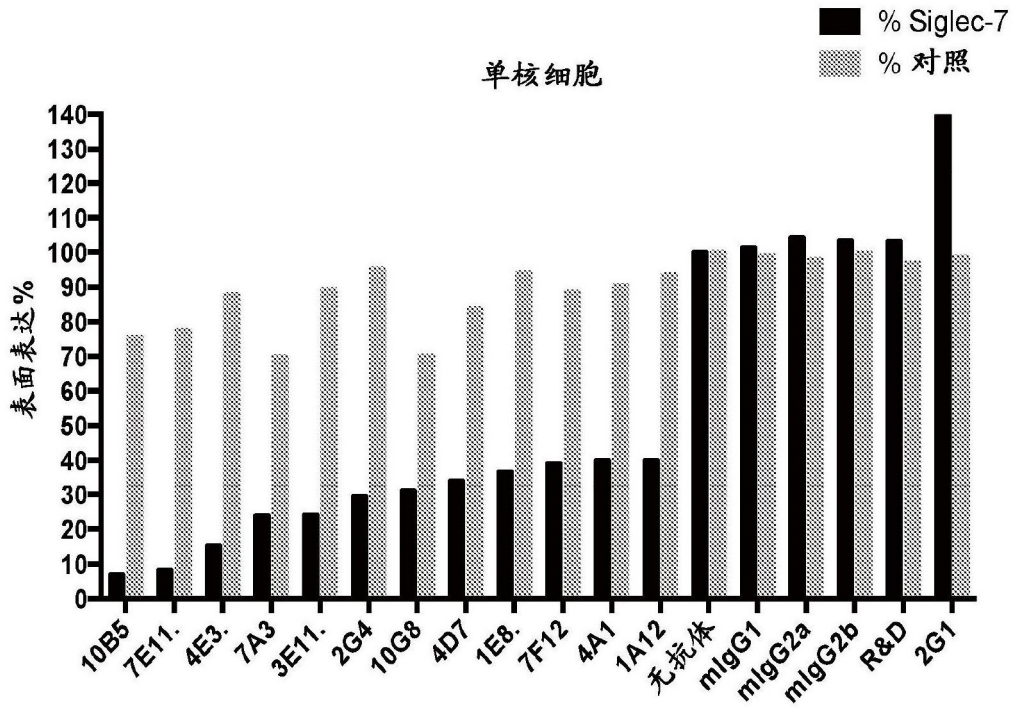

% Siglec-7
% 对照
单核细胞
表面表达%
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
10B5
7E11.
4E3.
7A3
3E11.
2G4
10G8
4D7
1E8.
7F12
4A1
1A12
无抗体
mIgG1
mIgG2a
mIgG2b
R&D
2G1

图7B

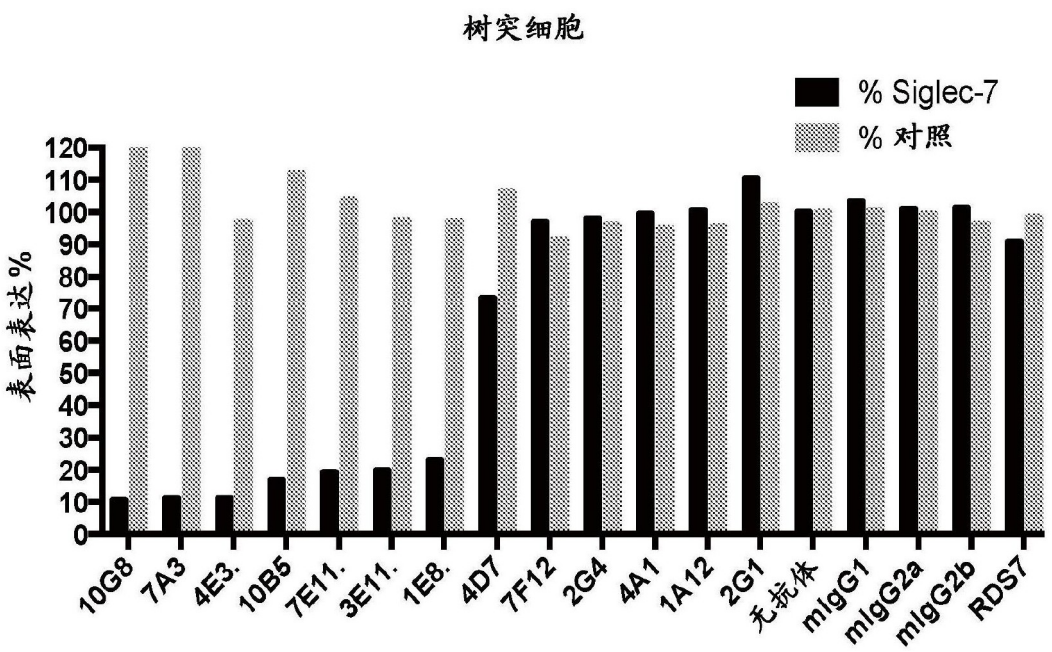

树突细胞
% Siglec-7
% 对照
表面表达%
120
110
100
90
80
70
60
50
40
30
20
10
0
10G8
7A3
4E3.
10B5
7E11.
3E11.
1E8.
4D7
7F12
2G4
4A1
1A12
2G1
无抗体
mIgG1
mIgG2a
mIgG2b
RDS7

图7C

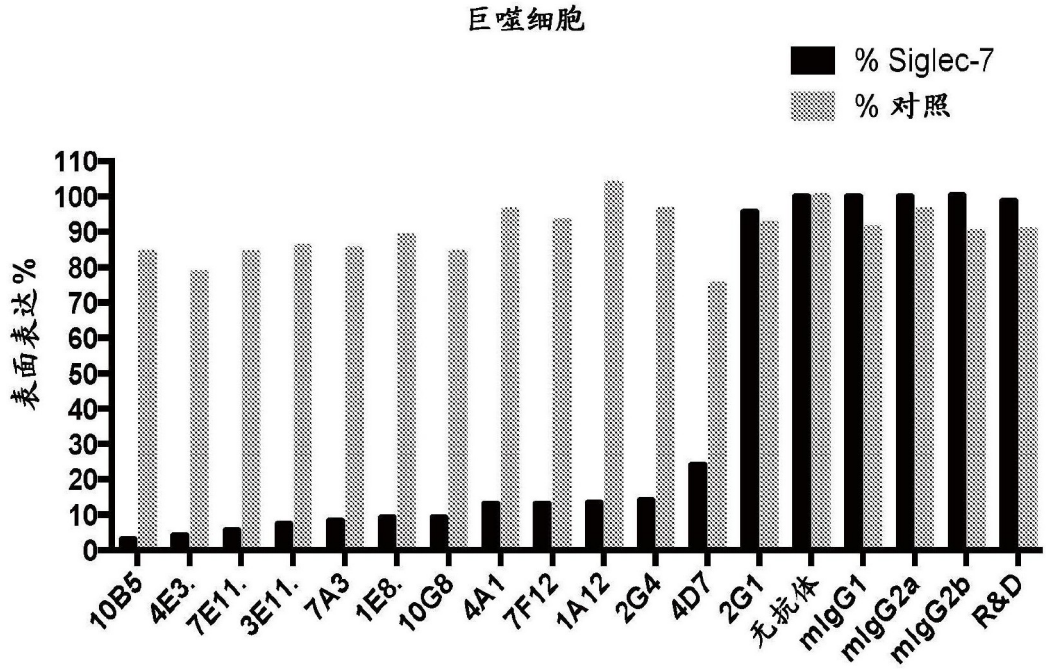

巨噬细胞
% Siglec-7
% 对照
表面表达%
110
100
90
80
70
60
50
40
30
20
10
0
10B5
4E3.
7E11.
3E11.
7A3
1E8.
10G8
4A1
7F12
1A12
2G4
4D7
2G1
无抗体
mIgG1
mIgG2a
mIgG2b
R&D

图7D

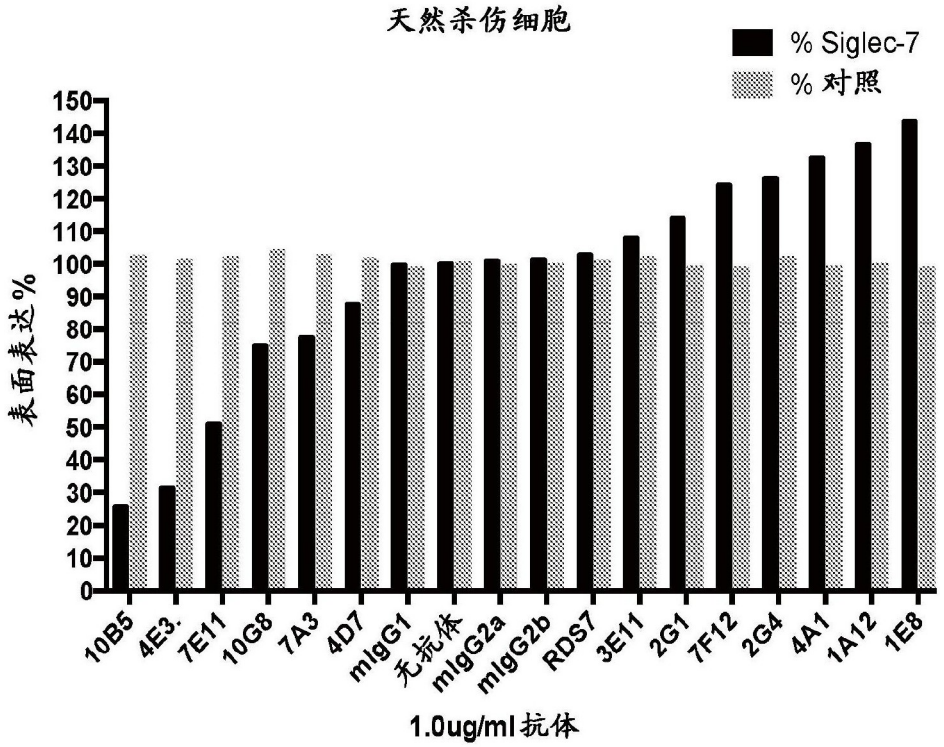

天然杀伤细胞
% Siglec-7
% 对照
表面表达%
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
10B5
4E3.
7E11
10G8
7A3
4D7
mIgG1
无抗体
mIgG2a
mIgG2b
RDS7
3E11
2G1
7F12
2G4
4A1
1A12
1E8
1.0ug/ml抗体

图7E

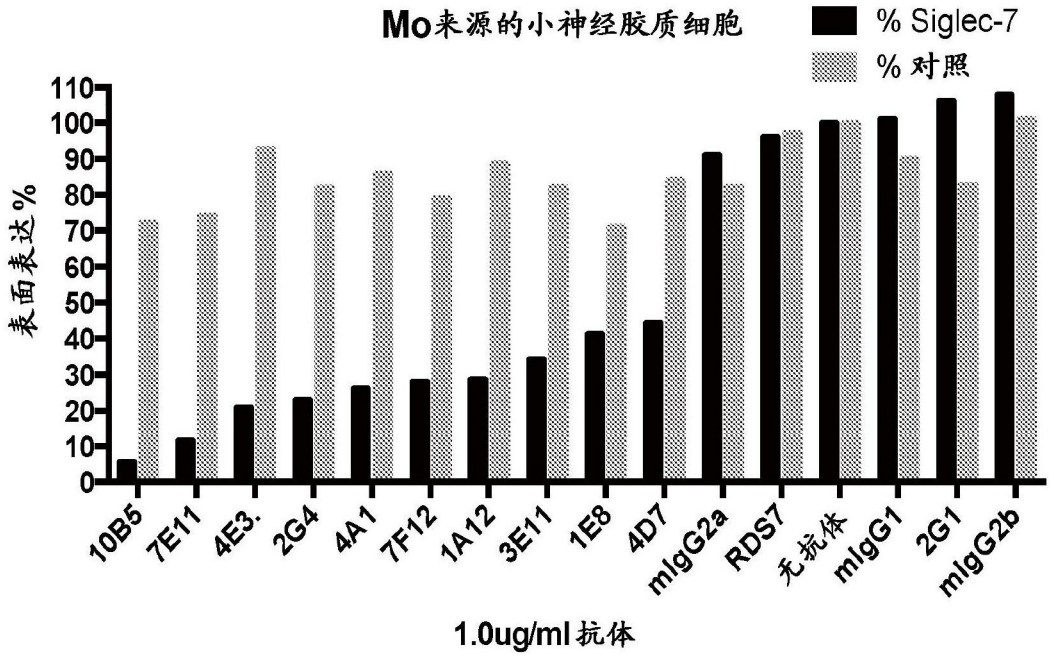

Mo来源的小神经胶质细胞
% Siglec-7
% 对照
表面表达%
110
100
90
80
70
60
50
40
30
20
10
0
10B5
7E11
4E3.
2G4
4A1
7F12
1A12
3E11
1E8
4D7
mIgG2a
RDS7
无抗体
mIgG1
2G1
mIgG2b
1.0ug/ml抗体

图7F

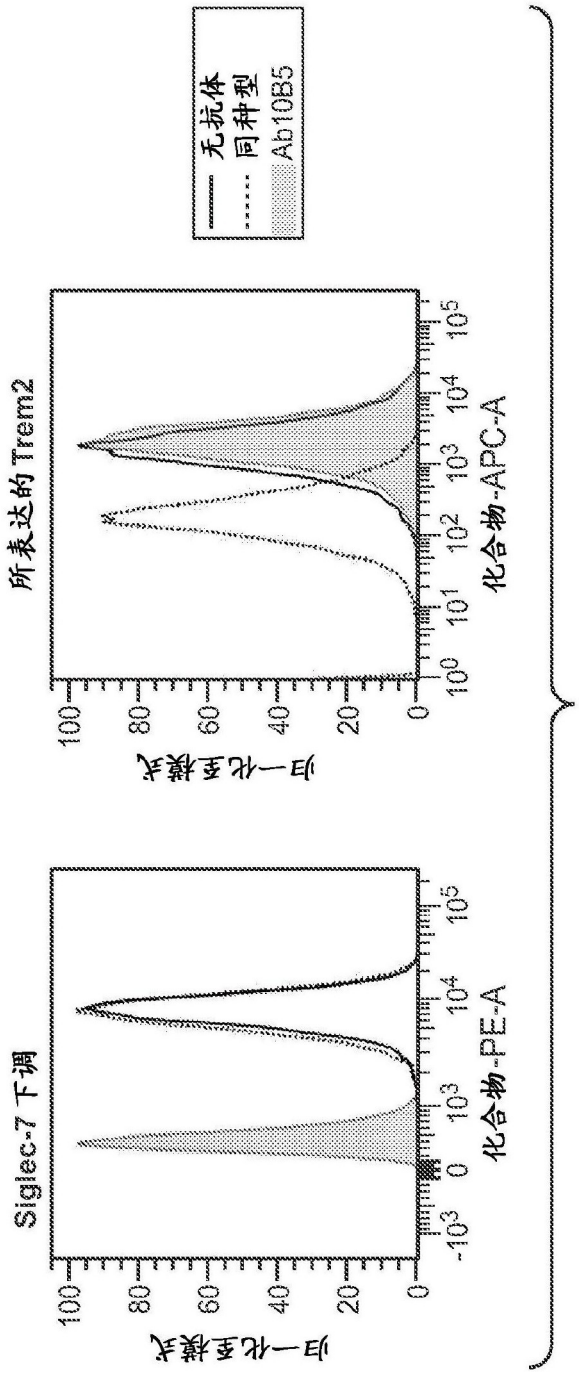

无抗体
同种型
Ab10B5
所表达的Trem2
归一化至模式
化合物-APC-A
Siglec-7下调
归一化至模式
化合物-PE-A

图7G

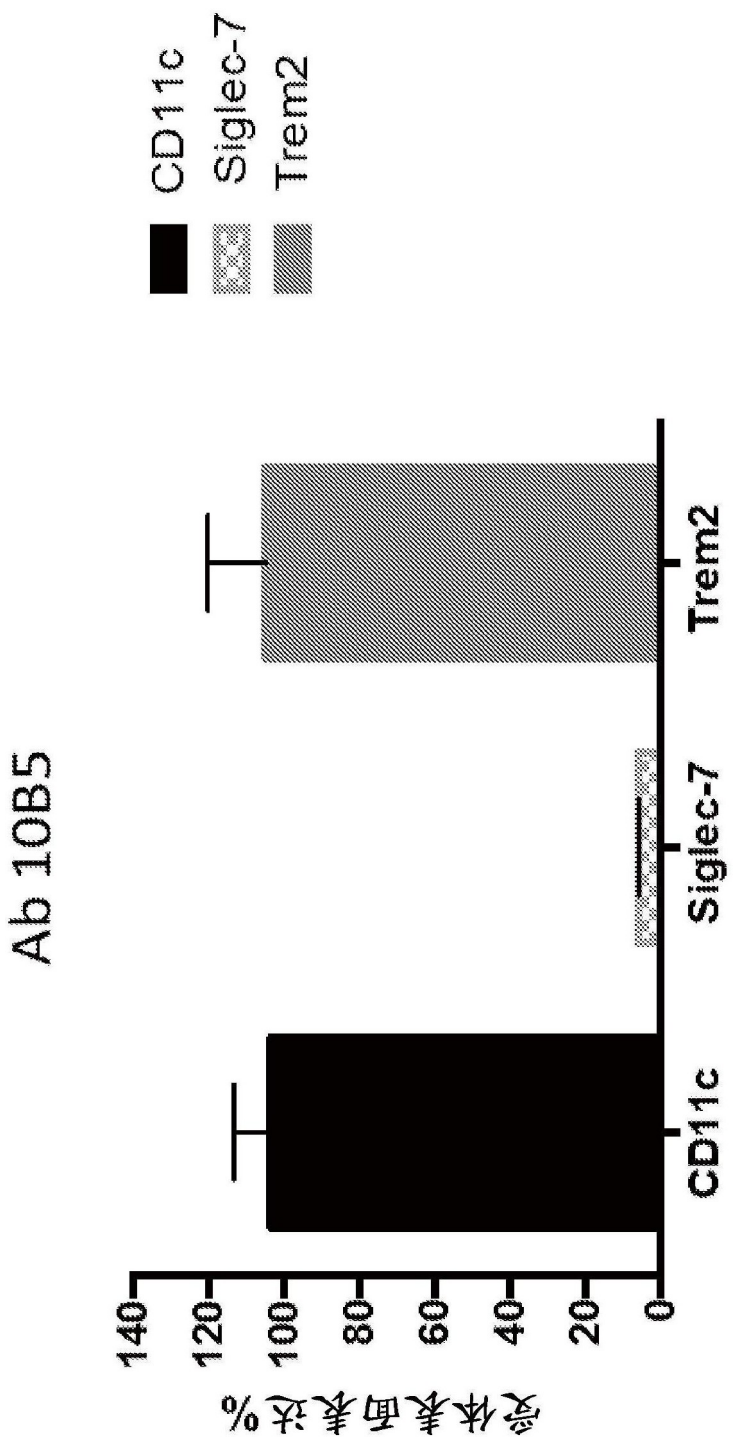

CD11c
Siglec-7
Trem2
Ab 10B5
140
120
100
80
60
40
20
0
受体表面表达%
CD11c
Siglec-7
Trem2

图7H

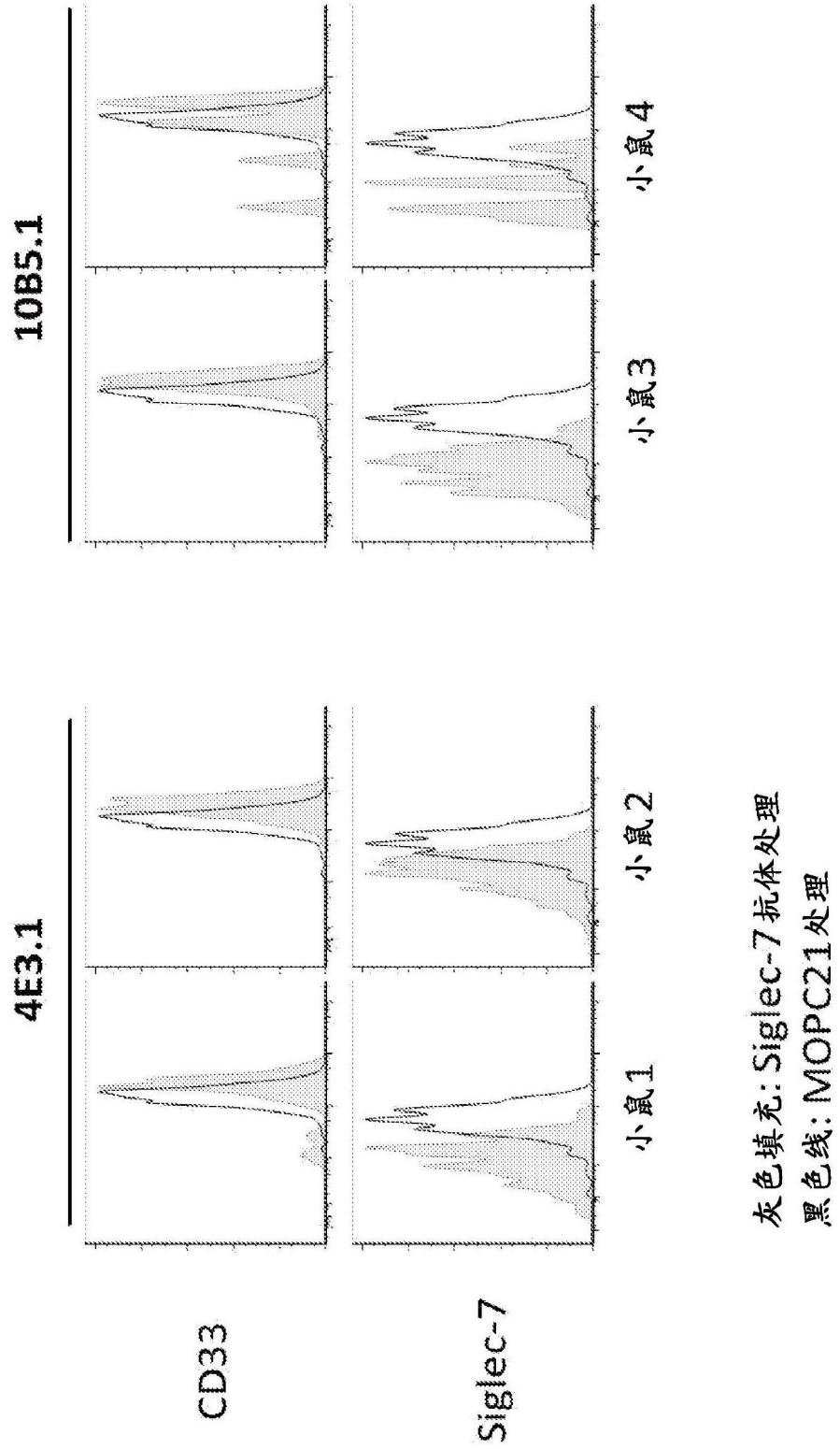

4E3.1
10B5.1
CD33
Siglec-7
小鼠1
小鼠2
小鼠3
小鼠4
灰色填充: Siglec-7抗体处理
黑色线: MOPC21处理

图7I

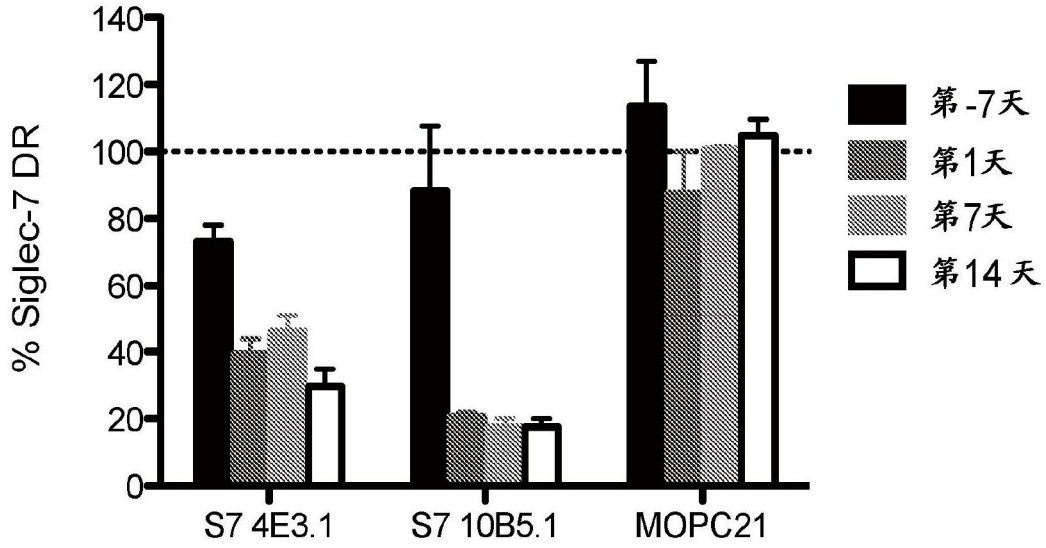

140
120
100
80
60
40
20
0
% Siglec-7 DR
S7 4E3.1
S7 10B5.1
MOPC21
第-7天
第1天
第7天
第14天

图7J

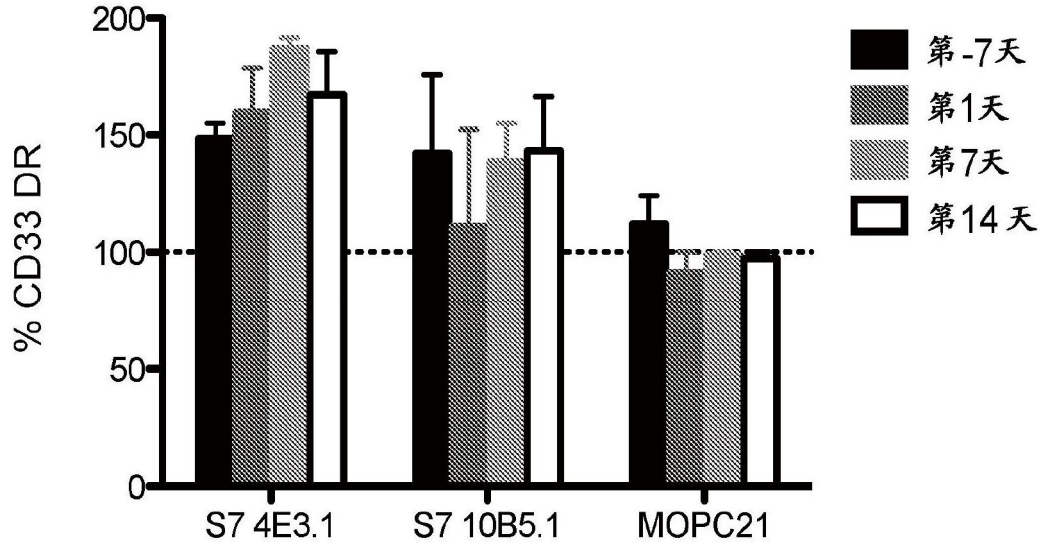

200
150
100
50
0
% CD33 DR
S7 4E3.1
S7 10B5.1
MOPC21
第-7天
第1天
第7天
第14天

图7K

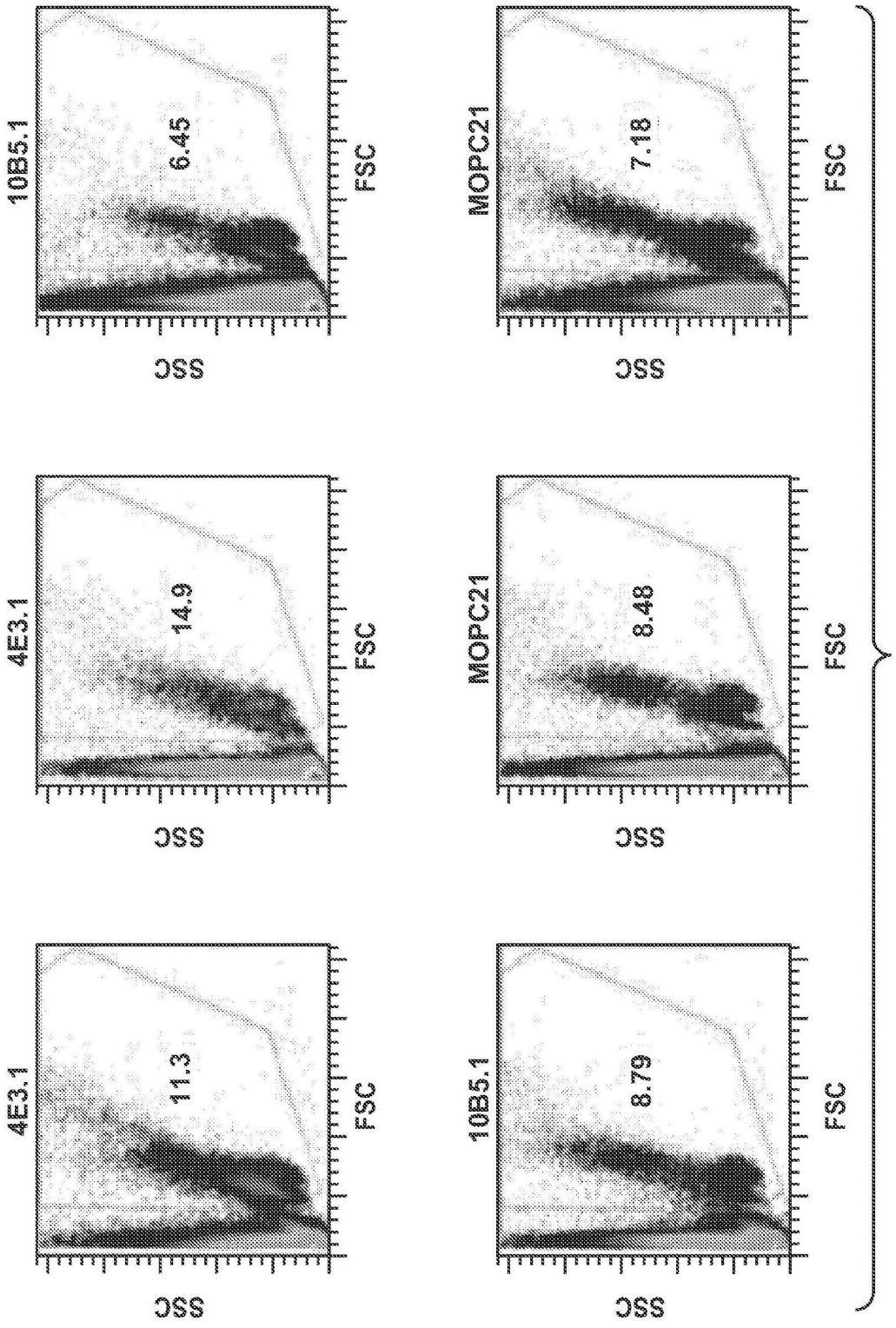

10B5.1
6.45
FSC
SSC
MOPC21
7.18
FSC
SSC
4E3.1
14.9
FSC
SSC
MOPC21
8.48
FSC
SSC
4E3.1
11.3
FSC
SSC
10B5.1
8.79
FSC
SSC

图7L

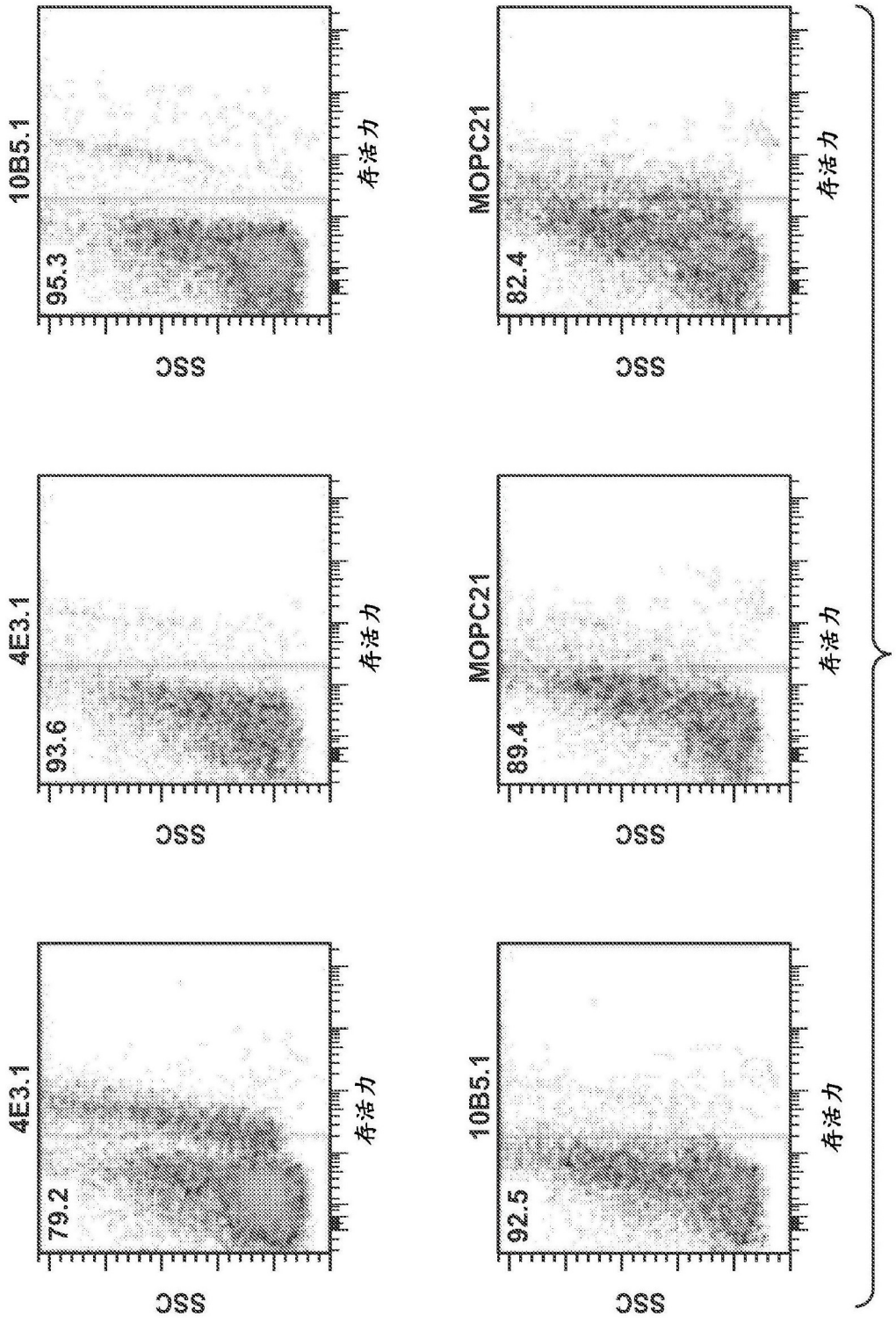

10B5.1
95.3
SSC
存活力
MOPC21
82.4
SSC
存活力
4E3.1
93.6
SSC
存活力
MOPC21
89.4
SSC
存活力
4E3.1
79.2
SSC
存活力
10B5.1
92.5
SSC
存活力

图7L(续)

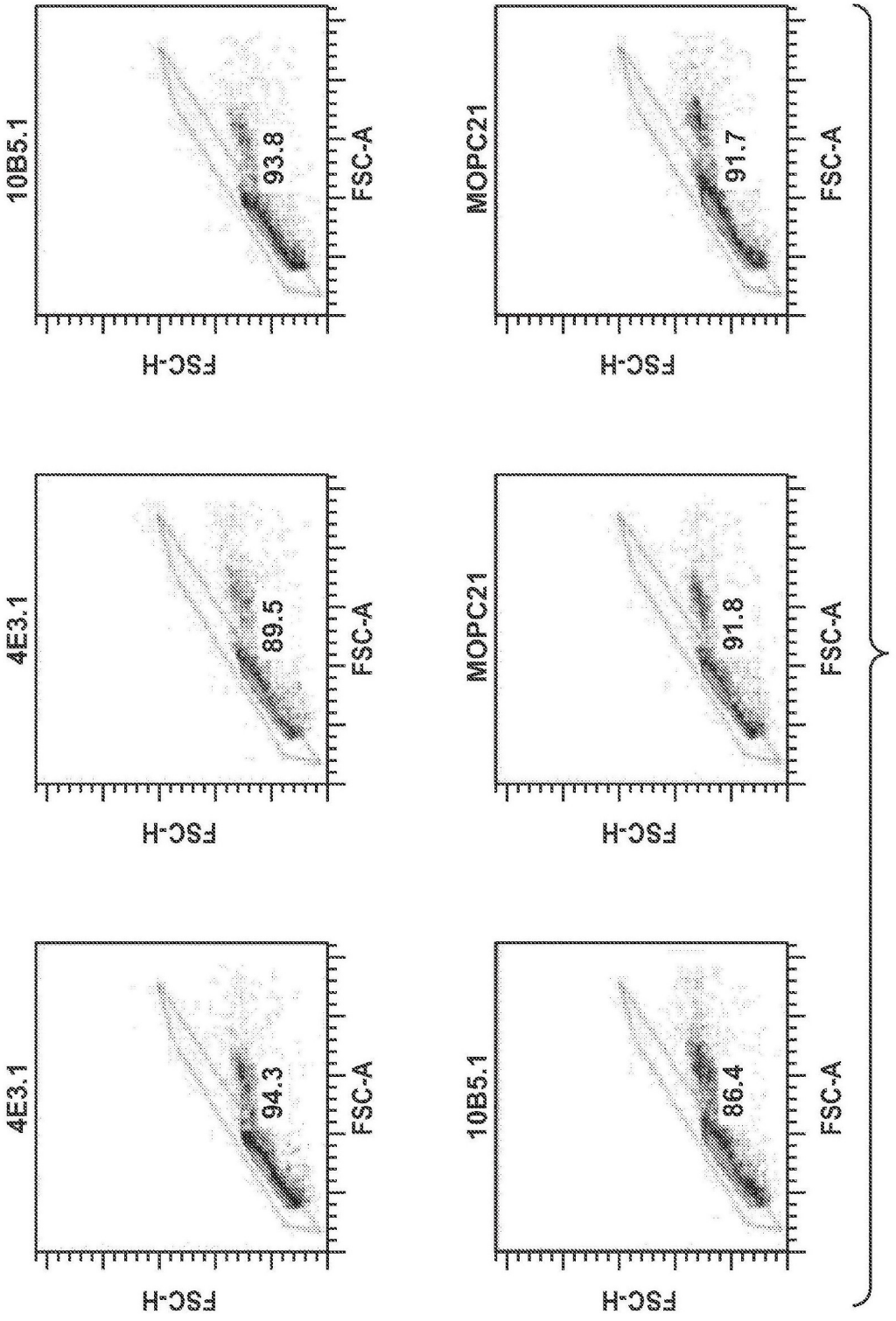

10B5.1
93.8
FSC-A
FSC-H
MOPC21
91.7
FSC-A
FSC-H
4E3.1
89.5
FSC-A
FSC-H
MOPC21
91.8
FSC-A
FSC-H
4E3.1
94.3
FSC-A
FSC-H
10B5.1
86.4
FSC-A
FSC-H

图7L(续)

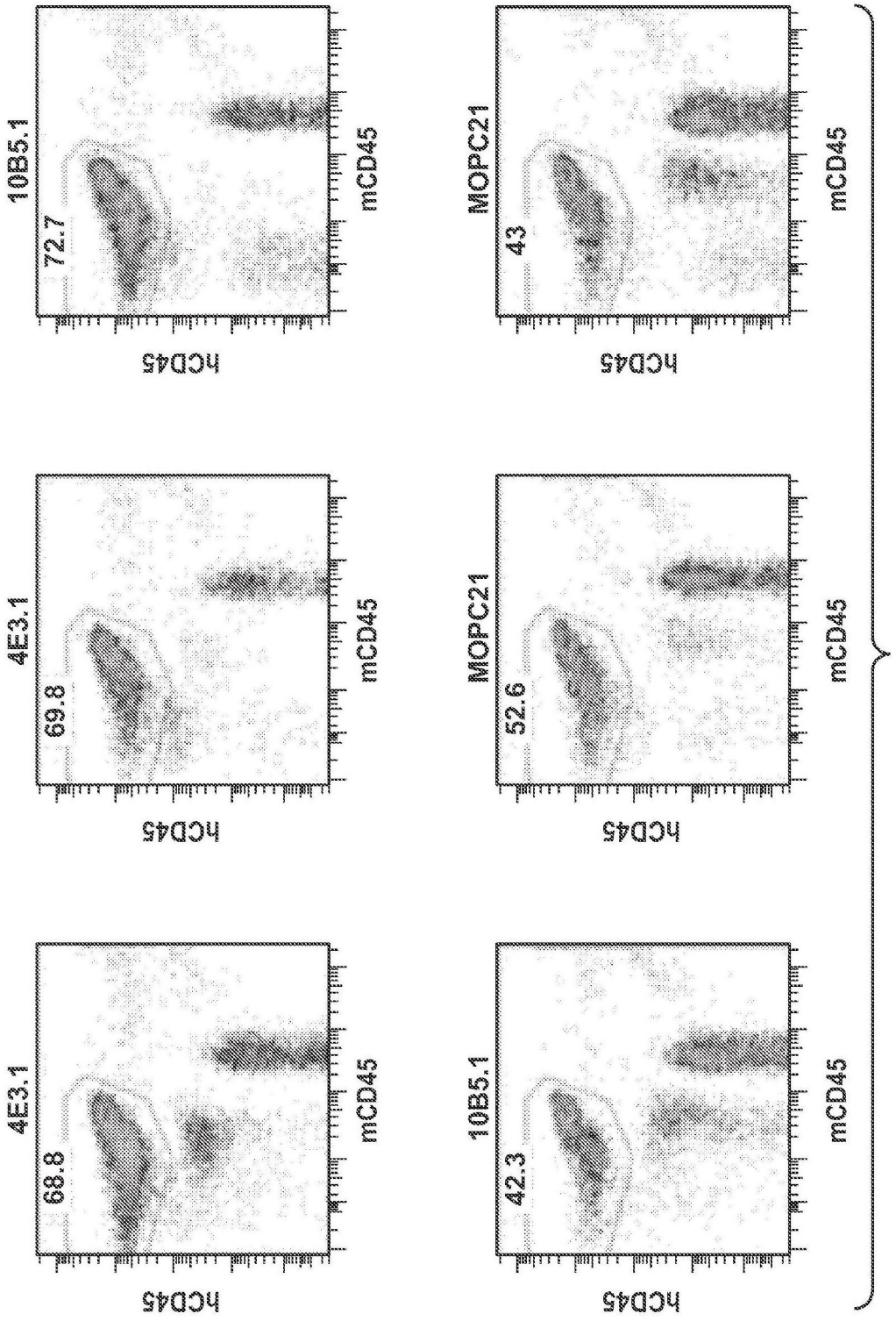

10B5.1
72.7
hCD45
mCD45
MOPC21
43
hCD45
mCD45
4E3.1
69.8
hCD45
mCD45
MOPC21
52.6
hCD45
mCD45
4E3.1
68.8
hCD45
mCD45
10B5.1
42.3
hCD45
mCD45

图7L(续)

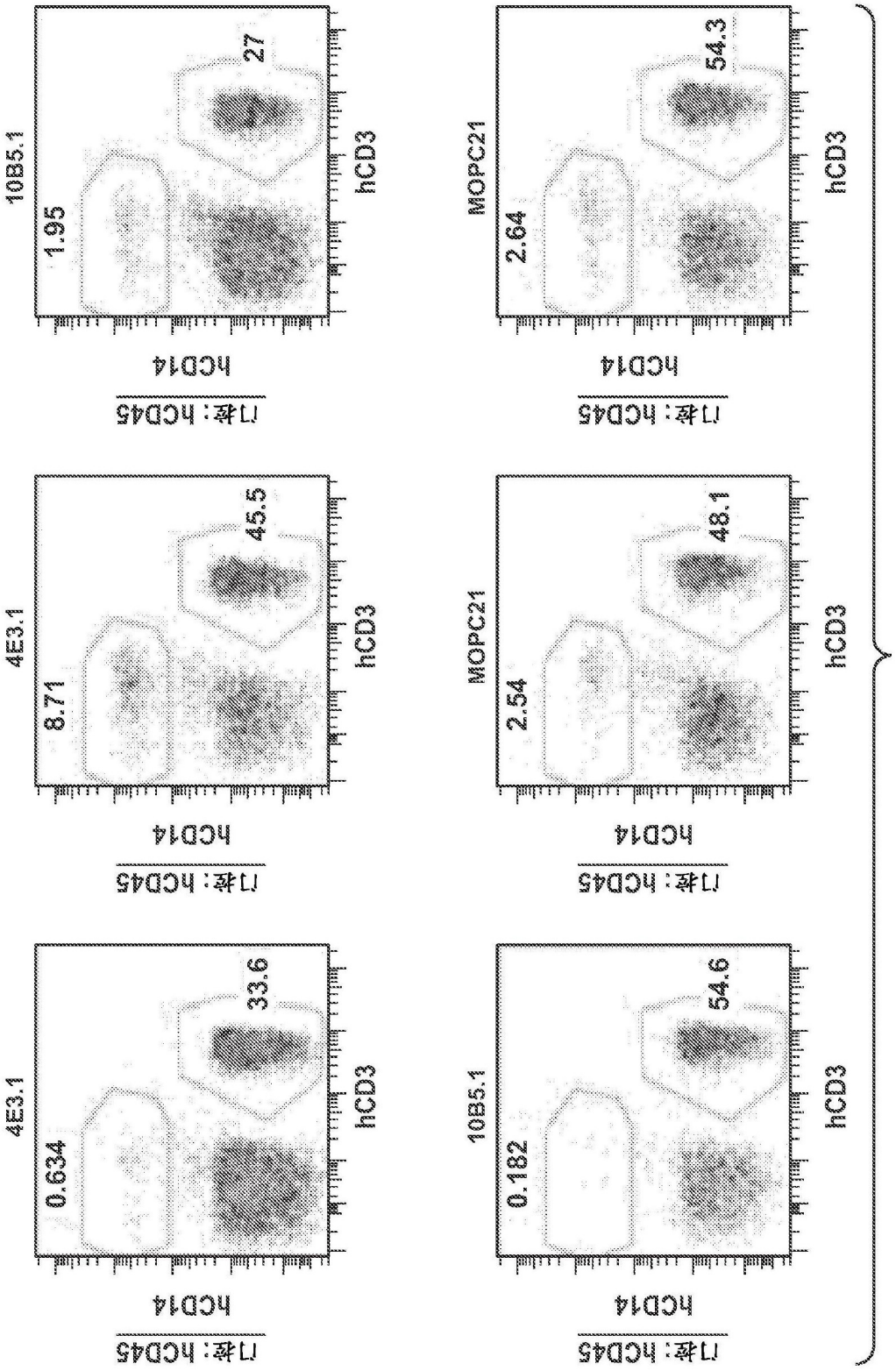

10B5.1
1.95
27
hCD3
hCD14
门控: hCD45
MOPC21
2.64
54.3
hCD3
hCD14
门控: hCD45
4E3.1
8.71
45.5
hCD3
hCD14
门控: hCD45
MOPC21
2.54
48.1
hCD3
hCD14
门控: hCD45
4E3.1
0.634
33.6
hCD3
hCD14
门控: hCD45
10B5.1
0.182
54.6
hCD3
hCD14
门控: hCD45

图7L(续)

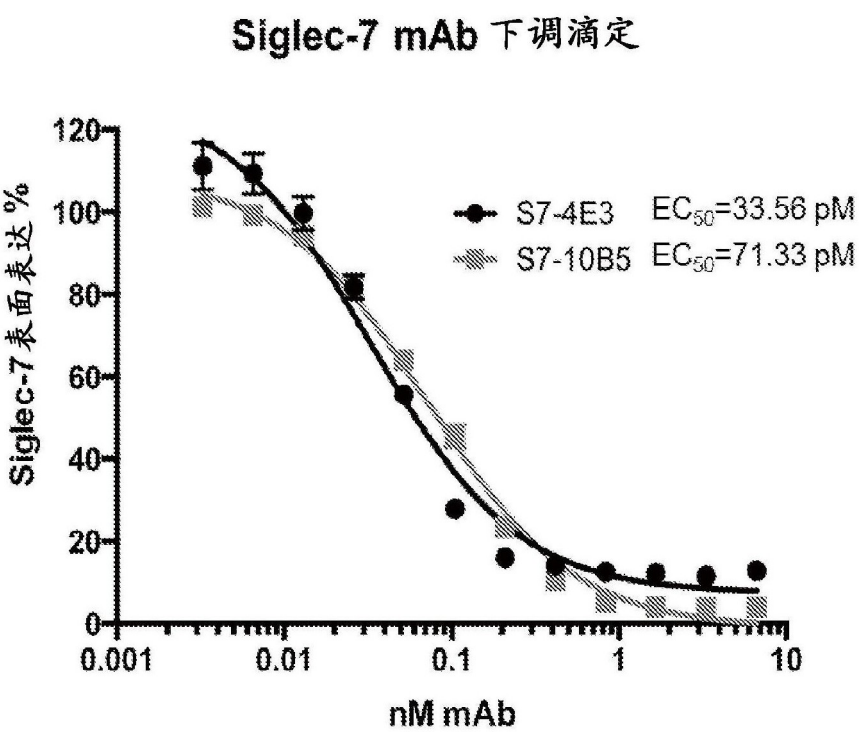

Siglec-7 mAb 下调滴定
Siglec-7表面表达%
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
nM mAb
S7-4E3 EC50=33.56 pM
S7-10B5 EC50=71.33 pM

图7M

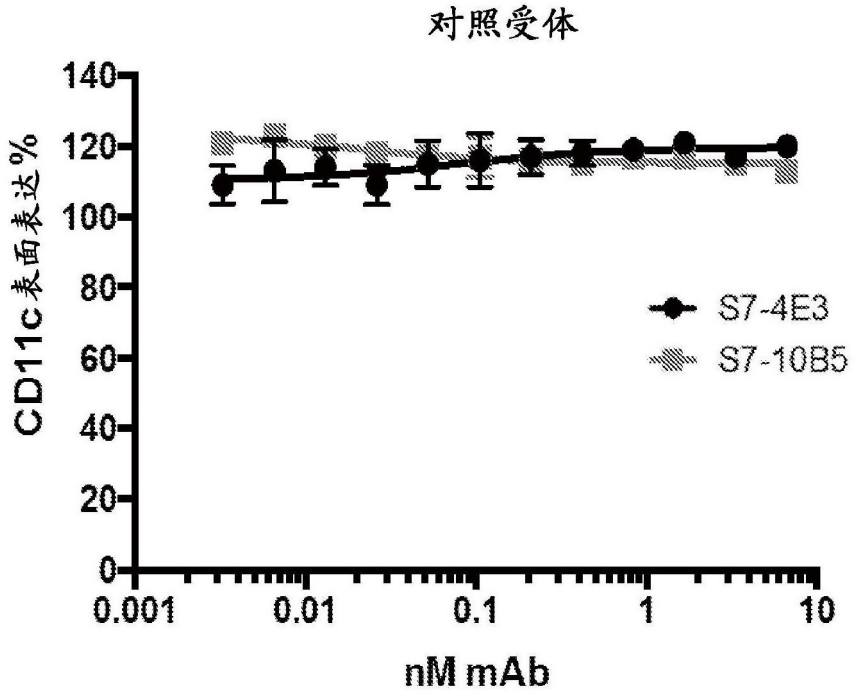

对照受体
CD11c表面表达%
140
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
nM mAb
S7-4E3
S7-10B5

图7N

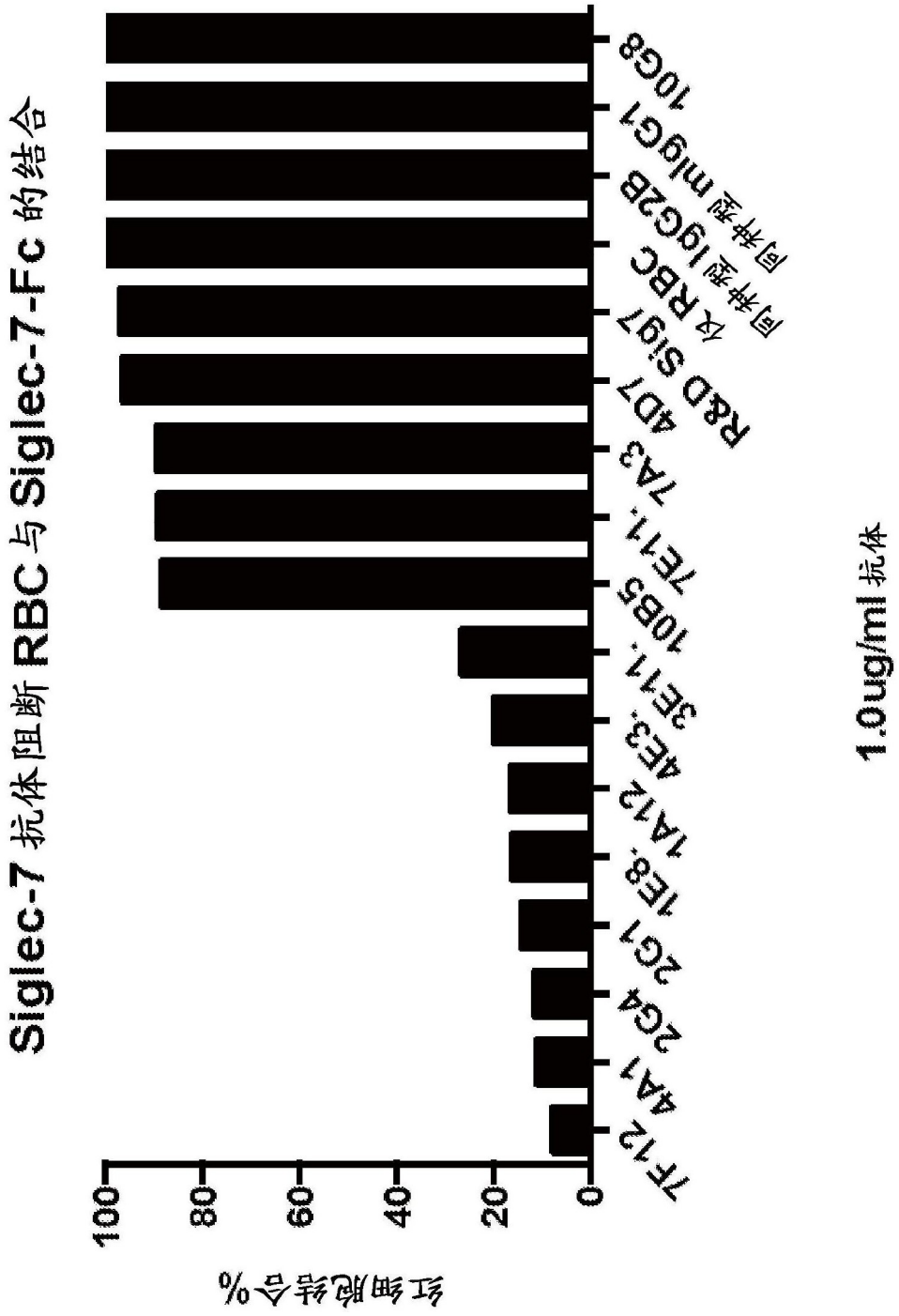

Siglec-7 抗体阻断 RBC 与 Siglec-7-Fc 的结合
1.0ug/ml 抗体
红细胞结合%
100
80
60
40
20
0
7F12
4A1
2G4
2G1
1E8.
1A12
4E3.
3E11.
10B5
7E11.
7A3
4D7
R&D Sig7
抗 RBC
同种型 IgG2B
同种型 mIgG1
10G8

图8

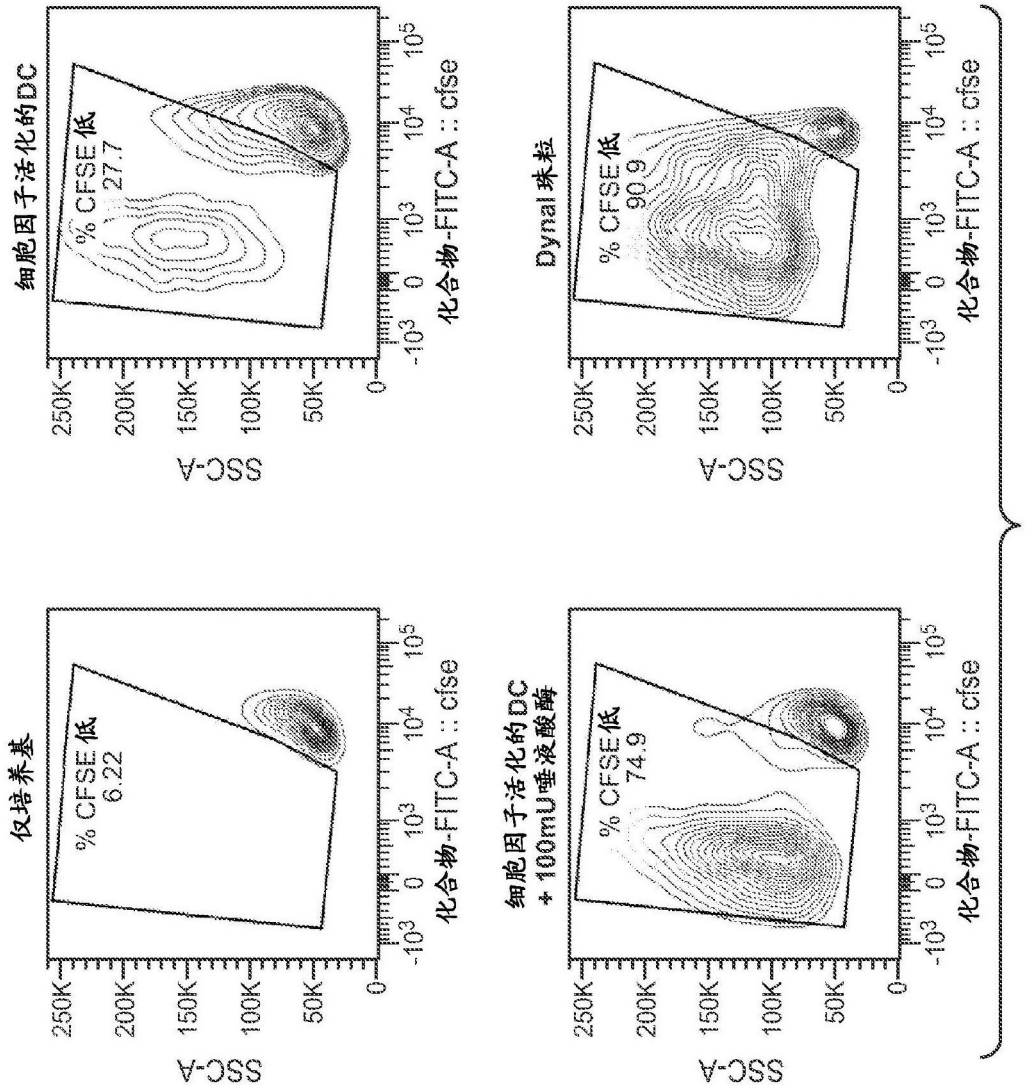

仅培养基
% CFSE 低
6.22
细胞因子活化的DC
% CFSE 低
27.7
细胞因子活化的DC
+ 100mU唾液酸酶
% CFSE 低
74.9
Dynal 珠粒
% CFSE 低
90.9
SSC-A
化合物-FITC-A :: cfse

图9

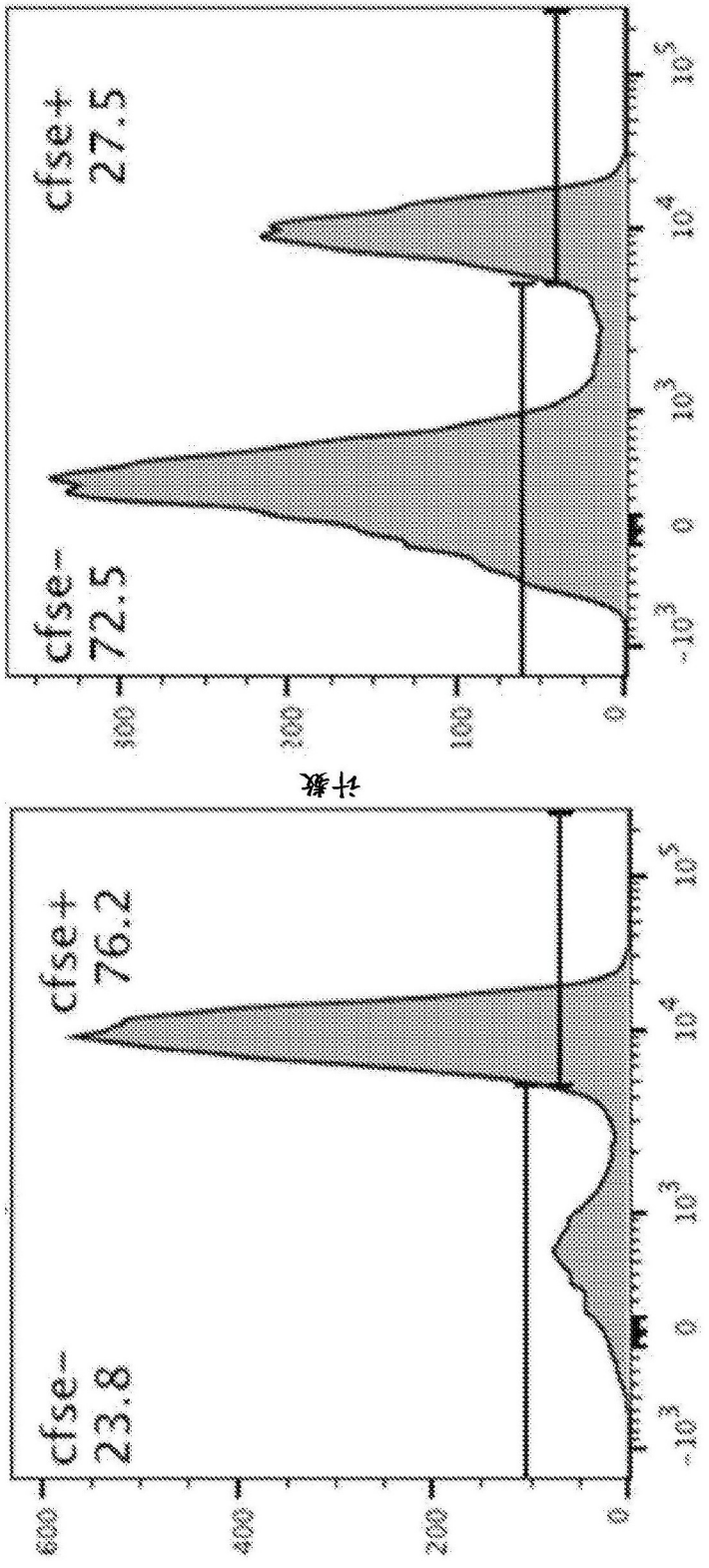


图10

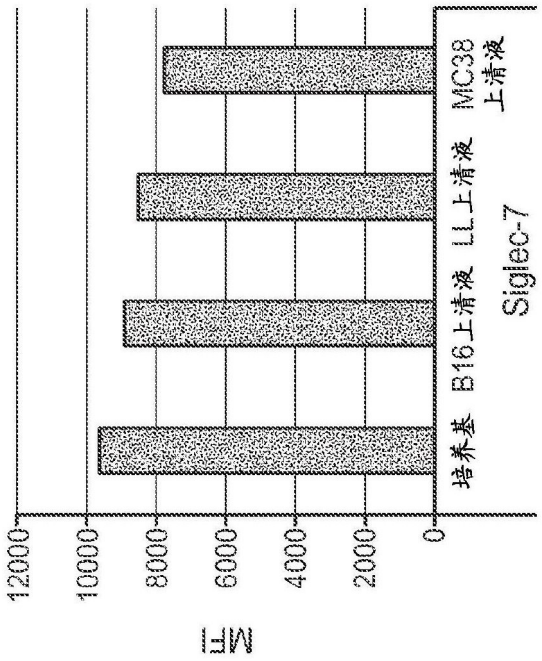

MFI
12000
10000
8000
6000
4000
2000
0
培养基
B16上清液
LL上清液
MC38上清液
Siglec-7

图11A

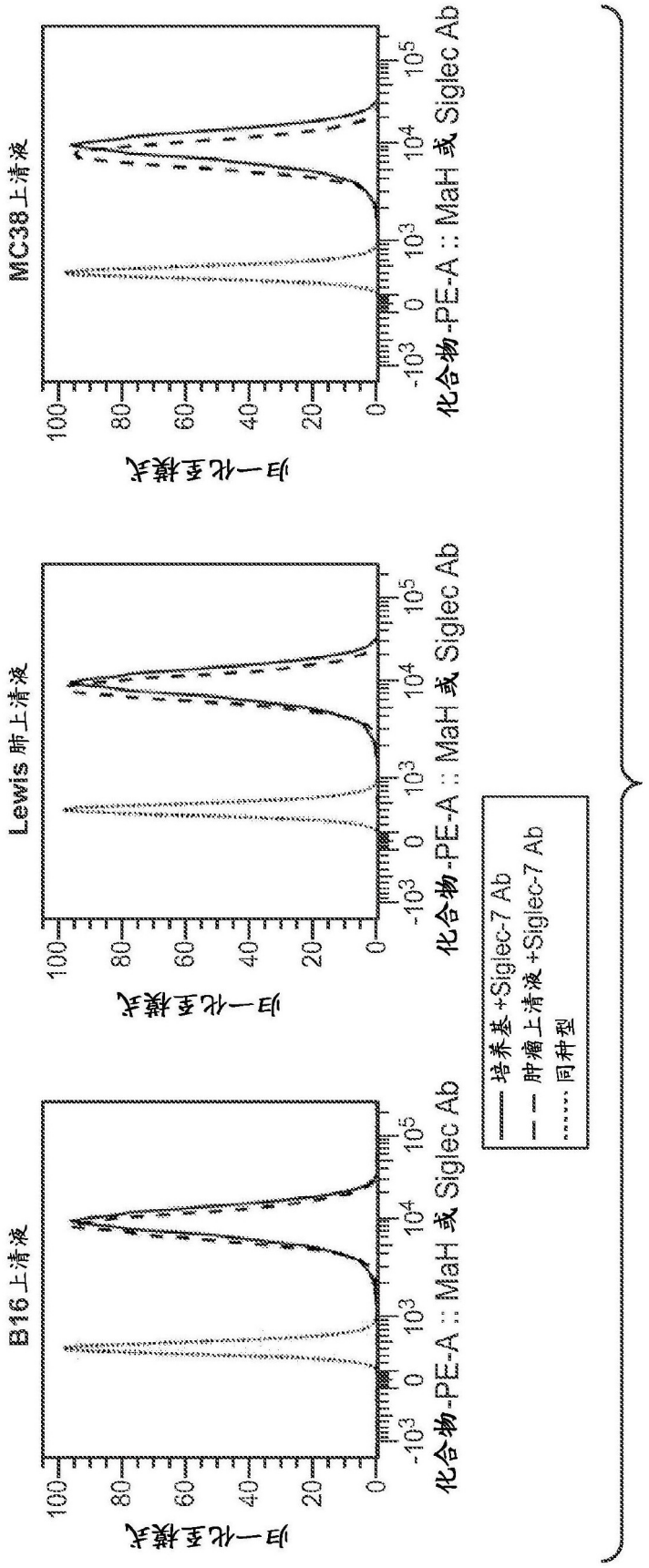

B16上清液
Lewis 肺上清液
MC38上清液
归一化至模式
化合物-PE-A :: MaH 或 Siglec Ab
培养基+Siglec-7 Ab
肿瘤上清液+Siglec-7 Ab
同种型

图11B

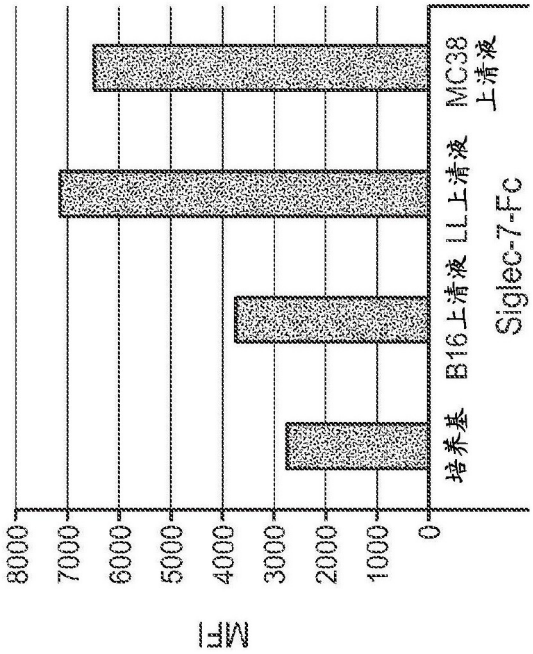

MFI
8000
7000
6000
5000
4000
3000
2000
1000
0
培养基
B16上清液
LL上清液
MC38上清液
Siglec-7-Fc

图11C

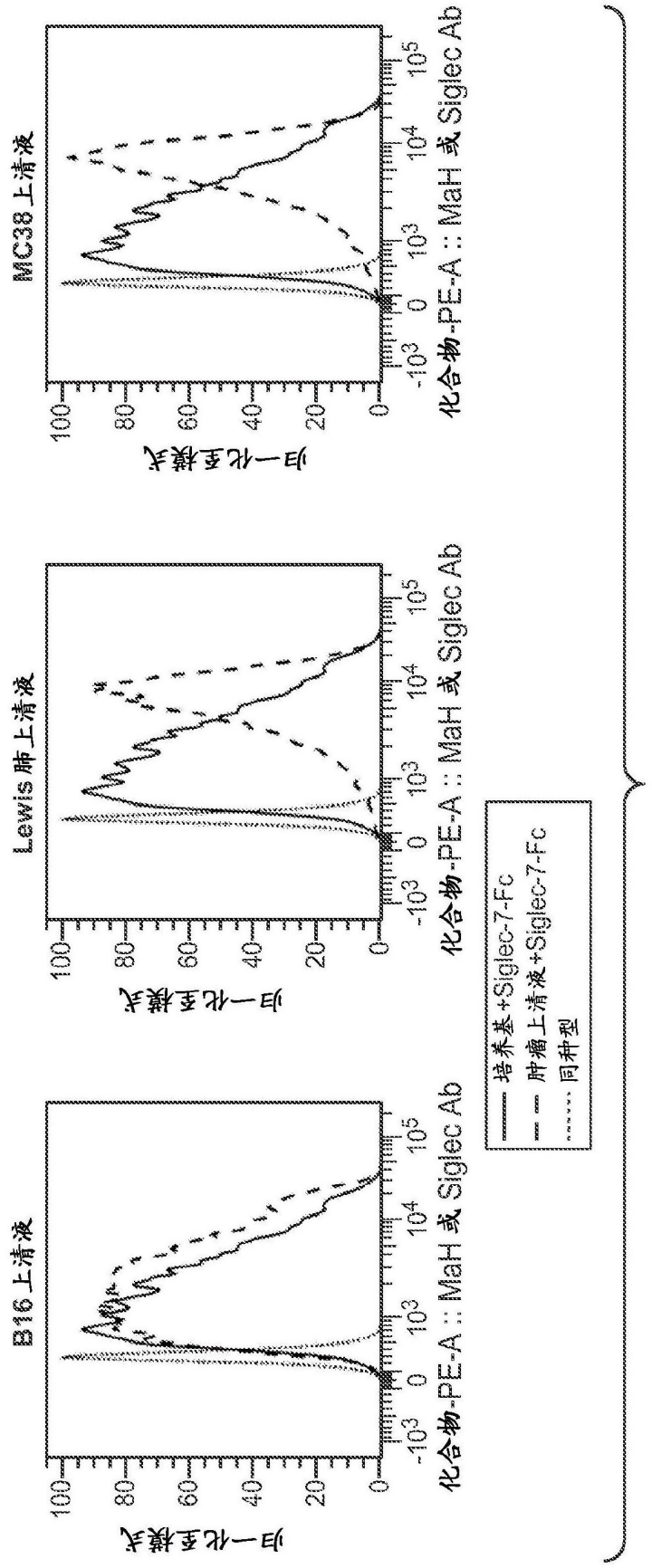

B16 上清液
Lewis 肺上清液
MC38 上清液
归一化至模式
化合物-PE-A :: MaH 或 Siglec Ab
培养基+Siglec-7-Fc
肿瘤上清液+Siglec-7-Fc
同种型

图11D

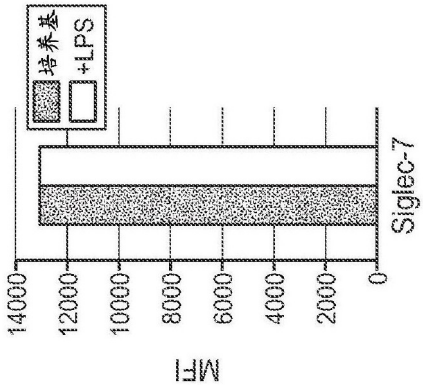


图11E

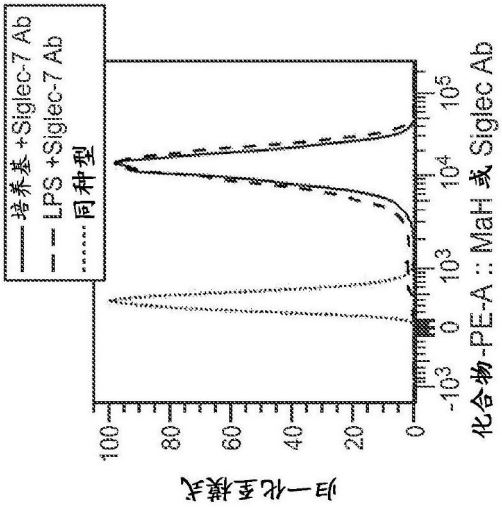


图11F

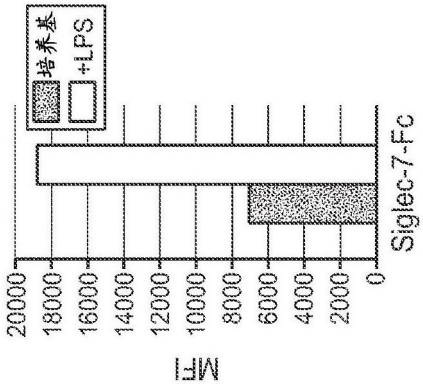


图11G

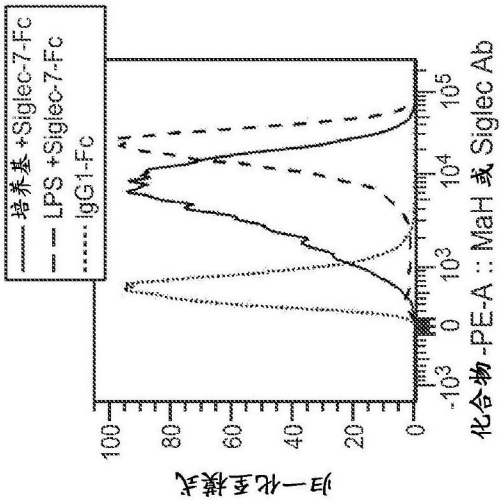

培养基+Siglec-7-Fc
LPS +Siglec-7-Fc
IgG1-Fc
归一化至模式
100
80
60
40
20
0
-10^3
0
10^3
10^4
10^5
化合物-PE-A :: MaH 或 Siglec Ab

图11H

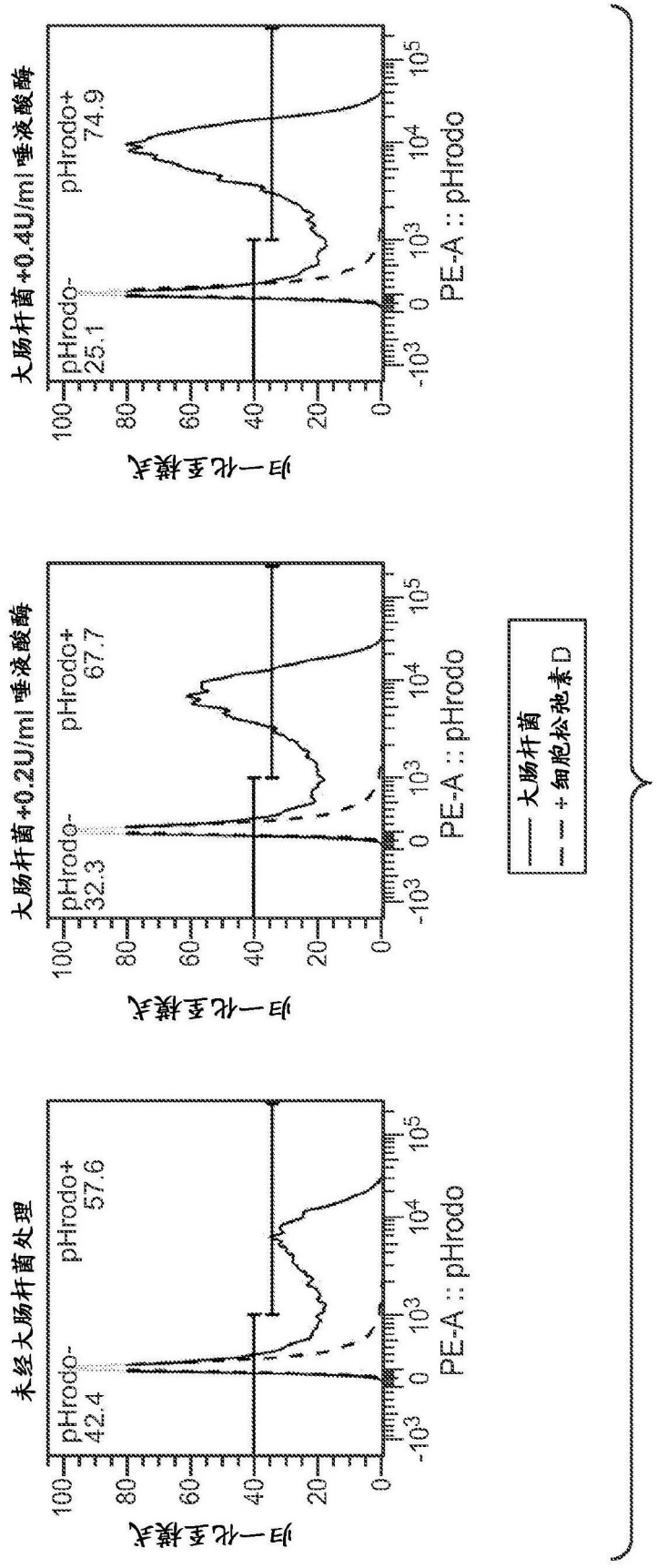

未经大肠杆菌处理
大肠杆菌+0.2U/ml 唾液酸酶
大肠杆菌+0.4U/ml 唾液酸酶
归一化至模式
PE-A :: pHrodo
pHrodo-
pHrodo+
42.4
57.6
32.3
67.7
25.1
74.9
大肠杆菌
+细胞松弛素D

图12

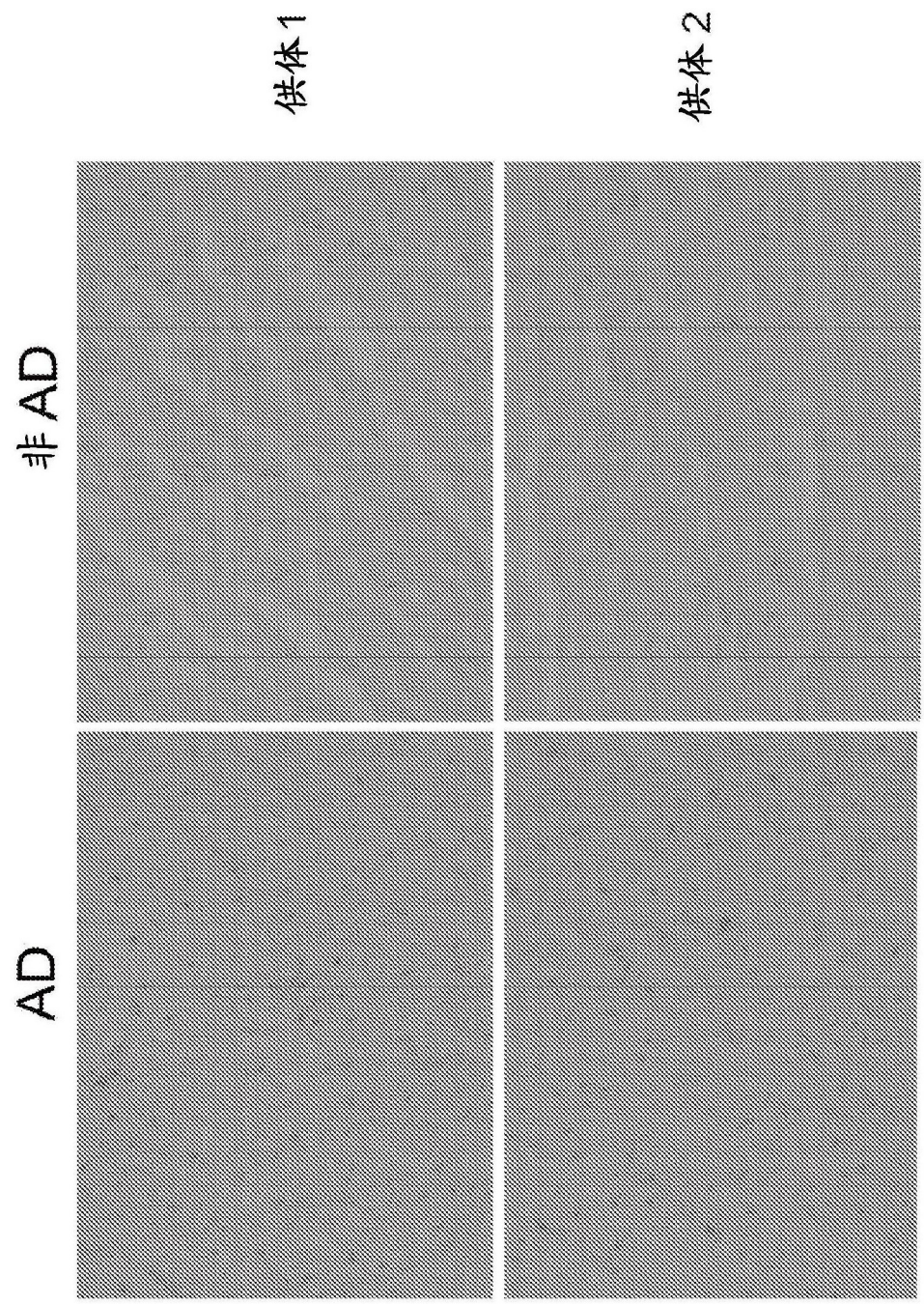


图13A

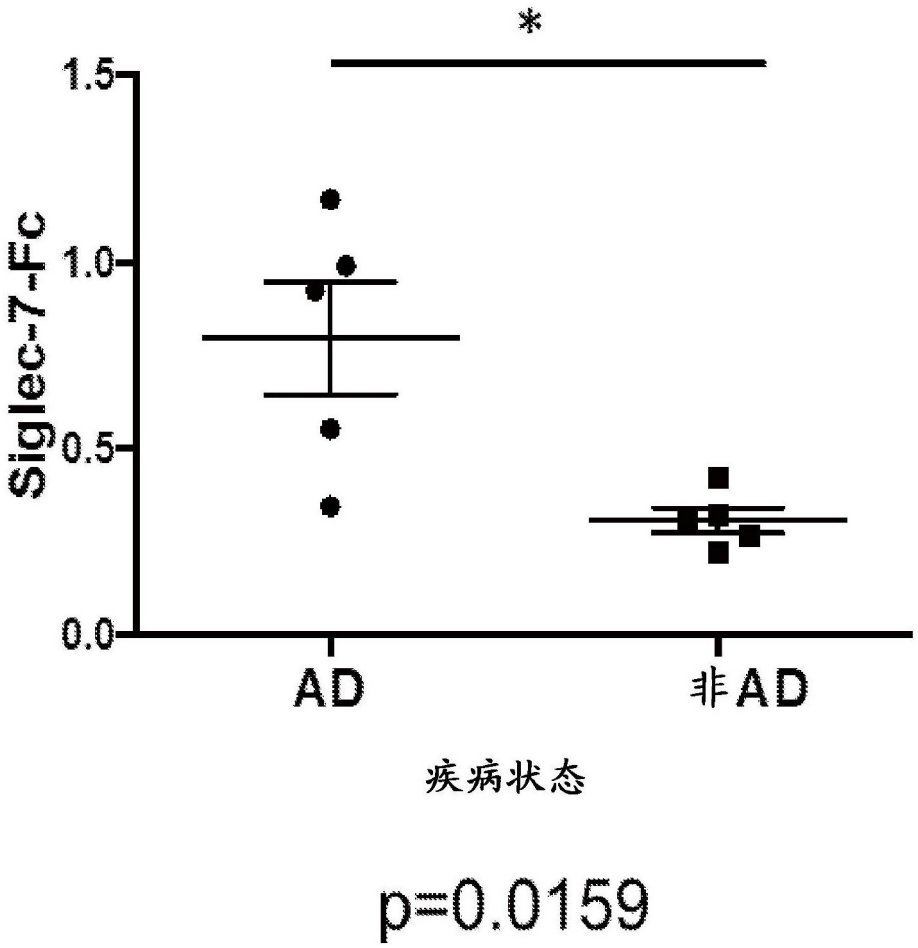


图13B

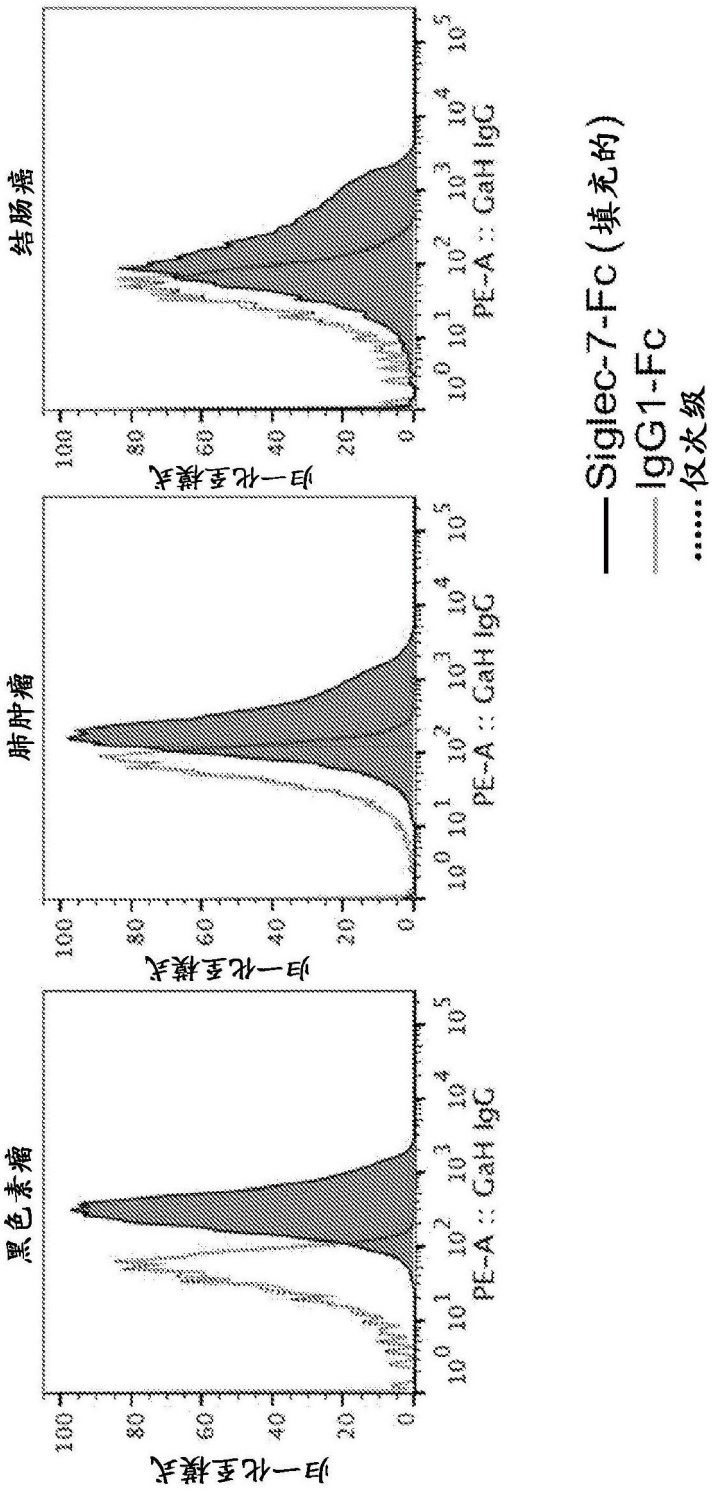


图14

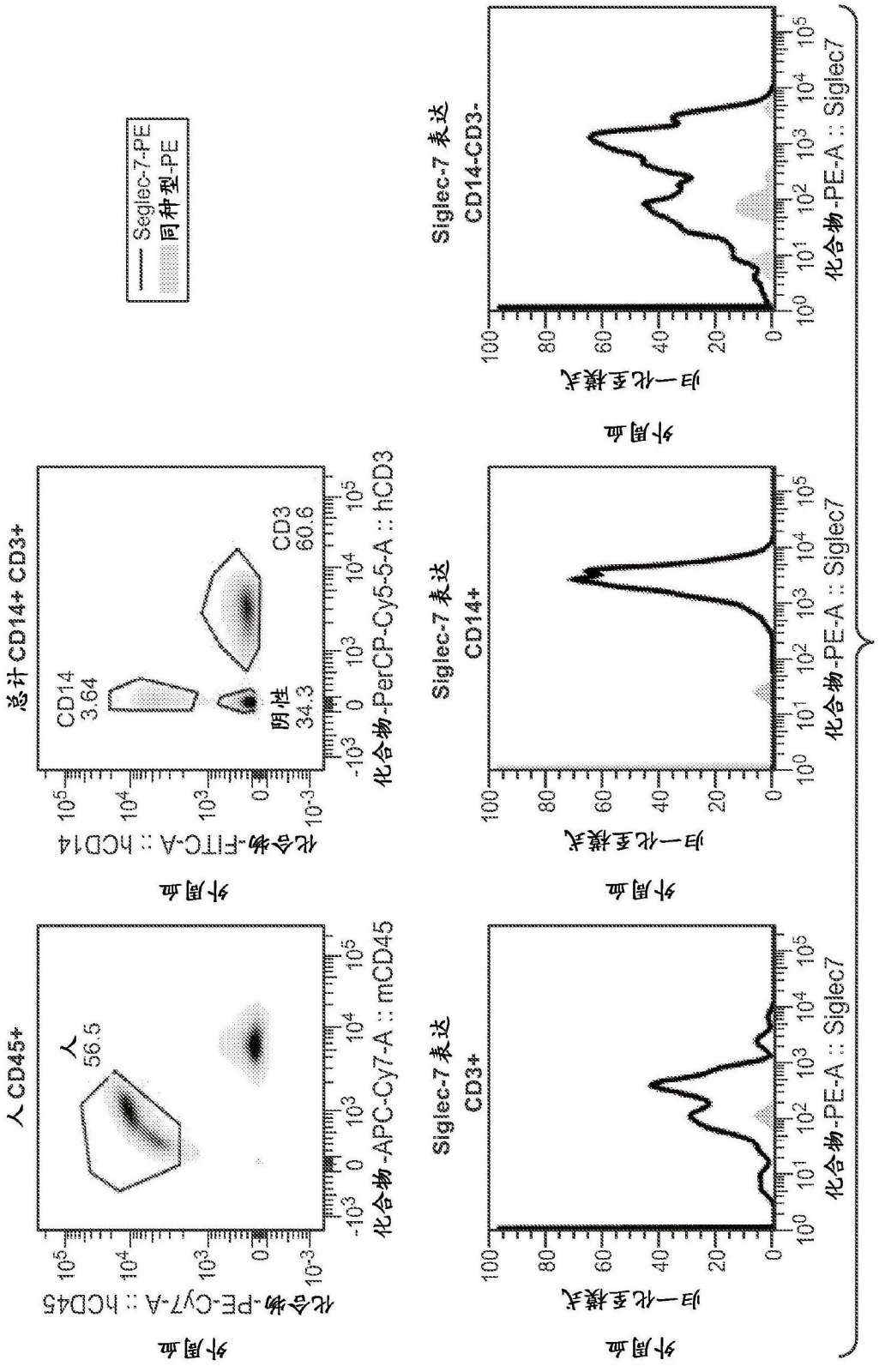

外周血
人 CD45+
人
56.5
化合物-PE-Cy7-A :: hCD45
化合物-APC-Cy7-A :: mCD45
外周血
总计 CD14+ CD3+
CD14
3.64
阴性
34.3
CD3
60.6
化合物-FITC-A :: hCD14
化合物-PerCP-Cy5-5-A :: hCD3
Seglec-7-PE
同种型-PE
外周血
Siglec-7 表达
CD3+
归一化至模式
化合物-PE-A :: Siglec7
外周血
Siglec-7 表达
CD14+
归一化至模式
化合物-PE-A :: Siglec7
外周血
Siglec-7 表达
CD14-CD3-
归一化至模式
化合物-PE-A :: Siglec7

图15

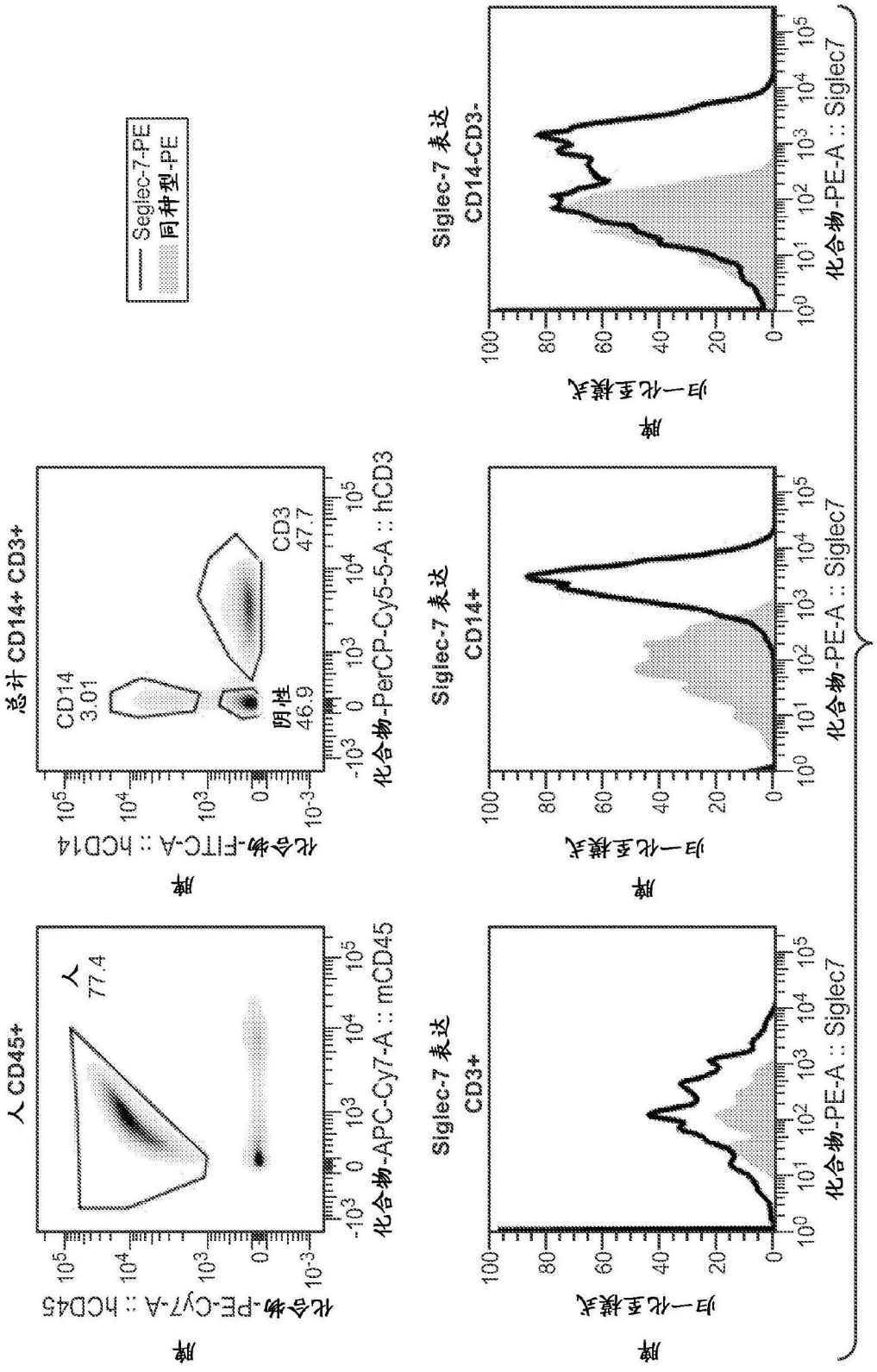

Seglec-7-PE
同种型-PE
人 CD45+
人
77.4
脾
化合物-PE-Cy7-A :: hCD45
化合物-APC-Cy7-A :: mCD45
总计 CD14+ CD3+
CD14
3.01
阴性
46.9
CD3
47.7
脾
化合物-FITC-A :: hCD14
化合物-PerCP-Cy5-5-A :: hCD3
Siglec-7 表达
CD3+
脾
归一化至模式
化合物-PE-A :: Siglec7
Siglec-7 表达
CD14+
脾
归一化至模式
化合物-PE-A :: Siglec7
Siglec-7 表达
CD14-CD3-
脾
归一化至模式
化合物-PE-A :: Siglec7

图15(续)

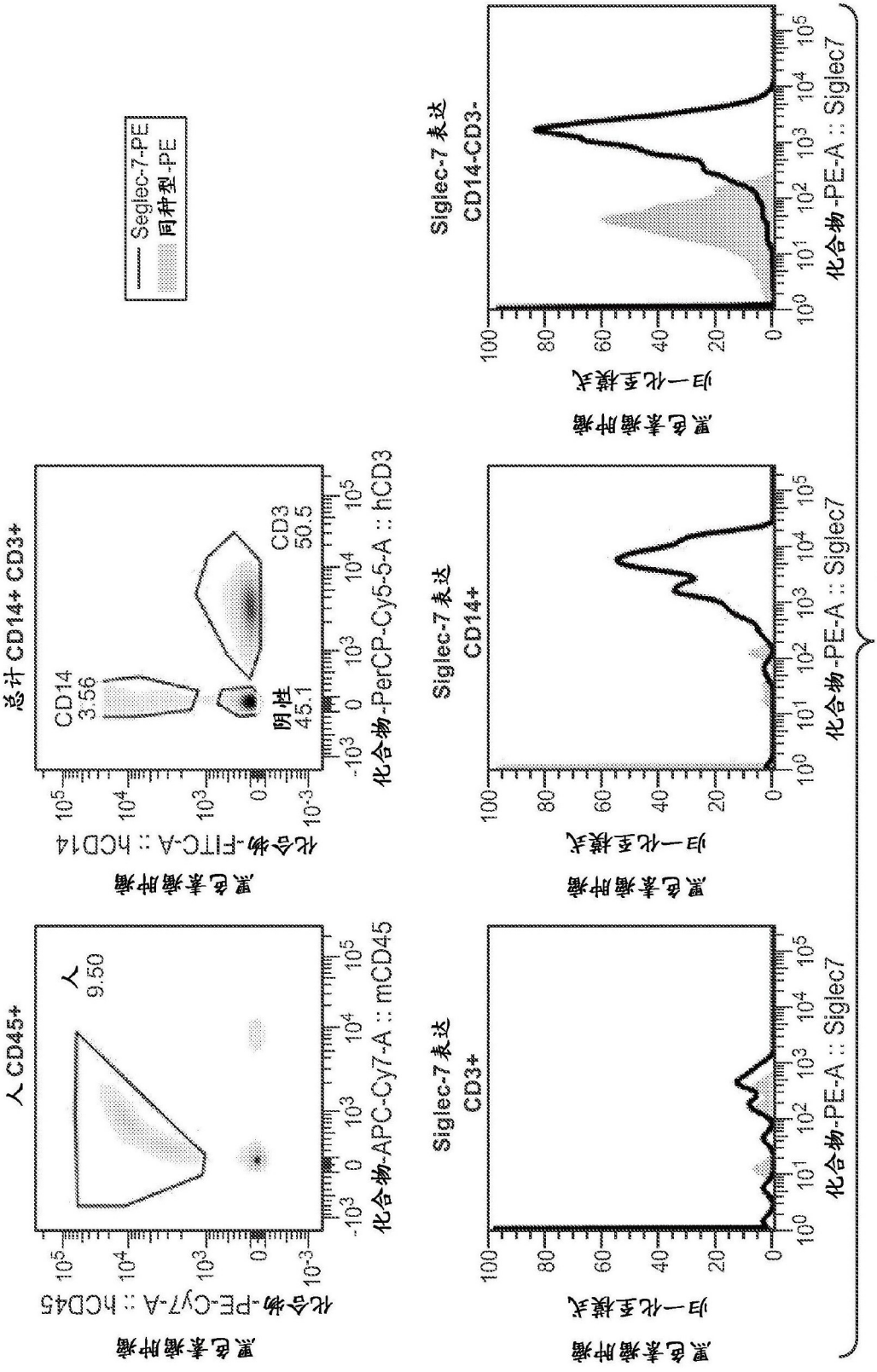

Seglec-7-PE
同种型-PE
人 CD45+
人
9.50
化合物-PE-Cy7-A :: hCD45
黑色素瘤肿瘤
化合物-APC-Cy7-A :: mCD45
总计 CD14+ CD3+
CD14
3.56
阴性
45.1
CD3
50.5
化合物-FITC-A :: hCD14
黑色素瘤肿瘤
化合物-PerCP-Cy5-5-A :: hCD3
Siglec-7 表达
CD3+
归一化至模式
黑色素瘤肿瘤
化合物-PE-A :: Siglec7
Siglec-7 表达
CD14+
归一化至模式
黑色素瘤肿瘤
化合物-PE-A :: Siglec7
Siglec-7 表达
CD14-CD3-
归一化至模式
黑色素瘤肿瘤
化合物-PE-A :: Siglec7

图15(续)

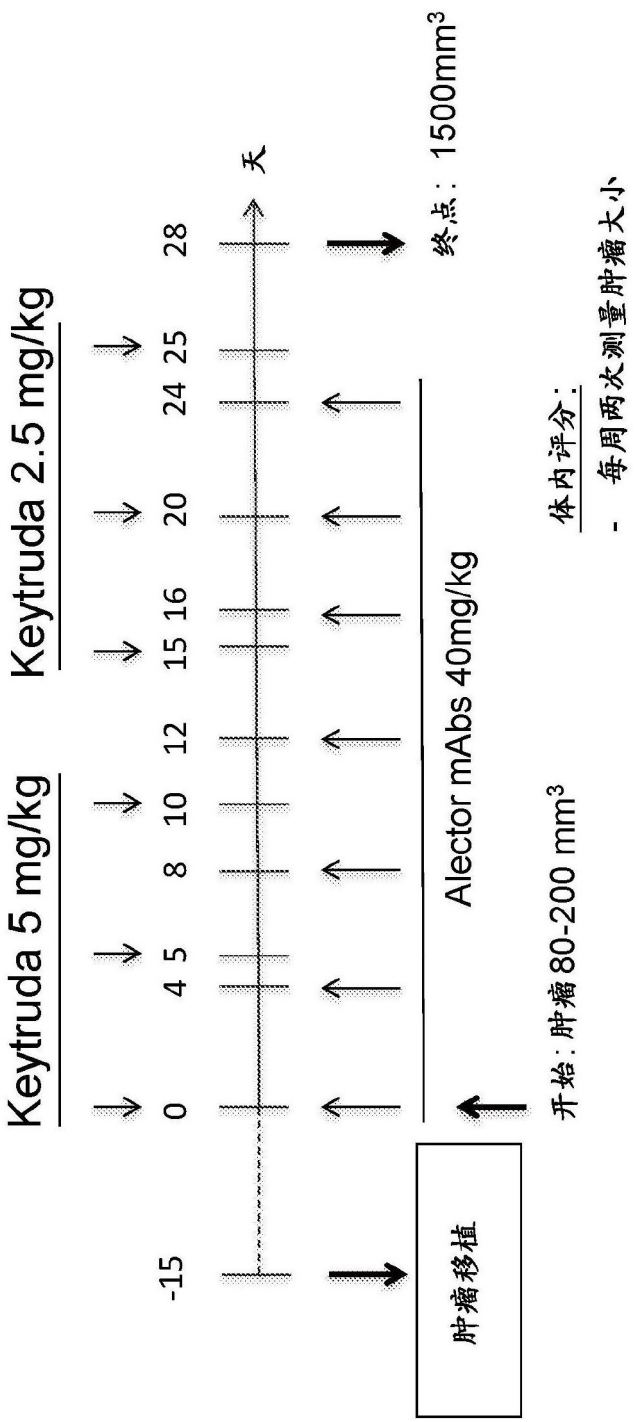

Keytruda 5 mg/kg
Keytruda 2.5 mg/kg
-15
0
4 5
8
10
12
15 16
20
24 25
28
天
肿瘤移植
开始：肿瘤 80-200 mm3
Alector mAbs 40mg/kg
终点：1500mm3
体内评分：
- 每周两次测量肿瘤大小

图16A

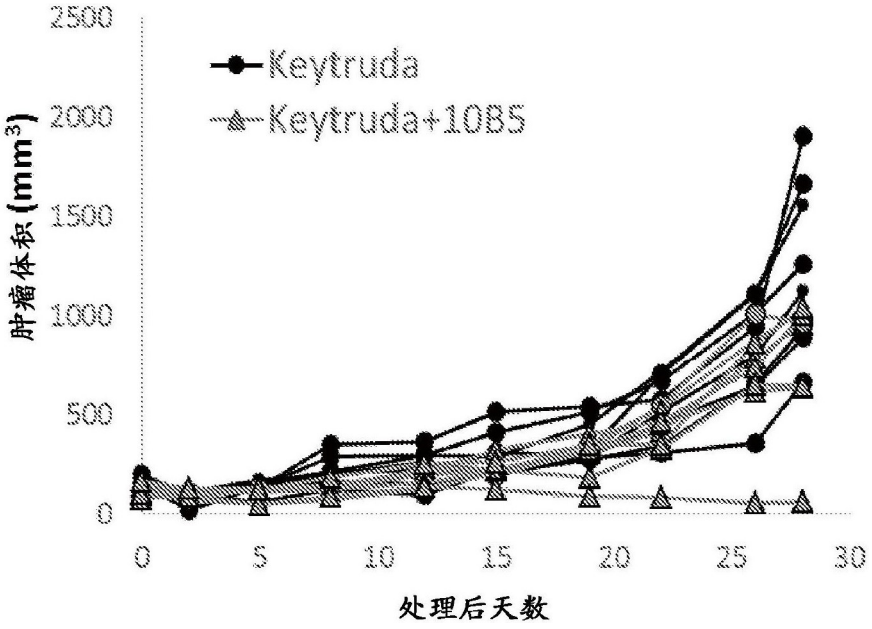

2500
2000
1500
1000
500
0
肿瘤体积 (mm³)
Keytruda
Keytruda+10B5
0
5
10
15
20
25
30
处理后天数

图16B

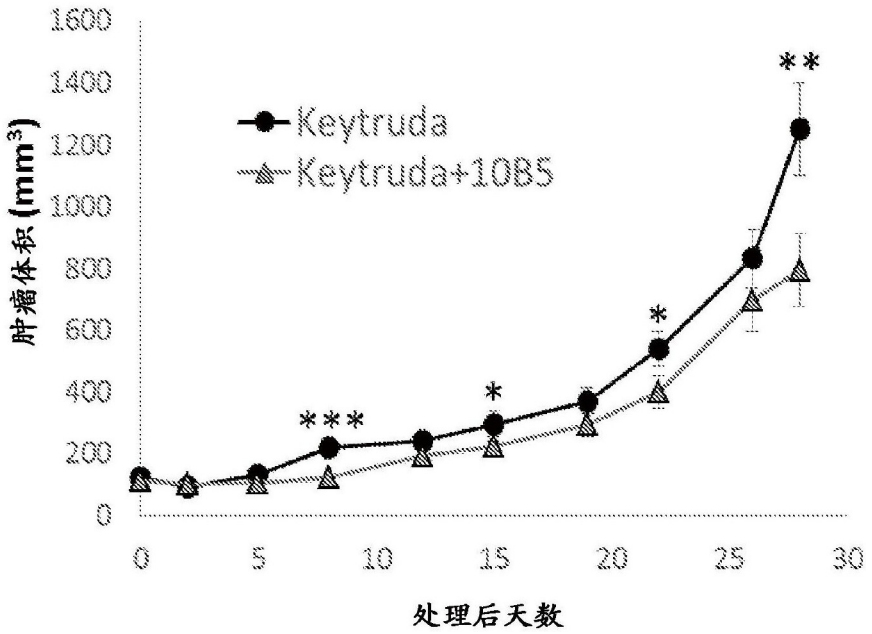

1600
1400
1200
1000
800
600
400
200
0
肿瘤体积 (mm³)
Keytruda
Keytruda+10B5
***
*
*
**
0
5
10
15
20
25
30
处理后天数

图16C

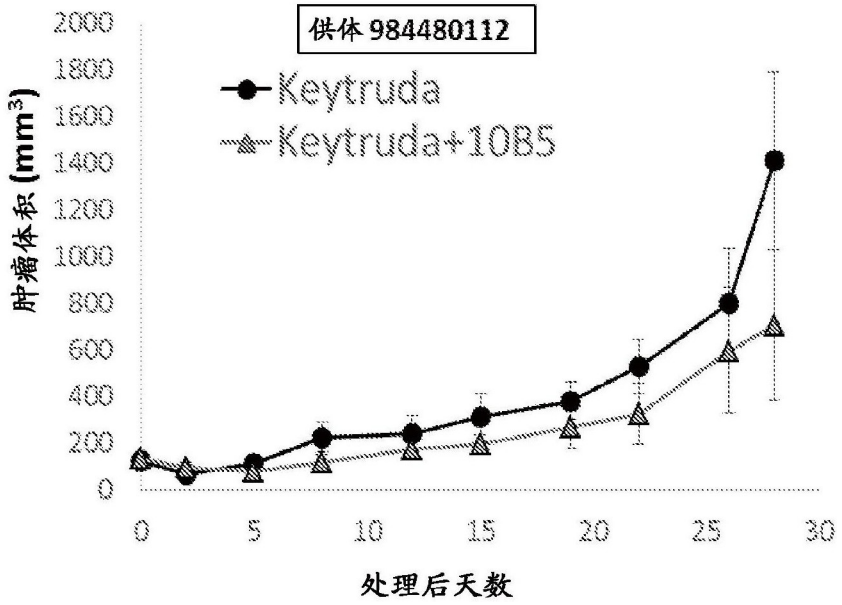

供体 984480112
Keytruda
Keytruda+10B5
肿瘤体积 (mm³)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
5
10
15
20
25
30
处理后天数

图16D

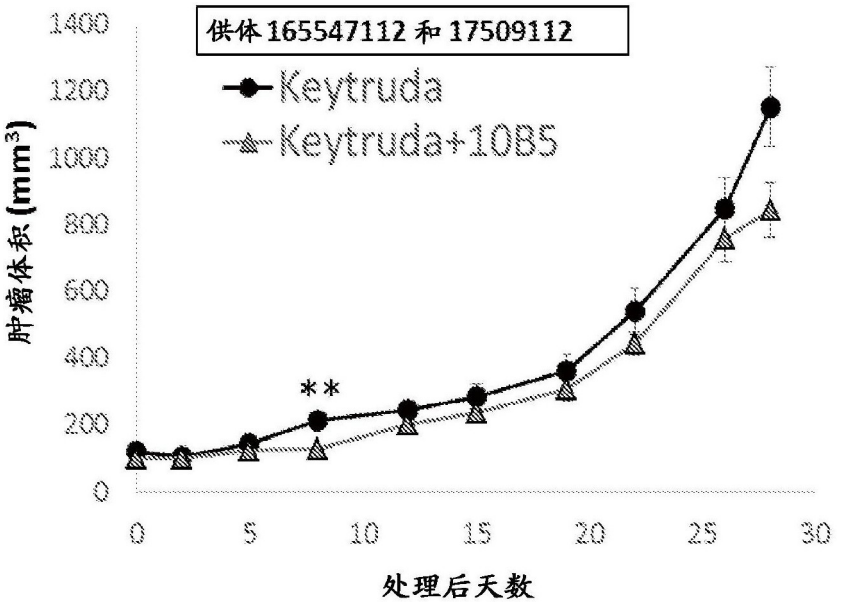

供体 165547112 和 17509112
Keytruda
Keytruda+10B5
肿瘤体积 (mm³)
1400
1200
1000
800
600
400
200
0
**
0
5
10
15
20
25
30
处理后天数

图16E

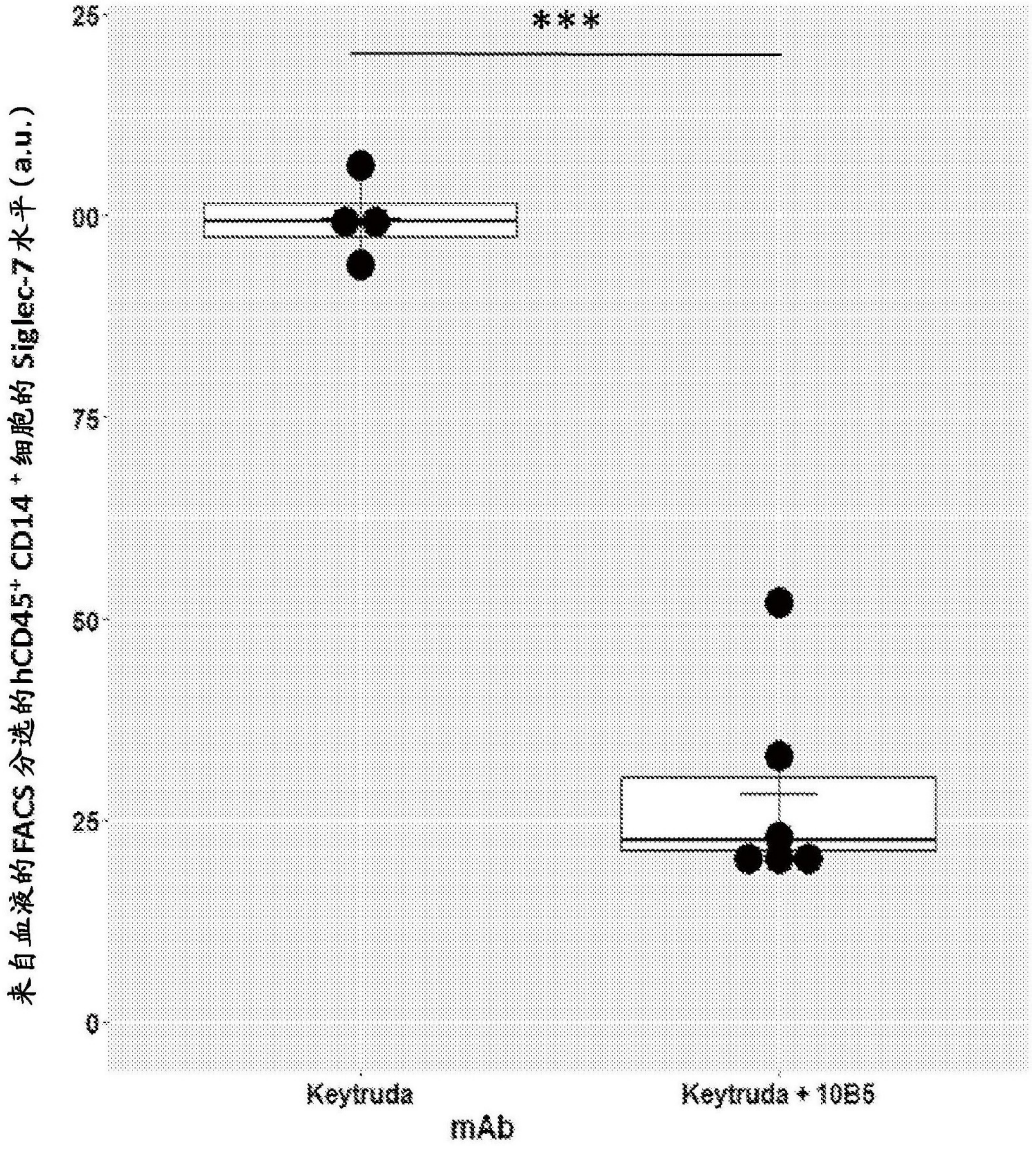

***
25
00
75
50
25
0
来自血液的FACS分选的hCD45+ CD14+细胞的Siglec-7水平(a.u.)
Keytruda
Keytruda + 10B5
mAb

图16F

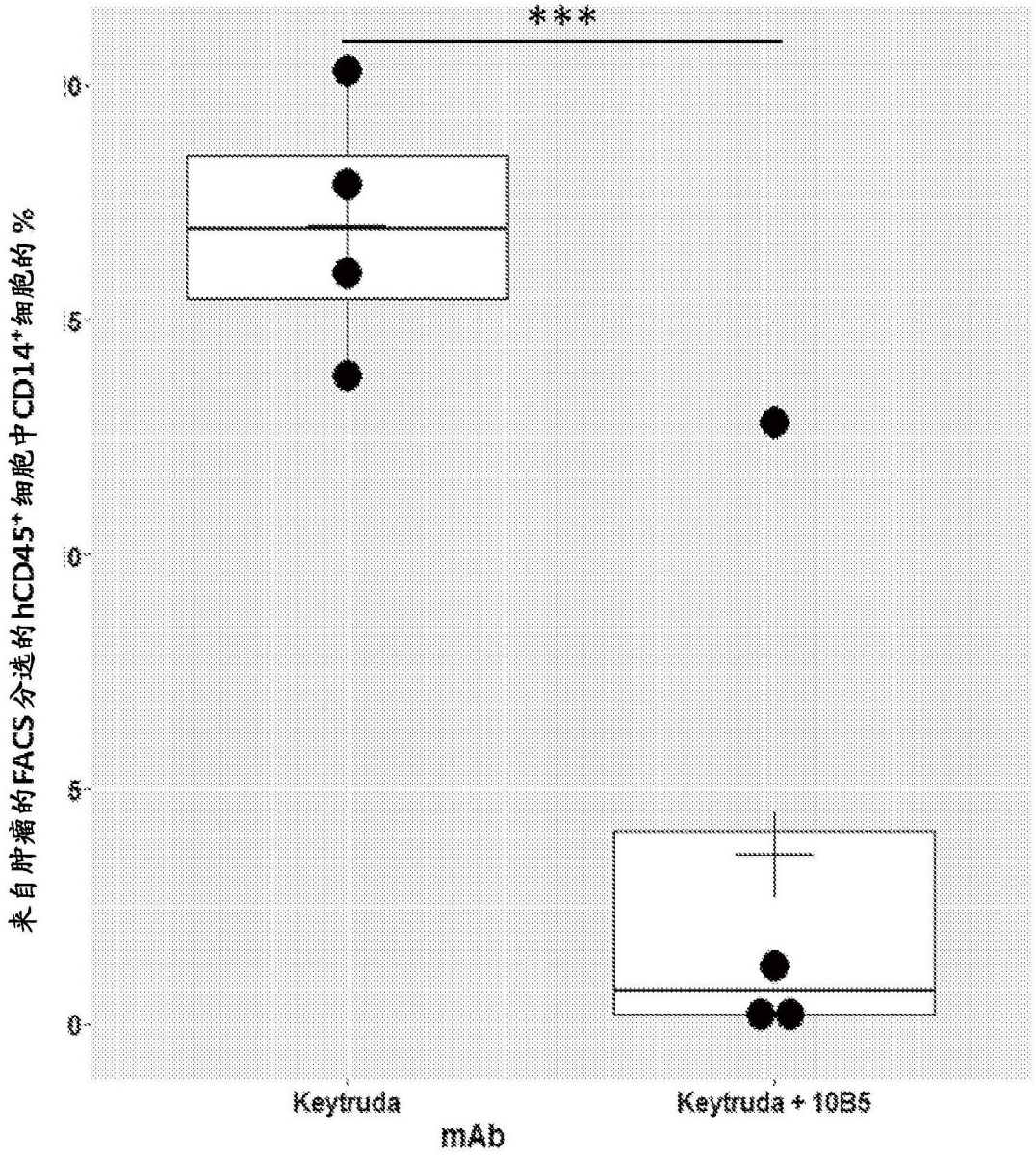

***
来自肿瘤的FACS分选的hCD45+细胞中CD14+细胞的%
Keytruda
Keytruda + 10B5
mAb

图16G

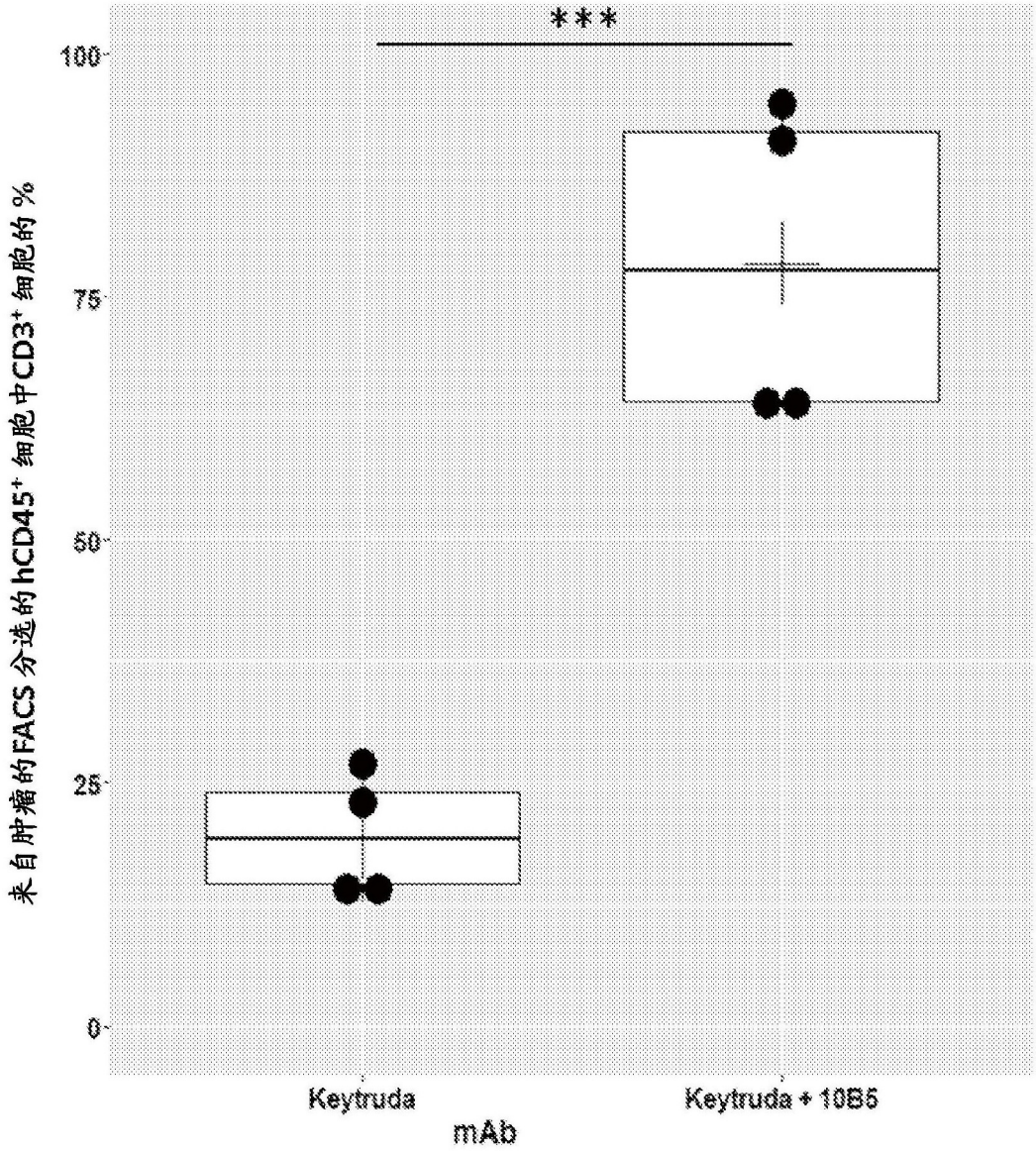

***
100
75
50
25
0
来自肿瘤的FACS分选的hCD45+细胞中CD3+细胞的%
Keytruda
Keytruda + 10B5
mAb

图16H

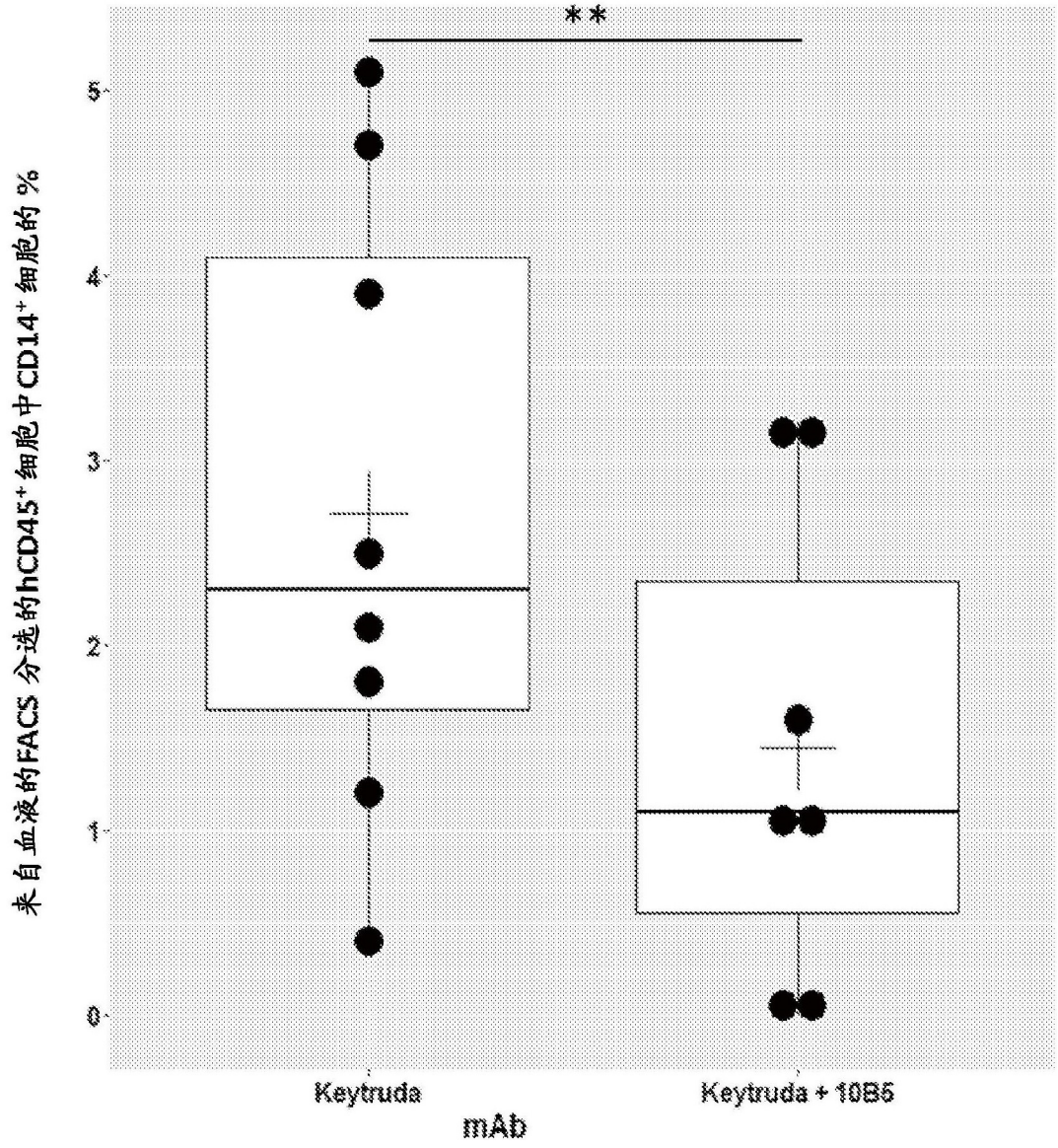

**
来自血液的FACS 分选的hCD45+细胞中CD14+细胞的 %
0
1
2
3
4
5
Keytruda
Keytruda + 10B5
mAb

图16I

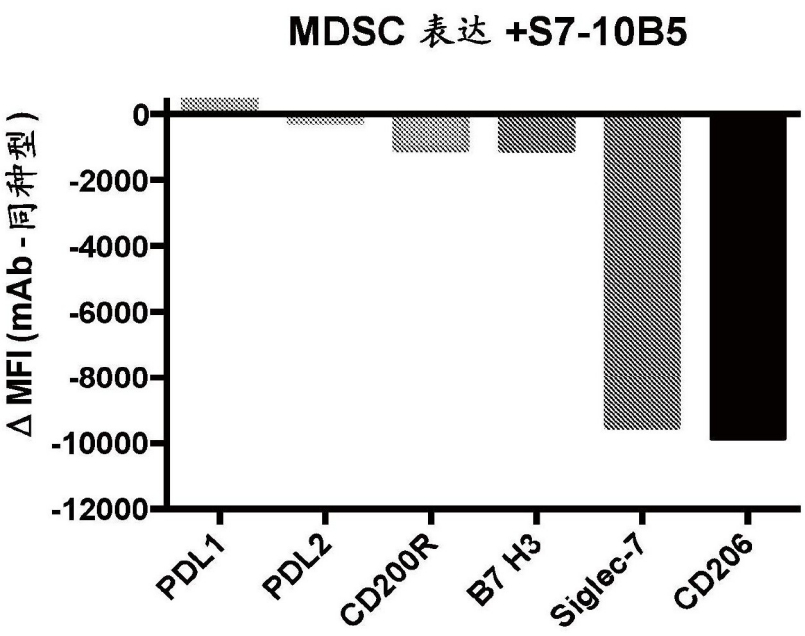

MDSC 表达 +S7-10B5
Δ MFI (mAb - 同种型)
0
-2000
-4000
-6000
-8000
-10000
-12000
PDL1
PDL2
CD200R
B7 H3
Siglec-7
CD206

图17A

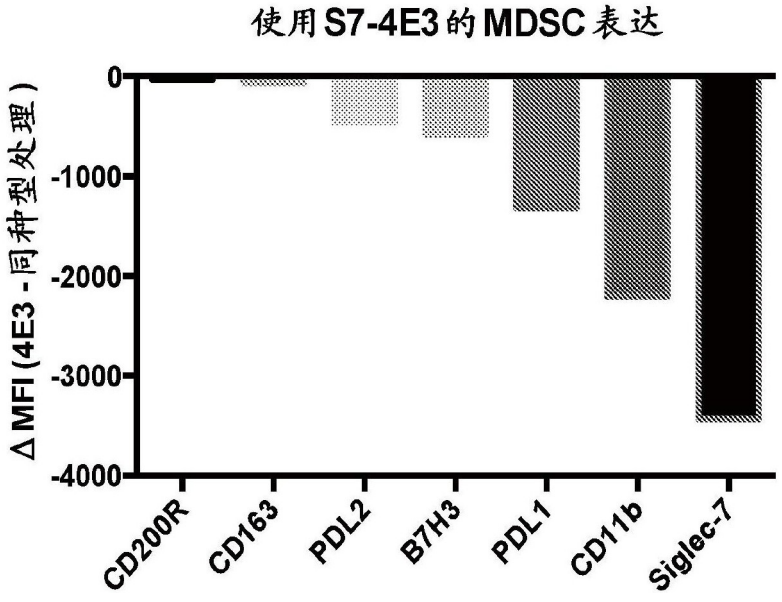

使用 S7-4E3 的 MDSC 表达
Δ MFI (4E3 - 同种型处理)
0
-1000
-2000
-3000
-4000
CD200R
CD163
PDL2
B7H3
PDL1
CD11b
Siglec-7

图17B

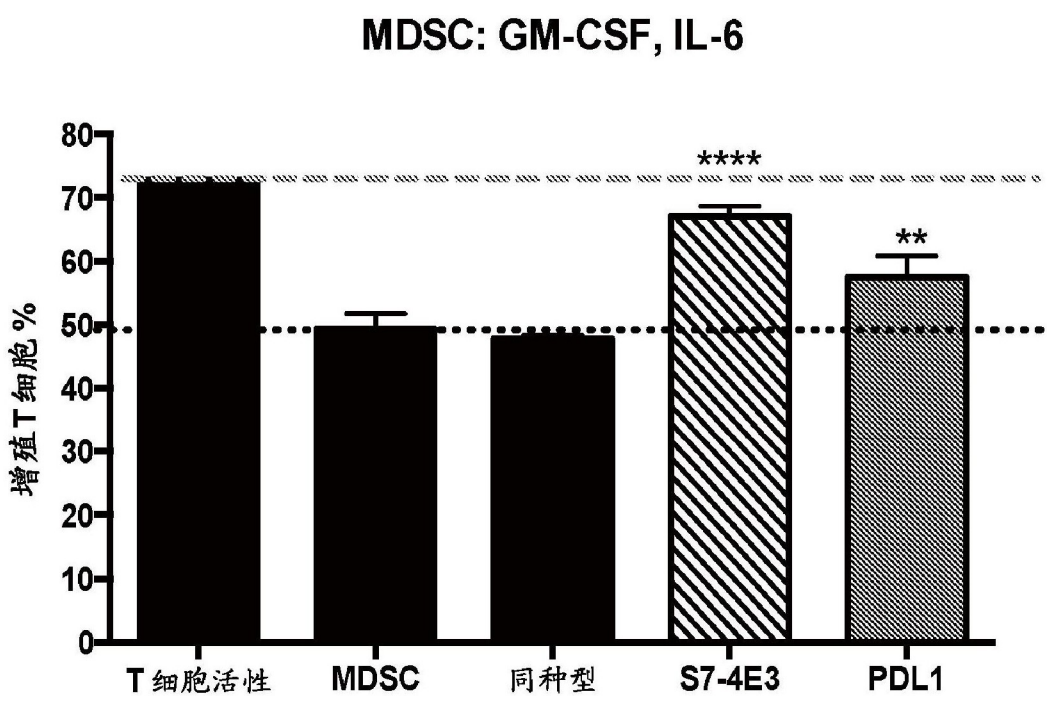

MDSC: GM-CSF, IL-6
增殖T细胞%
80
70
60
50
40
30
20
10
0
****
**
T细胞活性
MDSC
同种型
S7-4E3
PDL1

图17C

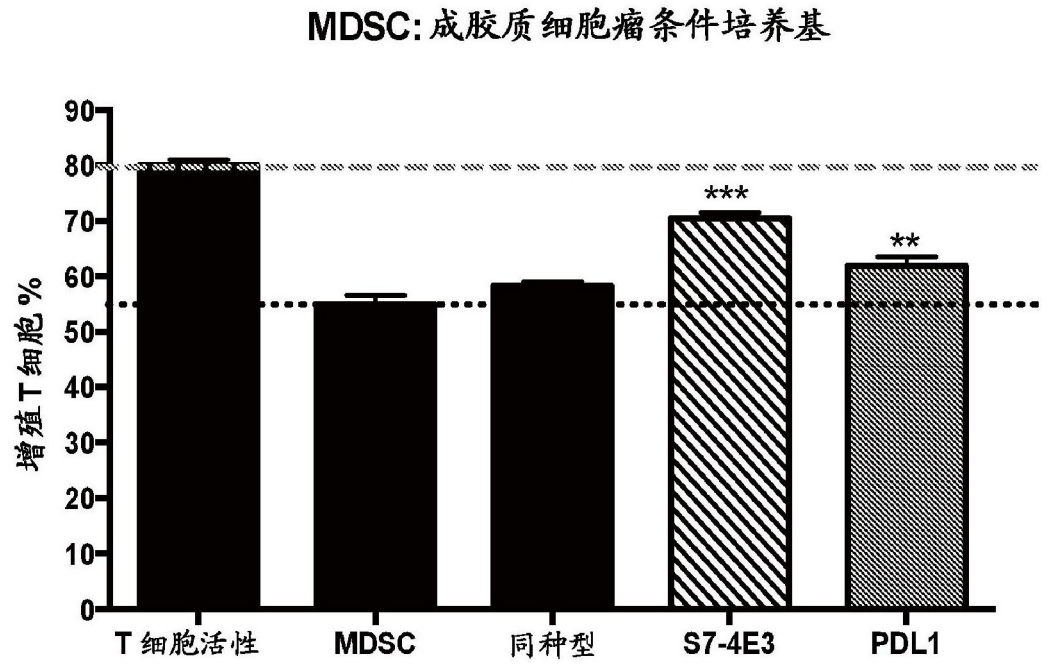

MDSC: 成胶质细胞瘤条件培养基
增殖T细胞%
90
80
70
60
50
40
30
20
10
0
***
**
T细胞活性
MDSC
同种型
S7-4E3
PDL1

图17D

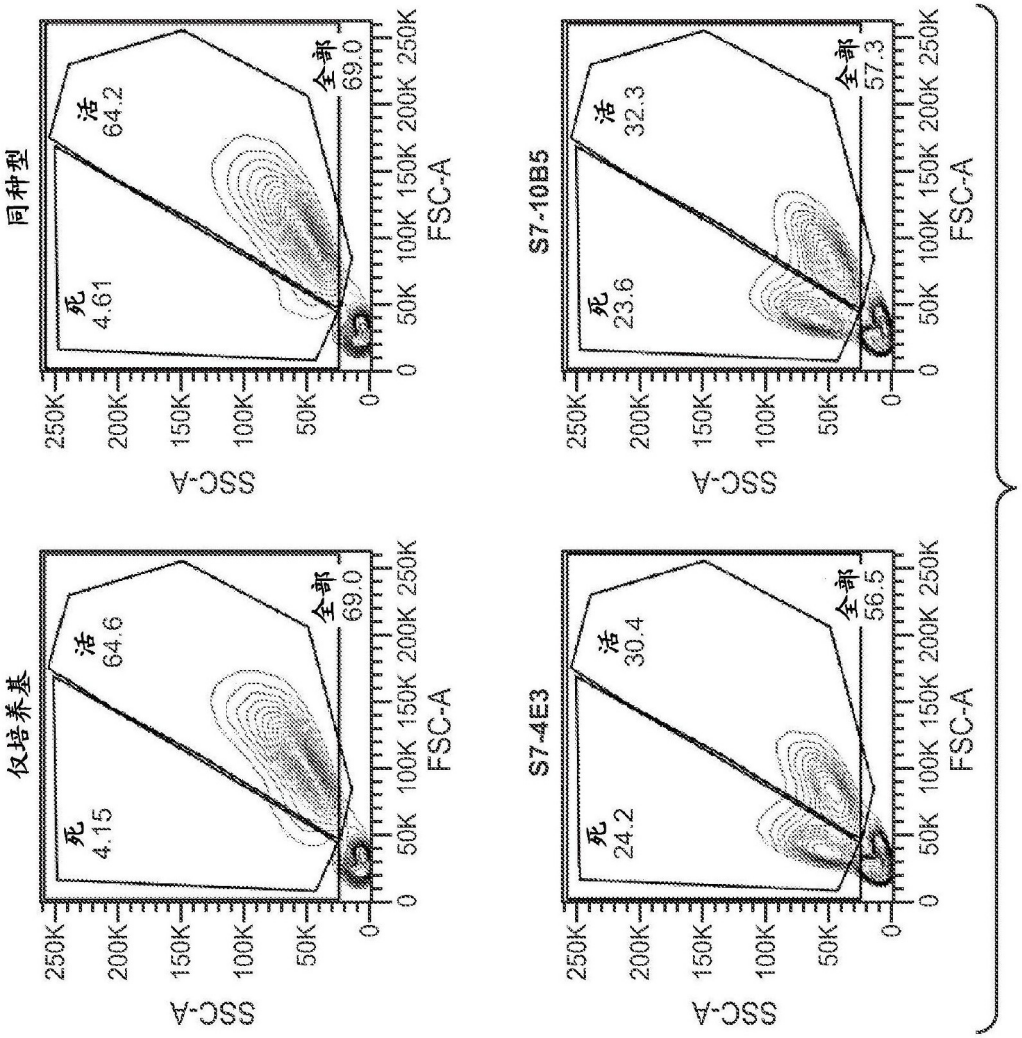

同种型
死
4.61
活
64.2
全部
69.0
仅培养基
死
4.15
活
64.6
全部
69.0
S7-10B5
死
23.6
活
32.3
全部
57.3
S7-4E3
死
24.2
活
30.4
全部
56.5
SSC-A
FSC-A
0
50K
100K
150K
200K
250K

图18

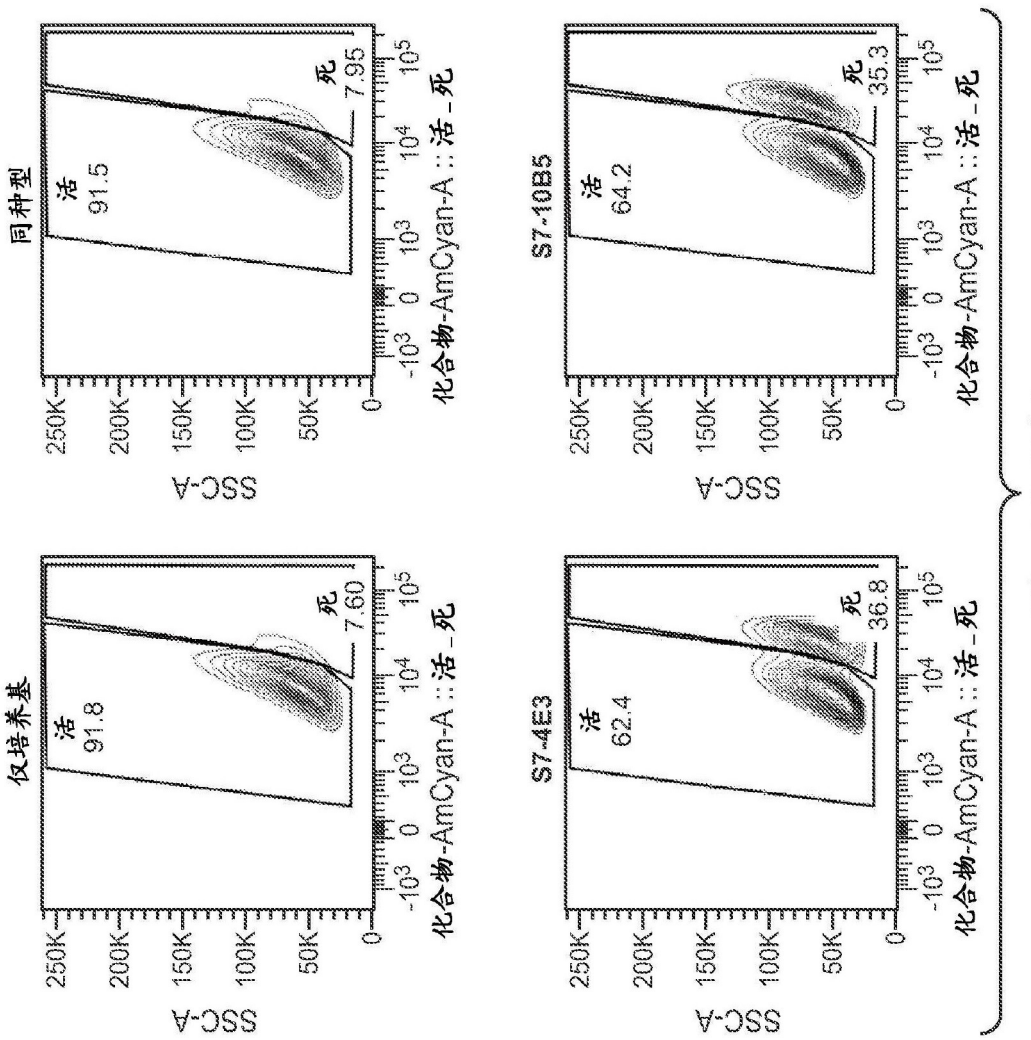

同种型
活
91.5
死
7.95
仅培养基
活
91.8
死
7.60
S7-10B5
活
64.2
死
35.3
S7-4E3
活
62.4
死
36.8
SSC-A
250K
200K
150K
100K
50K
0
-10³ 0 10³ 10⁴ 10⁵
化合物-AmCyan-A :: 活_死

图18(续)

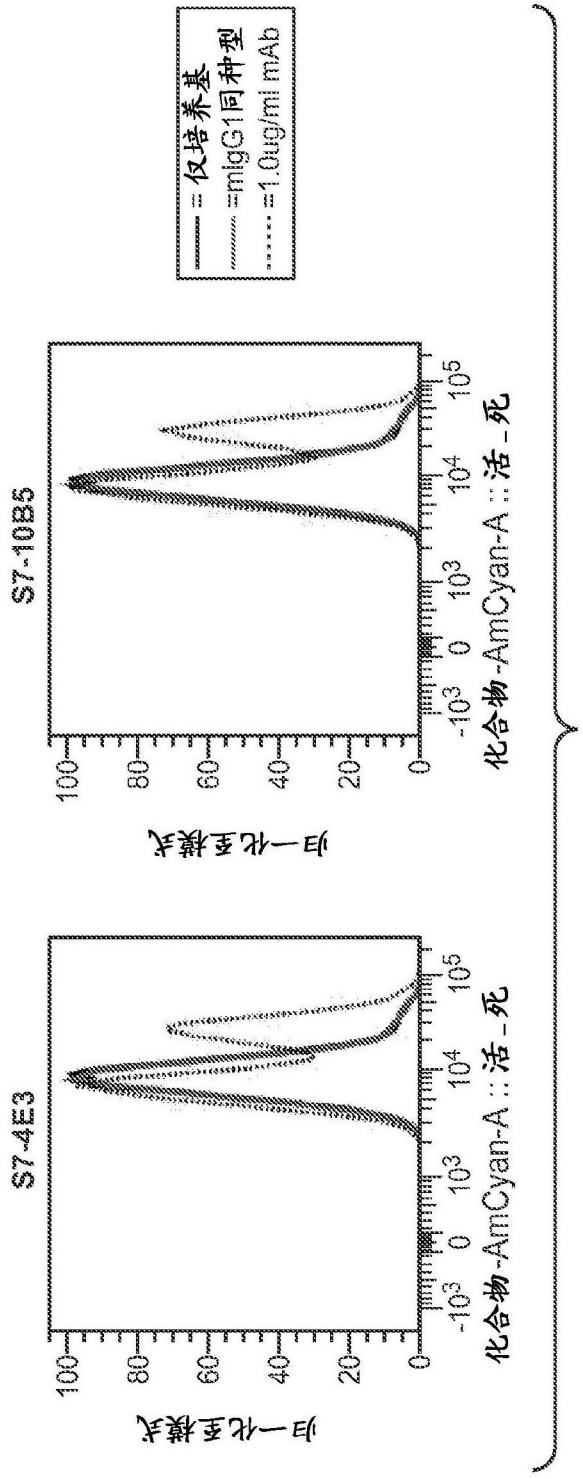

仅培养基
mIgG1同种型
1.0ug/ml mAb
S7-10B5
S7-4E3
归一化至模式
化合物-AmCyan-A :: 活_死
0
20
40
60
80
100
-10^3
0
10^3
10^4
10^5

图18(续)