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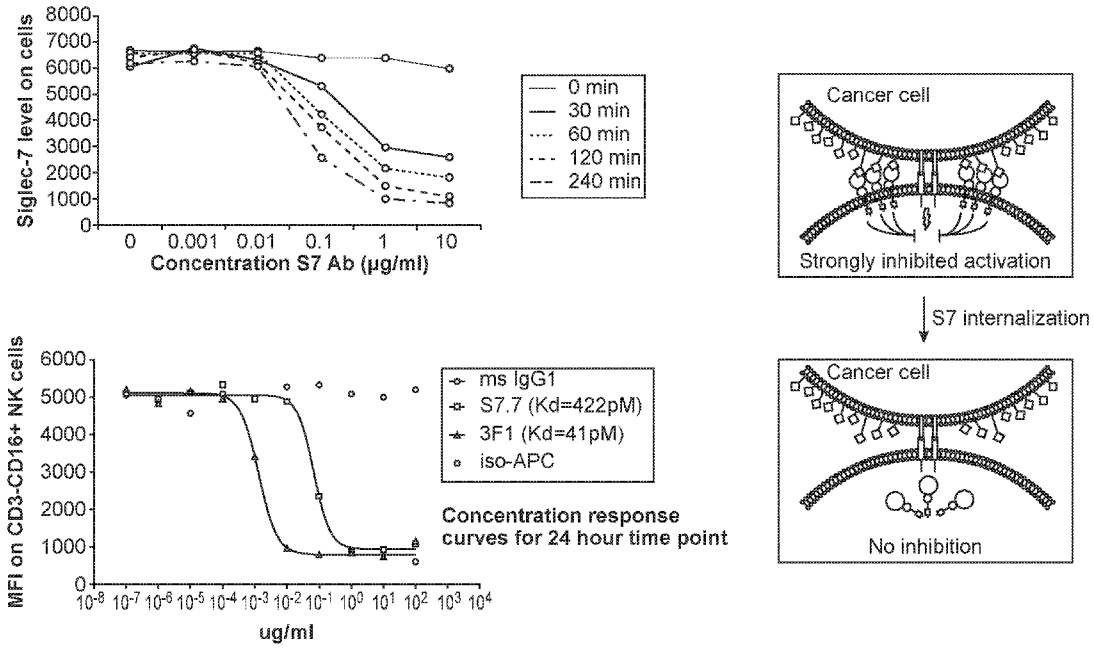

FIG. 10

(57) Abstract: The invention provides methods and compositions for the treatment of cancer using anti-Siglec-7 antibodies that have reduced effector function.

[Continued on next page]

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Declarations under Rule 4.17:

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ANTI-SIGLEC-7 ANTIBODIES HAVING REDUCED EFFECTOR FUNCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of U.S. Provisional Application No. 62/616,317, filed January 11, 2018, which is herein incorporated by referenced for all purposes.

REFERENCE TO A "SEQUENCE LISTING" SUBMITTED AS ASII TEXT FILES

[0002] This application includes a Sequence Listing written as a text file named 101413-1116918-000210PC_SL.txt created on January 11, 2019, containing 99,169 bytes. The material contained in this text file is incorporated by reference in its entirety for all purposes..

BACKGROUND OF THE INVENTION

[0003] Siglec-7, also known as p75 or AIRM, is a member of the sialic acid-binding lectins (Siglec) of the immunoglobulin (Ig) superfamily. Siglec receptors bind glycans containing sialic acid, but differ in their recognition of the linkage regiochemistry and spatial distribution of sialic residues. The members of the family also have distinct expression patterns. High level expression of Siglec-7 has been observed on Natural Killer (NK) cells. Expression has also been observed on a subset CD8+ T cells. Siglec-7 has also been observed to have an inhibitory role on NK cell-mediated tumor clearance (Jandus, *et al., J. Clin. Invest.* 124: 1810-20, 2014); Hudak *et al., Nat. Chem. Biol.* 10:69-77, 2014).

[0004] A broad range of human malignancies overexpress Siglec-7 ligands sialoglycans, including sialocglycans that are the ligands for Siglec-7. Siglec-7 has also been observed to have an inhibitory role on NK cell-mediated tumor clearance (Jandus, *et al., J. Clin. Invest.* 124: 1810-20, 2014).

BRIEF SUMMARY OF ASPECTS OF THE DISCLOSURE

[0005] In one aspect, provided herein are anti-Siglec-7 antibodies that comprise modifications to an Fc region, *e.g.,* a human Fc region, that modulate effector functions and/or antibody stability. In preferred embodiments, the Fc region comprises one or more mutations

that reduce effector function and/or one or more mutations that increase antibody stability. In some embodiments, the Fc region comprises mutations that reduce effector function and increase antibody stability.

[0006] In one aspect, the disclosure thus provides an anti-Siglec-7 antibody that comprises a variant Fc region comprising at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region. In some embodiments, the variant Fc region has at least 80%, at least 85%, at least 90%, or at least 95%, amino acid sequence identity to a native human Fc region. In some embodiments, the variant Fc region comprises at least one amino acid modification, or at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of the group consisting of 232, 233, 234, 235, 236, 237, 238, 242, 252, 254, 256, 259, 267, 268, 287, 292, 297, 302, 306, 309, 322, 323, 327, 328, 329, 330, 331, 332, and 334. In some embodiments, the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328 that reduces effector function. In further embodiments, the variant Fc region comprises at least two amino acid modifications, or at least three modifications, at positions 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, or 328. In some embodiments, the variant Fc region comprises at least one amino acid selected from the group consisting of 234A/V, 235A, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S. In further embodiments, the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from the group consisting of 234A/V/F, 235A/Q, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S. In some embodiments, the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334. In further embodiments, the variant Fc region comprises at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334. In some embodiments, the variant Fc region comprises at least one amino acid selected from the group consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C. In further embodiments, the variant Fc region comprises at least two amino acids, or at least three amino acids selected from the group consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and

334C, In some embodiments, the variant Fc region comprises at least one mutation that reduces effector function, *e.g.,* one or more modifications at positions 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, or 328; and further comprises at least one amino acid selected from the group consisting of 252Y, 254T, 256E, 232S and 233S. In some embodiments, the variant Fc region comprises at least one mutation that reduces effector function, *e.g.,* one or more modifications at positions 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, or 328; and further comprises amino acids 252Y, 254T, and 256E. In some embodiments, the variant Fc region is a human IgG1 region comprising amino acid modifications: (i) L234A and L235A; (ii) A327G, A330S, and P331S; (iii) E233P, L234V, L235A, and G236-; (iv) E233P, L234V, and L235A; (v) E233P, L234V, L235A, G236-, A327G, A330S, and P331S; (vi) E233P, L234V, L235A, A327G, A330S, and P331S; (vii) N297A, N297G, or N297Q; (viii) L242C, N297C, and K334C; (ix) A287C, N297G, and L306C; (x) R292C, N297G, and V302C; (xi) N297G, V323C, and I332C; (xii) V259C, N297G, and L306C; (xiii) L234F, L235Q, K322Q, M252Y, S254T, and T256E; or (xiv) L234A, L235A, and P329G. In some embodiments, the variant Fc region is a human IgG2 region comprising amino acid modifications: (i) A330S and P331S; (ii) V234A, G237A, P238S, H268A, V309L, A330S, and P331S; or (iii) V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, or T256E. In some embodiments, the variant Fc region is a human IgG4 region comprising amino acid modifications: (i) E233P, F234V, L235A, and G236-; (ii) E233P, F234V, and L235A; or (iii) S228P and L235E/A.

[0007] In some embodiments, an anti-Siglec-7 antibody as described herein, *e.g.,* in the preceding two paragraphs, blocks binding of ligand to Siglec-7 and competes with an antibody QA79 produced from the hybridoma deposited under accession number ICLC PD99003 for binding to Siglec-7, but does not compete with antibody Z176 or antibody S7.7 for binding to Siglec-7. In some embodiments, the antibody competes with an antibody comprising the V_H and V_L of 2G12 as designated in Figures 1 and 2 for binding to Siglec-7. In some embodiments, the anti-Siglec-7 antibody has a V_H region that comprises at least one CDR, or at least two CDRs, of a heavy chain variable region sequence of SEQ ID NO:2. In some embodiments, the anti-Siglec-7 antibody has a V_H region that comprises a CDR3 of a heavy chain variable region sequence of SEQ ID NO:2. In some embodiments, the anti-Siglec-7 antibody has a V_H region that comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence of SEQ ID NO:2. In some embodiments, the anti-Siglec-7 antibody has a V_L region that comprises at least one CDR, or at least two CDRs, of a light chain variable region

sequence of SEQ ID NO:16. In some embodiments, the anti-Siglec-7 antibody has a V_L region that comprises a CDR3 of a light chain variable region sequence of SEQ ID NO:16. In some embodiments, the anti-Siglec-7 antibody has a V_L region that comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence of SEQ ID NO:16. In some embodiments, the antibody has six CDRs of antibody 2G12 as designated in Figures 1 and 2.

[0008] In some embodiments, the anti-Siglec-7 antibody as described herein, *e.g.,* in the first two paragraphs of this section, has internalization activity, does not block ligand binding to Siglec-7, and competes with antibody S7.7, but not with antibody QA79 or antibody Z176 for binding to Siglec-7. In some embodiments, the antibody competes with an antibody comprising the V_H and V_L of 8A2 as designated in Figures 1 and 2 for binding to Siglec-7. In some embodiments, the anti-Siglec-7 antibody has a V_H region that comprises at least one CDR, or at least two CDRs, of a heavy chain variable region sequence of SEQ ID NO:4. In some embodiments, the anti-Siglec-7 antibody has a V_H region that comprises a CDR3 of a heavy chain variable region sequence of SEQ ID NO:4. In some embodiments, the anti-Siglec-7 antibody has a V_H region that comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence of SEQ ID NO:4. In some embodiments, the anti-Siglec-7 antibody has a V_L region that comprises at least one CDR, or at least two CDRs, of a light chain variable region sequence of SEQ ID NO:18. In some embodiments, the anti-Siglec-7 antibody has a V_L region that comprises a CDR3 of a light chain variable region sequence of SEQ ID NO:18. In some embodiments, the anti-Siglec-7 antibody has a V_L region that comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence of SEQ ID NO:18. In some embodiments, the anti-Siglec-7 antibody has six CDRs of the antibody designated as 8A2 in Figures 1 and 2.

[0009] In some embodiments, the anti-Siglec-7 antibody as described herein, *e.g.,* in the first two paragraphs of this section, has internalization activity, does not block ligand binding to Siglec-7, and competes with antibody Z176, but not with QA79 or S7.7 for binding to Siglec-7. In some embodiments, the anti-Siglec-7 antibody competes with an antibody comprising the V_H and V_L of the antibody designated as 5D1 for binding to Siglec-7. In some embodiments, the anti-Siglec-7 antibody has a V_H region that comprises at least one CDR, or at least two CDRs, of a heavy chain variable region sequence of SEQ ID NO:3. In some embodiments, the i) L234F, L235Q, K322Q, M252Y,$_H$ region that comprises a CDR3 of a heavy chain variable region sequence of SEQ ID NO:3. In some embodiments, the anti-Siglec-7 antibody has a V_H region that comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence of SEQ

ID NO:3. In some embodiments, the anti-Siglec-7 antibody has a V_L region that comprises at least one CDR, or at least two CDRs, of a light chain variable region sequence of SEQ ID NO:17. In some embodiments, the anti-Siglec-7 antibody has a V_L region that comprises a CDR3 of a light chain variable region sequence of SEQ ID NO:17. In some embodiments, the anti-Siglec-7 antibody has a VL region that comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence of SEQ ID NO:17. In some embodiments, the antibody has six CDRs of the antibody designated as 5D1 in Figures 1 and 2.

[0010] In some embodiments, the anti-Siglec-7 antibody as described herein, *e.g.,* in the first two paragraphs of this section, has internalization activity, does not block ligand binding to Siglec-7, and does not compete with antibody Z176, QA79, or S7.7 for binding to Siglec-7. In some embodiments, the antibody competes with an antibody comprising a V_H and V_L of the antibody designated as 4B12 in Figures 1 and 2 for binding to Siglec-7. In some embodiments, the anti-Siglec-7 antibody has a VH region that comprises at least one CDR, or at least two CDRs, of a heavy chain variable region sequence of SEQ ID NO:11. In some embodiments, the anti-Siglec-7 antibody has a VH region that comprises a CDR3 of a heavy chain variable region sequence of SEQ ID NO:11. In some embodiments, the anti-Siglec-7 antibody has a VH region that comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence of SEQ ID NO:11. In some embodiments, the anti-Siglec-7 antibody has a VL region that comprises at least one CDR, or at least two CDRs, of a light chain variable region sequence of SEQ ID NO:25. In some embodiments, the anti-Siglec-7 antibody has a VL region that comprises a CDR3 of a light chain variable region sequence of SEQ ID NO:25. In some embodiments, the anti-Siglec-7 antibody has a VL region that comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence of SEQ ID NO:25. In some embodiments, the anti-Siglec-7 antibody has six CDRs of the antibody designated as 4B12 in Figures 1 and 2.

[0011] In some embodiments, the anti-Siglec-7 antibody as described herein, *e.g.,* in the first two paragraphs of this section, comprises a V_H region that comprises at least one CDR, or at least two CDRs, of a V_H region sequence set forth in Figure 1; or a V_H region that comprises a CDR1, CDR2, and CDR3 of one of the heavy chain variable region sequences set forth in Figure 1.

[0012] In some embodiments, the anti-Siglec-7 antibody as described herein, *e.g.,* in the first two paragraphs of this section, comprises a V_L region that comprises at least one CDR, or at least two CDRs, of a V_L region sequence set forth in Figure 2; or a V_L region that comprises a

CDR1, CDR2, and CDR3 of one of the light chain variable region sequences set forth in Figure 2.

[0013] In some embodiments, the anti-Siglec-7 antibody as described herein, *e.g.,* in the first two paragraphs of this section, comprise a V_H region that comprises at least one CDR, or at least two CDRs, of a V_H region sequence set forth in Figure 1; and a V_L region that comprises at least one CDR, or at least two CDRs, of a V_L region sequence set forth in Figure 2, where the V_L sequence in Figure 2 has the same antibody designation as the V_H sequence in Figure 1.

[0014] In some embodiments, the anti-Siglec-7 antibody as described herein, *e.g.,* in the first two paragraphs of this section, comprise a V_H region that comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequences set forth in Figure 1; and a V_L region that comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence set forth in Figure 2, where the V_L sequence in Figure 2 has the same antibody designation as the VH sequence in Figure 1.

[0015] In some embodiments, the anti-Siglec-7 antibody as described herein, *e.g.,* in the first two paragraphs of this section, competes with an antibody having a variable heavy chain sequence of SEQ ID NO:1 and a variable light chain sequence of SEQ ID NO:15 for binding to Siglec-7. In some embodiments, the antibody has internalizing activity and does not block ligand binding to Siglec-7. In some embodiments, the antibody comprises a heavy chain variable region comprising a CDR3 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61, in which 1, 2, or 3 amino acids are substituted; or comprises a heavy chain variable region comprising a CDR3 as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61. In some embodiments, the heavy chain variable region comprises a CDR1 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which 1, 2, or 3 amino acids are substituted; and/or a CDR2 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which 1, 2, or 3 amino acids are substituted. In some embodiments, the heavy chain variable region comprises a CDR1 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 and a CDR2 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61. In some embodiments, which can be combined with any of the preceding embodiments in this paragraph, the anti-Siglec-7 antibody comprises a light chain variable region comprising a CDR3 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78 in which 1, 2, or 3 amino acids are substituted; or comprises a light chain variable region comprising a CDR3 as set forth in any one of SEQ ID

NOS:62 and 64-78. In some embodiments, the light chain variable region comprises a CDR1 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78 in which 1, 2, or 3 amino acids are substituted; and/or a CDR2 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78 in which 1, 2, or 3 amino acids are substituted. In some embodiments, the light chain variable region comprises a CDR1 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78 and a CDR2 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78. In some embodiments, the anti-Siglec-7 antibody has ligand blocking activity; and/or has a K_D of less than about 100 pM when measured as a monovalent Fab; and/or has an internalization activity of less than about 100 pM. In some embodiments, the anti-Siglec-7 antibody has a K_D of less than about 75 pM when measured as a monovalent Fab. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of about 70 pM or less. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of less than about 25 pM.

[0016] In another aspect, provided herein is an anti-Siglec-7 antibody, *e.g.*, as described in the first two paragraphs of this section, that comprises a heavy chain variable region having at least 80%, or at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of any one of SEQ ID NOS:29-31, 33, and 35-61; and/or a light chain variable region having at least 80%, or at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a light chain variable region of any one of SEQ ID NOS:62 and 64-78. In some embodiments, the anti-Siglec-7 antibody comprises a heavy chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of any of SEQ ID NOS:41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, 58, 59, 60 or 61; and a light chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a light chain variable region of SEQ ID NO:69, 70, 71, 72, 73, 74, 75, 76, 77, or 78. In some embodiments, the anti-Siglec-7 antibody has ligand blocking activity; and/or has a K_D of less than about 100 pM when measured as a monovalent Fab; and/or has an internalization activity of less than about 100 pM. In some embodiments, the anti-Siglec-7 antibody has a K_D of less than about 75 pM when measured as a monovalent Fab. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of about 70 pM or less. In some

embodiments, the anti-Siglec-7 antibody has an internalization activity of less than about 25 pM.

[0017] In a further aspect, provided herein is an anti-Siglec-7 antibody, *e.g.,* as described in the first two paragraphs of this section, that comprises a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in a heavy chain variable region sequence selected from SEQ ID NO:43, 45, 46, 47, 48, 49, 50, 51, 54, 55, 57, and 58; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO:69. Additionally provided herein is an anti-Siglec-7 antibody that comprises a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in a heavy chain variable region sequence selected from SEQ ID NO:53, 54, 51, 55, 58, and 59; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO:78. In some embodiments, the anti-Siglec-7 antibody has ligand blocking activity; and/or has a K_D of less than about 100 pM when measured as a monovalent Fab; and/or has an internalization activity of less than about 100 pM. In some embodiments, the anti-Siglec-7 antibody has a K_D of less than about 75 pM when measured as a monovalent Fab. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of about 70 pM or less. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of less than about 25 pM.

[0018] In a further aspect, provided herein is an anti-Siglec-7 antibody, *e.g.,* as described in the first two paragraphs of this section, that comprises:

a) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:43, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(b) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:45, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(c) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:46, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(d) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:47, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(e) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:48, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(f) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:49, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(g) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:50, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(h) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:51, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(i) CDR1, CDR2, and CDR3 sequences as set forth in a heavy chain variable region sequence SEQ ID NO:54, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(j) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:55, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(k) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:57, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69; or

(l) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:58, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69. In some embodiments, the anti-Siglec-7 antibody has ligand blocking activity; and/or has a K_D of less than about 100 pM when measured as a monovalent Fab; and/or has an internalization activity of less than about 100 pM. In some embodiments, the anti-Siglec-7 antibody has a K_D of less than about 75 pM when measured as a monovalent Fab. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of about 70 pM or less. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of less than about 25 pM.

[0019] In an additional aspect, provided herein is an anti-Siglec-7 antibody, *e.g.,* as described in the first two paragraphs of this section, that comprises:

a) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:53; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(b) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:54; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(c) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:51; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(d) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:55; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(e) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:58; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78; or

(f) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:59; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78. In some embodiments, the anti-Siglec-7 antibody has ligand blocking activity; and/or has a K_D of less than about 100 pM when measured as a monovalent Fab; and/or has an internalization activity of less than about 100 pM. In some embodiments, the anti-Siglec-7 antibody has a K_D of less than about 75 pM when measured as a monovalent Fab. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of about 70 pM or less. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of less than about 25 pM.

[0020] In a further aspect, provided herein is an anti-Siglec-7 antibody, *e.g.,* as described in the first two paragraphs of this section, that comprises:

a) a heavy chain variable region comprising the amino acid sequence SEQ ID NO:43 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:45 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:46 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:47 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;
(e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:48 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;
(f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:49 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;
(g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:50 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;
(h) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;
(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:54 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;
(j) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:55 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;
(k) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:57 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69; or
(l) a heavy chain variable comprising the amino acid sequence of SEQ ID NO:58 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69. In some embodiments, the anti-Siglec-7 antibody has ligand blocking activity; and/or has a K_D of less than about 100 pM when measured as a monovalent Fab; and/or has an internalization activity of less than about 100 pM. In some embodiments, the anti-Siglec-7 antibody has a K_D of less than about 75 pM when measured as a monovalent Fab. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of about 70 pM or less. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of less than about 25 pM.

[0021] In an additional aspect, provided herein is an anti-Siglec-7 antibody, *e.g.*, as described in the first two paragraphs of this section, that comprises:
a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78;
(b) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:54 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78;
(c) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78;

(d) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:55 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78;
(e) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:58 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78; or
(f) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:59 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78. In some embodiments, the anti-Siglec-7 antibody has ligand blocking activity; and/or has a K_D of less than about 100 pM when measured as a monovalent Fab; and/or has an internalization activity of less than about 100 pM. In some embodiments, the anti-Siglec-7 antibody has a K_D of less than about 75 pM when measured as a monovalent Fab. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of about 70 pM or less. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of less than about 25 pM.

[0022] In some embodiments, the anti-Siglec-7 antibody of the disclosure as described in the foregoing paragraphs is a multivalent form or bivalent form. In some embodiments, the antibody is an IgG, such as an IgG1, IgG2, IgG3, or IgG4.

[0023] In a further aspect, the invention provides a bispecific or multi-specific antibody that comprises an antibody of any one of the foregoing embodiments.

[0024] In one aspect, the disclosure provides a method of inhibiting proliferation of tumor cells, the method comprising administering a therapeutically effective amount of an anti-Siglec-7 antibody as described herein, *e.g.,* in the preceding paragraphs in this section, to a patient that has cancer, wherein the patient has a primary tumor or metastatic lesion that comprises an elevated level of CD8+ infiltrating-T cells that express Siglec-7, and further, wherein the tumor or metastatic lesion comprises cancer cells that express sialylated Siglec-7 ligands. In some embodiments, the anti-Siglec-7 antibody has a K_D of 50 pM or less. In some embodiments, the anti-Siglec-7 antibody blocks ligand binding at an IC_{50} of less than about 4000 pM, or blocks ligand binding at an IC_{50} of less than about 3500 pM, and optionally may have a K_D of 50 pM or less. In some embodiments, which may be combined with the foregoing embodiments, the anti-Siglec-7 antibody has an internalization activity of less than about 70 pM or than about 25 pM. In some embodiments, the anti-Siglec-7 antibody has an internalization activity of less than about 70 pM or than about 25 pM; and does not block ligand binding.

[0025] In an additional aspect, the invention provides a method of inhibiting proliferation of tumor cells, the method comprising administering a therapeutically effective amount of an antibody of any of the antibodies described in the foregoing paragraphs, or a bispecific or multi-specific antibody comprising such an antibody, to a patient that has a tumor that expresses sialylated Siglec-7 ligands. In some embodiments, the tumor expresses sialylated Siglec-7 ligands in an amount above that which is detected in normal cells of the corresponding cell type.

[0026] In a further aspect, the disclosure further provides use of an anti-Siglec-7 antibody as described herein in a method of treating a cancer as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] Figure 1 provides illustrative heavy chain variable region sequences of anti-Siglec-7 antibodies of the invention. The CDRs as defined by Kabat are underlined.

[0028] Figure 2 provides illustrative heavy chain variable region sequences of anti-Siglec-7 antibodies of the invention. The CDRs as defined by Chothia are underlined.

[0029] Figure 3 provides illustrative light chain variable region sequences of anti-Siglec-7 antibodies of the invention. The CDRs as defined by both Kabat and Chothia are underlined.

[0030] Figure 4 provides illustrative data showing that Siglec-7 is detected on a high percentage of tumor-infiltrating CD8+ cells in fresh primary tumors.

[0031] Figure 5 provides data illustrating that CD8+ T cells isolated from subsets of tumors have a high level of Siglec-7.

[0032] Figure 6 data illustrating that Siglec-7 ligands are expressed on subsets of tumors.

[0033] Figure 7 provides data showing anti-Siglec-7 antibodies of the present disclosure that have improved K_D values compared to antibodies Z176, S7.7, or QA79.

[0034] Figure 8 provides data showing anti-Siglec-7 antibodies of the present disclosure that have improved ligand blocking activity compared to antibodies Z176, S7.7, or QA79.

[0035] Figure 9 provides data showing anti-Siglec-7 antibodies of the present disclosure that have improved internalization activity compared to antibodies Z176, S7.7, or QA79.

[0036] Figure 10 provides data illustrating rapid concentration-dependent, antibody-induced internalization of Siglec-7 on human NK cells using an antibody of the present disclosure.

[0037] Figure 11 provides data illustrating non-ligand blocking, internalization activity of an antibody of the present disclosure.

DETAILED DESCRIPTION OF ASPECTS FO THE DISCLOSURE

Terminology

[0038] As used in herein, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "an antibody" optionally includes a combination of two or more such molecules, and the like.

[0039] 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, for example ± 20%, ± 10%, or ± 5%, are within the intended meaning of the recited value.

[0040] Siglec-7, also known as p75 or AIRM, is a member of the sialic acid-binding lectins (Siglec) of the immunoglobulin (Ig) superfamily. Siglec receptors bind glycans containing sialic acid, but differ in their recognition of specific carbohydrate structures. A human Siglec-7 protein sequence available under accession number NP_055200.1 is

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        1 mlllllllpll wgrervegqk snrkdysltm qssvtvqegm cvhvrcsfsy pvdsqtdsdp
       61 vhgywfragn diswkapvat nnpawavqee trdrfhllgd pqtknctlsi rdarmsdagr
      121 yffrmekgni kwnykydqls vnvtalthrp nilipgtles gcfqnltcsv pwaceqgtpp
      181 miswmgtsvs plhpsttrss vltlipqpqh hgtsltcqvt lpgagvttnr tiqlnvsypp
      241 qnltvtvfqg egtastalgn ssslsvlegq slrlvcavds npparlswtw rsltlypsqp
      301 snplvlelqv hlgdegeftc raqnslgsqh vslnlslqqe ytgkmrpvsg vllgavggag
      361 atalvflsfc vifivvrscr kksarpaadv gdigmkdant irgsasqgnl teswaddnpr
      421 hhglaahssg eereiqyapl sfhkgepqdl sgqeatnney seikipk (SEQ ID
NO:108).
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[0041] The term "antibody" is used herein in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies, such as bispecific antibodies, and antibody fragments so long as they exhibit the desired antigen-binding activity.

[0042] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, *e.g.,* containing naturally occurring mutations or arising during production of a

monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, 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 invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci.

[0043] An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody and that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, $F(ab')_2$; diabodies; linear antibodies; single-chain antibody molecules, such as scFv molecules; and multispecific antibodies formed from antibody fragments.

[0044] An "antibody that binds to the same epitope" as a reference antibody refers to an antibody that blocks binding of the reference antibody to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. An exemplary competition assay is provided herein.

[0045] As used herein, "V-region" refers to an antibody variable region domain comprising the segments of Framework 1, CDR1, Framework 2, CDR2, and Framework 3, including CDR3 and Framework 4, which segments are added to the V-segment as a consequence of rearrangement of the heavy chain and light chain V-region genes during B-cell differentiation.

[0046] As used herein, "complementarity-determining region (CDR)" refers to the three hypervariable regions (HVRs) in each chain that interrupt the four "framework" regions established by the light and heavy chain variable regions. The CDRs are the primary contributors to binding to an epitope of an antigen. The CDRs of each chain are referred to as CDR1, CDR2, and CDR3, numbered sequentially starting from the N-terminus, and are also identified by the chain in which the particular CDR is located. Thus, a VH CDR3 is located in the variable domain of the heavy chain of the antibody in which it is found, whereas a VL

CDR1 is the CDR1 from the variable domain of the light chain of the antibody in which it is found. The term "CDR" may be used interchangeably with "HVR".

[0047] The amino acid sequences of the CDRs and framework regions can be determined using various well known definitions in the art, e.g., Kabat, Chothia, international ImMunoGeneTics database (IMGT), and AbM (see, e.g., Johnson et al., supra; Chothia & Lesk, 1987, Canonical structures for the hypervariable regions of immunoglobulins. J. Mol. Biol. 196, 901-917; Chothia C. et al., 1989, Conformations of immunoglobulin hypervariable regions. Nature 342, 877-883; Chothia C. et al., 1992, structural repertoire of the human VH segments J. Mol. Biol. 227, 799-817; Al-Lazikani et al., J.Mol.Biol 1997, 273(4)). Definitions of antigen combining sites are also described in the following: Ruiz et al., IMGT, the international ImMunoGeneTics database. Nucleic Acids Res., 28, 219–221 (2000); and Lefranc,M.-P. IMGT, the international ImMunoGeneTics database. Nucleic Acids Res. Jan 1;29(1):207-9 (2001); MacCallum et al, Antibody-antigen interactions: Contact analysis and binding site topography, J. Mol. Biol., 262 (5), 732-745 (1996); and Martin et al, Proc. Natl Acad. Sci. USA, 86, 9268–9272 (1989); Martin, et al, Methods Enzymol., 203, 121–153, (1991); Pedersen et al, Immunomethods, 1, 126, (1992); and Rees et al, In Sternberg M.J.E. (ed.), Protein Structure Prediction. Oxford University Press, Oxford, 141–172 1996). Reference to CDRs as determined by Kabat numbering are based, for example, on Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institute of Health, Bethesda, MD (1991)). Chothia CDRs are determined as defined by Chothia (see, *e.g.*,Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)).

[0048] "Epitope" or "antigenic determinant" refers to a site on an antigen to which an antibody binds. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, e.g., Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66, Glenn E. Morris, Ed (1996).

[0049] As used herein, "chimeric antibody" refers to an immunoglobulin molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the

antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region, or portion thereof, having a different or altered antigen specificity; or with corresponding sequences from another species or from another antibody class or subclass.

[0050] An "Fc region" refers to the constant region of an antibody excluding the first constant region immunoglobulin domain. Thus, Fc refers to the last two constant region immunoglobulin domains of IgA, IgD, and IgG, and the last three constant region immunoglobulin domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM Fc may include the J chain. For IgG, Fc comprises immunoglobulin domains Cγ2 and Cγ3 and the hinge between Cγ1 and Cγ. It is understood in the art that the boundaries of the Fc region may vary, however, the human IgG heavy chain Fc region is usually defined to comprise residues C226 or P230 to its carboxyl-terminus. The C-terminal lysine (K447) of the Fc region may or may not be present. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991. The term "Fc region" may refer to this region in isolation or this region in the context of an antibody or antibody fragment. "Fc region " includes naturally occurring allelic variants of the Fc region, also referred to as a native Fc region, as well as modifications that modulate effector function. Fc regions also include variants that do not result in alterations to biological function. For example, one or more amino acids can be deleted from the N-terminus or C-terminus of the Fc region of an immunoglobulin without substantial loss of biological function. Such variants can be selected according to general rules known in the art so as to have minimal effect on activity (see, *e.g.*, Bowie, *et al.*, *Science* 247:306-1310, 1990). For example, for IgG4 antibodies, a single amino acid substitution (S228P according to Kabat numbering; designated IgG4Pro) may be introduced to abolish the heterogeneity observed in recombinant IgG4 antibody (see, *e.g.*, Angal, *et al.*, *Mol Immunol* 30:105-108, 1993).

[0051] A "variant Fc region" comprises an amino acid sequence which differs from that of a native sequence Fc region by at least one amino acid modification, such as one or more amino acid substitution(s) or deletion.

[0052] An antibody having "reduced" effector function" a used herein refers to an antibody that has an overall decrease, for example, of 20% or greater, of 50% or greater, or of 75%, 85%, 90%, 95%, or greater, of an effector function that is mediate by the antibody Fc region, including, *e.g.,* complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP).

[0053] The term "equilibrium dissociation constant" abbreviated (K_D), refers to the dissociation rate constant (k_d, $time^{-1}$) divided by the association rate constant (k_a, $time^{-1}$ M^{-1}). Equilibrium dissociation constants can be measured using any method. Thus, in some embodiments antibodies of the present disclosure have a K_D of less than about 50 nM, typically less than about 25 nM, or less than 10 nM, *e.g.,* less than about 5 nM or than about 1 nM and often less than about 10 nM as determined by surface plasmon resonance analysis using a biosensor system such as a Biacore® system performed at 37°C. In some embodiments, an antibody of the present disclosure has a K_D of less than 5 x 10^{-5} M, less than 10^{-5} M, less than 5 x 10^{-6} M, less than 10^{-6} M, less than 5 x 10^{-7} M, less than 10^{-7} M, less than 5 x 10^{-8} M, less than 10^{-8} M, less than 5 x 10^{-9} M, less than 10^{-9} M, less than 5 x10^{-10} M, less than 10^{-10} M, less than 5 x 10^{-11} M, less than 10^{-11} M, less than 5 x 10^{-12} M, less than 10^{-12} M, less than 5 x 10^{-13} M, less than 10^{-13} M, less than 5 x 10^{-14} M, less than 10^{-14} M, less than 5 x 10^{-15} M, or less than 10^{-15} M or lower as measured as a bivalent antibody. In the context of the present invention, an "improved" K_D refers to a lower K_D. In some embodiments, an antibody of the present disclosure has a K_D of less than 5 x 10^{-5} M, less than 10^{-5} M, less than 5 x 10^{-6} M, less than 10^{-6} M, less than 5 x 10^{-7} M, less than 10^{-7} M, less than 5 x 10^{-8} M, less than 10^{-8} M, less than 5 x 10^{-9} M, less than 10^{-9} M, less than 5 x10^{-10} M, less than 10^{-10} M, less than 5 x 10^{-11} M, less than 10^{-11} M, less than 5 x 10^{-12} M, less than 10^{-12} M, less than 5 x 10^{-13} M, less than 10^{-13} M, less than 5 x 10^{-14} M, less than 10^{-14} M, less than 5 x 10^{-15} M, or less than 10^{-15} M or lower as measured as a monovalent antibody, typically a monovalent Fab. In some embodiments, an anti-Siglec-7 antibody of the present disclosure has K_D less than 100 pM, *e.g.,* or less than 75 pM, *e.g.,* in the range of 1 to 100 pM, when measured as a monovalent Fab by surface plasmon resonance analysis using a biosensor system such as a Biacore® system performed at 37°C. In some embodiments, an anti-Siglec-7 antibody of the present disclosure has K_D less than 500 pM, *e.g.,* in the range of 1 to 500 pM, or 1 to 200, or 1 to 250 pM, when measured as a monovalent Fab by surface plasmon resonance analysis using a biosensor system such as a Biacore® system performed at 37°C. In the context of the present invention, an "improved" K_D refers to a lower K_D.

[0054] The term "monovalent molecule" as used herein refers to a molecule that has one antigen-binding site, *e.g.,* a Fab.

[0055] The term "bivalent molecule" as used herein refers to a molecule that has two antigen-binding sites. In some embodiments, a bivalent molecule of the present invention is a bivalent antibody or a bivalent fragment thereof. In some embodiments, a bivalent molecule of the present invention is a bivalent antibody. In some embodiments, a bivalent molecule of the present invention is an IgG. In general monoclonal antibodies have a bivalent basic structure. IgG and IgE have only one bivalent unit, while IgA and IgM consist of multiple bivalent units (2 and 5, respectively) and thus have higher valencies. This bivalency increases the avidity of antibodies for antigens.

[0056] The terms "monovalent binding" or "monovalently binds to" as used herein refer to the binding of one antigen-binding site to its antigen.

[0057] The terms "bivalent binding" or "bivalently binds to" as used herein refer to the binding of both antigen-binding sites of a bivalent molecule to its antigen. Preferably both antigen-binding sites of a bivalent molecule share the same antigen specificity.

[0058] The term "valency" as used herein refers to the number of different binding sites of an antibody for an antigen. A monovalent antibody comprises one binding site for an antigen. A bivalent antibody comprises two binding sites for the same antigen.

[0059] The term “avidity” as used herein in the context of antibody binding to an antigen refers to the combined binding strength of multiple binding sites of the antibody. Thus, “bivalent avidity” refers to the combined strength of two binding sites.

[0060] The phrase “specifically (or selectively) binds” to an antigen or target or “specifically (or selectively) immunoreactive with,” when referring to a protein or peptide, refers to a binding reaction whereby the antibody binds to the antigen or target of interest. In the context of this invention, the antibody binds to SIGLEC-7 with a K_D that is at least 100-fold greater than its affinity for other antigens.

[0061] The terms “identical” or percent “identity,” in the context of two or more polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues that are the same (e.g., at least 70%, at least 75%, at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher)

identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region. Alignment for purposes of determining percent amino acid sequence identity can be performed in various methods, including those using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Examples of algorithms that are suitable for determining percent sequence identity and sequence similarity the BLAST 2.0 algorithms, which are described in Altschul et al., Nuc. Acids Res. 25:3389-3402 (1977) and Altschul et al., J. Mol. Biol. 215:403-410 (1990). Thus, BLAST 2.0 can be used with the default parameters described to determine percent sequence.

[0062] A "conservative" substitution as used herein refers to a substitution of an amino acid such that charge, hydrophobicity, and/or size of the side group chain is maintained. Illustrative sets of amino acids that may be substituted for one another include (i) positively-charged amino acids Lys, Arg and His; (ii) negatively charged amino acids Glu and Asp; (iii) aromatic amino acids Phe, Tyr and Trp; (iv) nitrogen ring amino acids His and Trp; (v) large aliphatic nonpolar amino acids Val, Leu and Ile; (vi) slightly polar amino acids Met and Cys; (vii) small-side chain amino acids Ser, Thr, Asp, Asn, Gly, Ala, Glu, Gln and Pro; (viii) aliphatic amino acids Val, Leu, Ile, Met and Cys; and (ix) small hydroxyl amino acids Ser and Thr. Reference to the charge of an amino acid in this paragraph refers to the charge at physiological pH.

Anti-Siglec-7 antibodies

[0063] Anti-Siglec-7 antibodies of the present invention have improved binding characteristics compared to known anti-Siglec 7 antibodies, such as improved internalization activity and/or improved ligand-blocking activity. Further, an anti-Siglec-7 antibody of the present invention, comprise a variant Fc region, *e.g.,* a human Fc region, that has reduced effector function compared to the counterpart wildtype Fc region. In some embodiments, an antibody of the invention has internalizing activity, but does not block ligand binding.

[0064] An anti-Siglec-7 antibody of the invention typically has a lower K_D when compared to known anti-Siglec 7 monoclonal antibodies such as Z176, QA79, and S7.7. In some embodiments, an antibody of the invention has a K_D of less than about 100 pM, or less than about 75 pM, or less than about 50 pM, or less than about 40 pM or less than about 35 pM. In some embodiments, an antibody of the invention has a K_D of about 1 pM or less. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_H

sequence of the antibody designated as 16H11, 3F1, SL9, 8A2, 5D1, or 5G10 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention that has an improved K_D has at least one, at least two, or three CDRs of a V_L sequence of the antibody designated as 16H11, 3F1, SL9, 8A2, 5D1, or 5G10 in Figure 3. In embodiments has six CDRs of an antibody designated as 16H11, 3F1, SL9, 8A2, 5D1, or 5G10 in Figures 1-3.

[0065] In some embodiments, has an enhanced ability to block ligand binding compared to previously characterized anti-Siglec 7 monoclonal antibodies. In the context of the present invention, the ability to block ligand binding refers to the concentration of monoclonal antibody at which 50% of Siglec-7 does not bind ligand. In some embodiments, an antibody of the invention is more potent in ligand-blocking activity, i.e., the IC_{50} for an antibody for ligand blocking, is lower than that of a known antibody, such as such as Z176, QA79, and S7. Ligand blocking activity can be assessed using known assays. For example, ligand blocking activity may be determined using a cell line, such as the human melanoma cell line A375, that expresses high levels of ligands for Siglec-7 on the cell surface. IC_{50} values for blocking can be determined, for example, as explained in the examples section. In some embodiments, an antibody of the invention that has improved ligand blocking activity has an IC50 of less than 4000 pM, or less than about 3500 pM or less than about 3000 pM or less than about 2000 pM or less than about 1500 pM or less than about 1000 pM or about 500 pM or less when assayed under the assay conditions described in the Examples section. I n some embodiments, an antibody of the invention that exhibits improved ligand blocking activity has at least one, at least two, or three CDRs of a V_H sequence of the antibody designated as 9D4, SL13, or 5G10 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence of the antibody designated as 9D4, SL13, or 5G10 in Figure 3. In embodiments has six CDRs of an antibody designated as 9D4, SL13, or 5G10 in Figures 1-3.

[0066] In some embodiments, an anti-Siglec-7 antibody of the present invention exhibits improved internalization compared to previously characterized anti-Siglec-7 monoclonal antibodies. In the present disclosure, internalization activity refers to the concentration of antibody at which 50% of Siglec-7 is internalized in 24 hours on healthy donor Natural Killer (NK) cells. In the context of the present invention, an "enhanced" or "improved" internalization activity means that the IC_{50} for internalization is lower than that of a known antibody, such as such as Z176, QA79, and S7. Internalization can be assessed using known

assays. For example, PBMC obtained from healthy donors may be used to determine internalization activity of anti-Siglec-7 antibodies. IC_{50} values for internalization can be determined, for example, as described in the Examples section. In some embodiments, an antibody of the invention has an internalizing IC50 of less than about 70 pM, In some embodiments, an antibody has an internalizing IC50 of less than about 60 pM, or less than about 50 pM, or less than about 40 pM, or less than about 30 pM, or less than about 25 pM, or less than about 20, or less than about 10 pM when assayed under the assay conditions described in the Examples section. In some embodiments, an antibody of the invention having an improved internalization activity has at least one, at least two, or three CDRs of a V_H sequence of the antibody designated as 3F1, SL9, 16H11, 8A2, SL2, 5D1, or 10E11 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence of the antibody designated as 3F1, SL9, 16H11, 8A2, SL2, 5D1, or 10E11 in Figure 3. In embodiments has six CDRs of an antibody designated as 3F1, SL9, 16H11, 8A2, SL2, 5D1, or 10E11 in Figures 1-3. In some embodiments, an antibody of the invention having an improved internalization activity has at least one, at least two, or three CDRs of a V_H sequence of the antibody designated as 3F1 or 16H11 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence of the antibody designated as 3F1 or 16H11 in Figure 3. In embodiments has six CDRs of an antibody designated as 9D4, SL13, or 5G10 in Figures 1-3.

[0067] In some embodiments, an anti-Siglec 7 antibody of the present invention, internalizes Siglec-7, but does not block binding of the Siglec-7 ligand to Siglec-7. In the context of the present invention, an antibody that does not block binding of ligand to Siglec-7 refers to an antibody that does not result in more than a 25% reduction in ligand binding when assayed under conditions as explained in the Examples section. In some embodiments, an antibody of the invention that internalizes Siglec-7 ligand, but does not block ligand binding to Siglec-7 has at least one, at least two, or three CDRs of a V_H sequence of the antibody designated as 4B12 or 8A2 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention has at least one, at least two, three CDRs of a V_L sequence of the antibody designated as 4B12 or 8A2 in Figure 3. In embodiments has six CDRs of an antibody designated as 4B12 or 8A2 in Figures 1-3.

[0068] In some embodiments, an anti-Siglec 7 antibody of the present invention binds to distinct epitopes relative to described anti-Siglec-7 antibodies such as such as Z176, QA79,

and S7. Z176, and S7.7 are commercially available anti-Siglec-7 antibodies. QA79 is commercially available from eBiosciences. The hybridoma that produces QA79 is also available under ICLC accession number PD99003. Z176 is available from Beckman Coulter and S7.7 is available from BioLegend.

[0069] In some embodiments an antibody of the present invention does not compete with any of Z176, QA79, and S7 for binding to Siglec-7 ligand. In some embodiments, an antibody of the present invention competes with an antibody designated as 4B12 in Figures 1-3 for binding to Siglec-7. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_H sequence of the antibody designated as 4B12 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence of the antibody designated as 4B12 in Figure 3. In embodiments has six CDRs of an antibody designated as 4B12 in Figures 1-3.

[0070] In some embodiments, an anti-Siglec-7 antibody of the present invention that binds to an epitope comprising W132 such that a W132A mutation compromises binding activity. In some embodiments, such an antibody competes with an antibody designated as 2G12 in Figures 1-3 for binding to Siglec-7. In some embodiments, such an antibody competes with an antibody designated as 2G12 in Figures 1-3 for binding to Siglec-7 ligand. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_H sequence of the antibody designated as 2G121 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence of the antibody designated as 2G12 in Figure 3. In embodiments has six CDRs of an antibody designated as 2G12 in Figures 1-3.

[0071] In some embodiments, an anti-Siglec-7 antibody of the present invention competes with an antibody designated as 5D1 in Figures 1-3 for binding to Siglec-7. In some embodiments, such an antibody competes with an antibody designated as 2G12 in Figures 1-3 for binding to Siglec-7 ligand. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_H sequence of the antibody designated as 5D1 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence of the antibody designated as 5D1 in Figure 3. In embodiments has six CDRs of an antibody designated as 5D1 in Figures 1-3.

[0072] In some embodiments, an anti-Siglec-7 antibody of the present invention competes with an antibody designated as 8A2 in Figures 1-3 for binding to Siglec-7 . In some

embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_H sequence of the antibody designated as 8A2 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence of the antibody designated as 8A2 in Figure 3. In embodiments has six CDRs of an antibody designated as 8A2 in Figures 1-3.

[0073] In some embodiments, an anti-Siglec-7 antibody of the invention comprises at least one, two, or three CDRs selected from a heavy chain variable amino acid sequence set forth in Figure 1 or Figure 2. In some embodiments, an anti-Siglec-7 antibody of the invention comprise one, two, or three CDRs selected from a light chain variable region set forth in Figure 3. In some embodiments, an anti-Siglec-7 antibody comprises an HCDR3 selected from the HCDR3 sequence presented in Figure 1 and an LCDR3 selected from the LCDR3 sequences presented in Figure 3.

[0074] In some embodiments, an anti-Siglec-7 antibody of the present invention competes with an antibody designated as 16H11 in Figures 1-3 for binding to Siglec-7. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_H sequence of the antibody designated as 8A2 in Figure 1 or Figure 2. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence of the antibody designated as 8A2 in Figure 3. In embodiments has six CDRs of an antibody designated as 8A2 in Figures 1-3.

[0075] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a heavy chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of Figure 1. In certain embodiments, a V_H sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence of a heavy chain variable region of Figure 1 or Figure 2 contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-Siglec-7 antibody comprising that sequence retains the ability to bind to Siglec-7. In certain embodiments, a total of 1 to 20 amino acids have been substituted, inserted and/or deleted in the amino acid sequence of a heavy chain variable region of Figure 1. In certain embodiments, the substitutions, insertions, or deletions occur in the framework regions.

[0076] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a light chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,

97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a light chain variable region of Figure 3. In certain embodiments, a V_L sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence of a light chain variable region of Figure 3 contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-Siglec-7 antibody comprising that sequence retains the ability to bind to Siglec-7. In certain embodiments, a total of 1 to 20 amino acids have been substituted, inserted and/or deleted in the amino acid sequence of a light chain variable region of Figure 3. In certain embodiments, the substitutions, insertions, or deletions occur in the framework regions.

[0077] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a heavy chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of Figure 1 or Figure 2; and a light chain variable region of the corresponding antibody of Figure 3, where the light chain variable region has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of the light chain variable region of Figure 3. In some embodiments, the anti-Siglec-7 antibody has a modification to the heavy chain variable region and/or the light chain variable region as described in the preceding two paragraphs.

[0078] In some embodiments, an anti-Siglec-7 antibody comprises a heavy chain variable region that comprises a CDR3 as set forth in Figure 1 in which 1, 2, or 3 amino acids are substituted, *e.g.,* conservatively substituted. In some embodiments, a heavy chain variable region comprises three CDRs of a variable region sequence set forth in Figure 1 in which the CDR1 has 1, 2, or 3 amino acid substitutions and/or the CDR2 has at least 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some embodiments, a heavy chain variable region comprises three CDRs of a variable region sequence set forth in Figure 2 in which the CDR1 has 1, 2, 3, or 4 amino acid substitutions and/or the CDR2 has at least 1, 2, or 3 amino acid substitutions.

[0079] In some embodiments, an anti-Siglec-7 antibody comprises a heavy chain variable region that comprises a CDR3 as set forth in Figure 2 in which 1, 2, or 3 amino acids are substituted, *e.g.,* conservatively substituted. In some embodiments, such a heavy chain variable region comprises three CDRs of a variable region sequence set forth in Figure 2 in which the CDR1 has 1, 2, or 3 amino acid substitutions and/or the CDR2 has at least 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; or comprises three CDRs of a variable region sequence

set forth in Figure 2 in which the CDR1 has 1, 2, 3, or 4 amino acid substitutions and/or the CDR2 has at least 1, 2, or 3 amino acid substitutions.

[0080] In some embodiments, an anti-Siglec-7 antibody comprises a light chain variable region comprising a CDR3 as set forth in Figure 3 in which 1, 2, or 3 amino acids are substituted, *e.g.,* conservatively substituted. In some embodiments, a light chain variable region comprises three CDRs of a variable region sequence set forth in Figure 3 in which the CDR1 and/or the CDR2 have at least 1, 2, 3, or 4 amino acid substitutions.

[0081] In some embodiments, an anti-Siglec-7 antibody of the present invention internalizes Siglec-7 and competes with an antibody designated as 16H11 in Figures 1-3 for binding to Siglec-7. In some embodiments, an anti-Siglec-7 antibody of the present invention internalizes Siglec-7 and competes with an antibody designated as 16H11 in Figures 1-3 for binding to Siglec-7 ligand. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_H sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61. In some embodiments, an antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence as set forth in any one of SEQ ID NOS:62 and 64-78. In some embodiments, an anti-Siglec-7 antibody comprises an HCDR3 selected from the HCDR3 sequences as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 and an LCDR3 selected from the LCDR3 sequences as set forth in any one of SEQ ID NOS:62 and 64-78. In embodiments has six CDRs as set forth in any one of the VH-VL region pairs set forth in Table 1.

[0082] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a heavy chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of any one of SEQ ID NOS:29-31, 33, and 35-61. In certain embodiments, a V_H sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence of a heavy chain variable region of any one of SEQ ID NOS:29-31, 33, and 35-61 contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-Siglec-7 antibody comprising that sequence retains the ability to bind to Siglec-7. In certain embodiments, a total of 1 to 20 amino acids have been substituted, inserted and/or deleted in the amino acid sequence of a heavy chain variable region of any one of SEQ ID NOS:29-31, 33, and 35-61.

In certain embodiments, all of the substitutions, insertions, or deletions occur in the framework regions. In certain embodiments, 1, 2, or 3 substitutions occur in a CDR region.

[0083] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a light chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a light chain variable region of any one of SEQ ID NOS:62 and 64-78. In certain embodiments, a V_L sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence of a light chain variable region of any one of SEQ ID NOS:62 and 64-78 contains substitutions (e.g., conservative substitutions), insertions, or nt Fc region comprises at least one amino acid modificatioSiglec-7 antibody comprising that sequence retains the ability to bind to Siglec-7. In certain embodiments, a total of 1 to 20 amino acids have been substituted, inserted and/or deleted in the amino acid sequence of a light chain variable region of any one of SEQ ID NOS:62 and 64-78. In certain embodiments, all of the substitutions, insertions, or deletions occur in the framework regions. In certain embodiments, 1, 2, or 3 substitutions occur in a CDR region.

[0084] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a heavy chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of any of SEQ ID NOS:41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, 58, 59, 60 or 61; and a light chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a light chain variable region of SEQ ID NO:69, 70, 71, 72, 73, 74, 75, 76, 77, or 78. In some embodiments, the anti-Siglec-7 antibody has a modification to the heavy chain variable region and/or the light chain variable region as described in the preceding two paragraphs.

[0085] In some embodiments, an anti-Siglec-7 antibody comprises a heavy chain variable region that comprises a CDR3 as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which 1, 2, or 3 amino acids are substituted, *e.g.,* conservatively substituted; or 1 or 2 amino acids are substituted, *e.g.,* conservatively substituted. In some embodiments, a heavy chain variable region comprises a CDR3 as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which one amino acid is substituted, *e.g.,* conservatively substituted. In some embodiments, a heavy chain variable region comprises three CDRs of a variable region

sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which the CDR1 has 1, 2, or 3 amino acid substitutions, *e.g.,* conservative substitutions and/or the CDR2 has 1, 2, or 3 amino acid substitutions, *e.g.,* conservative substitutions. In some embodiments, a heavy chain variable region comprises three CDRs of a variable region sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which the CDR1 has 1 or 2 amino acid substitutions, *e.g.,* conservative substitutions; and/or the CDR2 has 1 or 2 amino acid substitutions, *e.g.,* conservative substitutions. In some embodiments, the heavy chain variable region comprises three CDRs of a variable region sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which the CDR1 and/or the CDR2 has 1 amino acid substitution *e.g.,* a conservative substitution.

[0086] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a heavy chain CDR1 sequence G(G/Y)(K/T)FS(W/S/Y)(F/Y)(SEQ ID NO:109), a heavy chain CDR2 sequence YP(G/I)(D/F)GE (SEQ ID NO:110), and a heavy chain CDR3 sequence DYLRAMD(Y/I/V) (SEQ ID NO:111). In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a heavy chain variable region comprising: a heavy chain CDR3 (HCDR3) sequence DDYLRAMDY (SEQ ID NO:81), DDYLRAMDV (SEQ ID NO:91), or DDYLRAMDI (SEQ ID NO:92); a heavy chain CDR1 (HCDR1) sequence GYDFSNF (SEQ ID NO:79), GYTFSNF (SEQ ID NO:82), GGDFSNF (SEQ ID NO:83), GYDFSSY (SEQ ID NO:87), GYDFSSF (SEQ ID NO:88), or GYDFSNY (SEQ ID NO:89); and a heavy chain CDR2 (HCDR2) sequence YPGDGE (SEQ ID NO:80), YPIDGE (SEQ ID NO:85), or YPGFGE (SEQ ID NO:90). Illustrative CDR2 sequences having mutations that abolish binding are IPGDGE (SEQ ID NO:84) and YPGDGT (SEQ ID NO:86).

[0087] In some embodiments, an anti-Siglec-7 antibody comprises a light chain variable region that comprises a CDR3 as set forth in any one of SEQ ID NOS:62 and 64-78 in which 1, 2, or 3 amino acids are substituted, *e.g.,* conservatively substituted; or 1 or 2 amino acids are substituted, *e.g.,* conservatively substituted. In some embodiments, a light chain variable region comprises a CDR3 as set forth in any one of SEQ ID NOS:62 and 64-78 in which one amino acid is substituted, *e.g.,* conservatively substituted. In some embodiments, a light chain variable region comprises three CDRs of a variable region sequence as set forth in any one of SEQ ID NOS:62 and 64-78 in which the CDR1 has 1, 2, 3, or 4 amino acid substitutions, or 1, 2, or 3 amino acid substitutions, *e.g.,* conservative substitutions; and/or the CDR2 has 1, 2, 3, or 4 amino acid substitutions, or 1, 2, or 3 amino acid substitutions, *e.g.,* conservative

substitutions. In some embodiments, a light chain variable region comprises three CDRs of a variable region sequence as set forth in any one of SEQ ID NOS:62 and 64-78 in which the CDR1 and/or the CDR2 has 1 or 2 amino acid substitutions, *e.g.*, conservative substitutions. In some embodiments, a light chain variable region comprises three CDRs of a variable region sequence as set forth in any one SEQ ID NOS:62 and 64-78 in which the CDR1 and/or the CDR2 has 1 amino acid substitution *e.g.*, a conservative substitution.

[0088] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a light chain CDR1 sequence RAS(G/Q)(N/G)I(H/S)NYLA (SEQ ID NO:112), a light chain CDR2 sequence (S/A)A(K/S)RL(E/A)(S/D) (SEQ ID NO:113) and a light chain CDR3 sequence QHFWSSPYT (SEQ ID NO:95). In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a light chain variable region comprising: a light chain CDR3 (LCDR3) sequence QHFWSSPYT (SEQ ID NO:95); a light chain CDR1 (LCDR1) sequence RASGNIHNYLA (SEQ ID NO:93), RASGGIHNYLA (SEQ ID NO:99), RASQNIHNYLA (SEQ ID NO:100), or RASGNISNYLA (SEQ ID NO:101); and a light chain CDR2 (LCDR2) sequence SAKRLES (SEQ ID NO:94), AASRLES (SEQ ID NO:97), SASRLES (SEQ ID NO:98), SAKRLAS (SEQ ID NO:102), or SAKRLED (SEQ ID NO:103). An illustrative CDR1 mutation that abolishes binding is RASGNIHNSLA (SEQ ID NO:96).

[0089] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a heavy chain variable region, wherein the heavy chain variable region comprises: a heavy chain CDR3 (HCDR3) sequence DDYLRAMDY (SEQ ID NO:81), DDYLRAMDV (SEQ ID NO:91), or DDYLRAMDI (SEQ ID NO:92); a heavy chain CDR1 (HCDR1) sequence GYDFSNF (SEQ ID NO:79), GYTFSNF (SEQ ID NO:82), GGDFSNF (SEQ ID NO:83), GYDFSSY (SEQ ID NO:87), GYDFSSF (SEQ ID NO:88), or GYDFSNY (SEQ ID NO:89); and a heavy chain CDR2 (HCDR2) sequence YPGDGE (SEQ ID NO:80), YPIDGE (SEQ ID NO:85), or YPGFGE (SEQ ID NO:90); and a light chain variable region, wherein the light chain variable region comprises: a light chain CDR3 (LCDR3) sequence QHFWSSPYT (SEQ ID NO:95); a light chain CDR1 (LCDR1) sequence RASGNIHNYLA (SEQ ID NO:93), RASGGIHNYLA (SEQ ID NO:99), RASQNIHNYLA (SEQ ID NO:100), or RASGNISNYLA (SEQ ID NO:101); and a light chain CDR2 (LCDR2) sequence SAKRLES (SEQ ID NO:94), AASRLES (SEQ ID NO:97), SASRLES (SEQ ID NO:98), SAKRLAS (SEQ ID NO:102), or SAKRLED (SEQ ID NO:103).

[0090] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a heavy chain variable region comprises CDR1, CDR2, and CDR3 sequences as set forth in a heavy chain variable region sequence selected from SEQ ID NO:43, 45, 46, 47, 48, 49, 50, 51, 54, 55, 57, and 58; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO:69. In some embodiments, the heavy chain variable region comprises CDR1, CDR2, and CDR3 sequences as set forth in a heavy chain variable region sequence selected from SEQ ID NO:53, 54, 51, 55, 58, and 59; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO:78.

[0091] In some embodiments, an anti-Siglec-7 of the present invention comprises:

(a) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:43, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(b) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:45, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(c) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:46, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(d) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:47, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(e) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:48, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(f) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:49, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(g) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:50, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(h) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:51, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(i) CDR1, CDR2, and CDR3 sequences as set forth in a heavy chain variable region sequence SEQ ID NO:54, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(j) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:55, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(k) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:57, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69; or

(l) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:58, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69.

[0092] In some embodiments, an anti-Siglec-7 of the present invention comprises:

(a) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:53; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(b) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:54; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(c) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:51; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(d) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:55; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(e) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:58; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78; or

(f) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:59; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78.

[0093] In some embodiments, an anti-Siglec-7 antibody of the present invention internalizes Siglec-7 and competes with an antibody designated as 8A2 in Figures 1-3 for binding to Siglec-7. In some embodiments, an anti-Siglec-7 antibody of the invention has at least one, at least two, or three CDRs of a V_H sequence as set forth in any one of SEQ ID NO:104 or 106. In some embodiments, an anti-Siglec-7 antibody of the invention has at least one, at least two, or three CDRs of a V_L sequence as set forth in SEQ ID NO:105 or 107. In some embodiments, an anti-Siglec-7 antibody comprises an HCDR3 sequence as set forth in SEQ ID NO:104 or 106 and an LCDR3 sequence as set forth in SEQ ID NO:105 or 107.

[0094] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a heavy chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of SEQ ID NO:104 or 106. In certain embodiments, a V_H sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence of a heavy chain variable region of SEQ ID NO:104 or 106 contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-Siglec-7 antibody comprising that sequence retains the ability to bind to Siglec-7 and has internalization activity. In certain embodiments, a total of 1 to 20 amino acids have been substituted, inserted and/or deleted in the amino acid sequence of a heavy chain variable region of SEQ ID NO:104 or 106. In certain embodiments, all of the substitutions, insertions, or deletions occur in the framework regions. In certain embodiments, 1, 2, or 3 substitutions occur in a CDR region.

[0095] In some embodiments, an anti-Siglec-7 antibody of the present invention comprises a light chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a light chain variable region of SEQ ID NO:105 or 107. In certain embodiments, a V_L sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence of a light chain variable region of SEQ ID NO:105 or 107 contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-Siglec-7 antibody comprising that sequence retains the ability to bind to Siglec-7. In certain embodiments, a total of 1 to 20 amino acids have been substituted, inserted and/or deleted in the amino acid sequence of a light chain variable region of SEQ ID NO:105

or 107. In certain embodiments, all of the substitutions, insertions, or deletions occur in the framework regions. In certain embodiments, 1, 2, or 3 substitutions occur in a CDR region.

[0096] In some embodiments, an anti-Siglec-7 antibody of the present invention that comprises a heavy chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of SEQ ID NO:104 or 106; and a light chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a light chain variable region of SEQ ID NO:105 or 107. In some embodiments, the anti-Siglec-7 antibody has a modification to the heavy chain variable region and/or the light chain variable region as described in the preceding two paragraphs.

[0097] In some embodiments, an anti-Siglec-7 antibody comprises a heavy chain variable region that comprises a CDR3 as set forth SEQ ID NO:104 or 106 in which 1, 2, or 3 amino acids are substituted, *e.g.,* conservatively substituted; or 1 or 2 amino acids are substituted, *e.g.,* conservatively substituted. In some embodiments, a heavy chain variable region comprises a CDR3 as set forth in SEQ ID NO:104 or 106 in which one amino acid is substituted, *e.g.,* conservatively substituted. In some embodiments, a heavy chain variable region comprises three CDRs of a variable region sequence as set forth in SEQ ID NO:104 or 106 in which the CDR1 has 1, 2, or 3 amino acid substitutions, *e.g.,* conservative substitutions and/or the CDR2 has 1 or 2, or 1 only, amino acid substitution, *e.g.,* conservative substitutions.

[0098] In some embodiments, an anti-Siglec-7 antibody comprises a light chain variable region that comprises a CDR3 as set forth SEQ ID NO:105 or 107 in which 1, 2, or 3 amino acids are substituted, *e.g.,* conservatively substituted; or 1 or 2 amino acids are substituted, *e.g.,* conservatively substituted. In some embodiments, a light chain variable region comprises a CDR3 as set forth in SEQ ID NO:105 or 107 in which one amino acid is substituted, *e.g.,* conservatively substituted. In some embodiments, a light chain variable region comprises three CDRs of a variable region sequence as set forth in SEQ ID NO:105 or 107 in which the CDR1 has 1, 2, or 3 amino acid substitutions, *e.g.,* conservative substitutions and/or the CDR2 has 1 or 2, or 1 only, amino acid substitution, *e.g.,* conservative substitutions.

[0099] In a further aspect of the invention, an anti-Siglec-7 antibody according to any of the above embodiments is a monoclonal antibody, including a chimeric, humanized or human

antibody. In one embodiment, the antibody is a substantially full length antibody, e.g., an IgG antibody or other antibody class or isotype as defined herein.

[0100] In some embodiments an anti-Siglec-7 antibody in accordance with the present disclosure is a ligand blocking antibody in a monovalent format.

[0101] In some embodiments, an anti-Siglec-7 antibody of the present invention is employed in a bispecific or multi-specific format. For example, in some embodiments, the antibody may be incorporated into a bispecific or multi-specific antibody that comprises a therapeutic antibody, as further discussed below.

Fc engineering

[0102] An anti-Siglec-7 antibody of the present disclosure comprises an Fc region, which as described herein, may be a variant Fc region engineered to alter one or more functional properties of the antibody, such as extending serum half-life and/or reducing effector function, including reducing complement fixation, Fc receptor binding, and/or antibody-dependent cell-mediated cytotoxicity. Furthermore, an antibody of the disclosure may be chemically modified (e.g., one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. For purposes of describing amino acids present in an Fc region, the positions are numbered using EU index numbering where the designation "positon numberX" means that X is an amino acid that is present at the indicated position. For purposes of describing mutations in an Fc region, the designation "Xpositon numberY" means that Y is an amino acid that is substituted for X relative to a reference sequence at the indicated position. For example, L234A, means that A is substituted for an L that occurs in a reference Fc region sequence at position 234. Similarly, the designation "-" when coupled with a position number, *e.g.*, "position number-", refers to a deletion, relative to a reference sequence, at the indicated position in the Fc region. For example, "236-" indicates that the residue at position 236 is deleted in an Fc region relative to a reference Fc region sequence.

[0103] In some embodiments, one or more amino acid modifications may be introduced into the Fc region of an anti-Siglec-7 antibody, *e.g.*, to increase stability and/or reduce effector function. An Fc region variant may thus comprise a human Fc region sequence, such as a human IgG1, IgG2, IgG3, or IgG4 Fc region sequence, that comprises at least one amino acid modification, such as a substitution, compared to a native Fc region sequence. An Fc region

variant may also comprise further modifications. Accordingly, in some embodiments, the Fc region variant has at least 80% identity, or at least 85%, at least 90%, or at least 95% identity to a native human IgG1, IgG2, IgG3, or IgG4 region and comprises specific Fc region modifications as described herein.

[0104] In some embodiments, an anti-Siglec-7 antibody of the present disclosure having reduced effector function includes one or more amino acid modifications; or two or more modifications. In some embodiments, at least one modification is at an Fc region position selected from the group consisting of positions 228, 233, 234, 235, 236, 237, 238, 268, 309, 322, 327, 330, 331, 233, 242,259, 287, 292, 297, 302, 306, 323, 332, 334, 252, 254, 256, 232, 233, 267, 328, 252, 254, 256, and 329.

[0105] In some embodiments, an anti-Siglec-7 antibody of the present disclosure that has reduced effector function includes one or more amino acid modifications at an Fc region position selected from the group consisting of positions 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328. In some embodiments, the antibody further comprises at least one modification in the Fc region at a position selected from the group consisting of positions 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

[0106] In some embodiments, an anti-Siglec-7 antibody as described herein that has reduced effector function comprises an Fc region having at least one residue selected from the group consisting of 228P, 233P, 234V, 234A/V, 234F, 235A, 235E, 235Q, 236- (i.e., a deletion of the residue at position 236), 237A, 238S, 242C, 252Y, 254T, 256E, 259C, 268A, 287C, 292C, 297C, 297A, 297G, 297Q, 302C, 306C, 309L, 322Q, 323C, 327G, 329G, 330S, 331S, 332C, and 334C. In some embodiments, an anti-Siglec-7 antibody as described herein that has reduced effector function comprises an Fc region having at least two residues, or at least three residues, selected from the group consisting of 228P, 233P, 234V, 234A/V, 234F, 235A, 235E, 235Q, 236- (i.e., a deletion of the residue at position 236), 237A, 238S, 242C, 252Y, 254T, 256E, 259C, 268A, 287C, 292C, 297C, 297A, 297G, 297Q, 302C, 306C, 309L, 322Q, 323C, 327G, 329G, 330S, 331S, 332C, and 334C. In some embodiments, the antibody comprises an Fc region comprising 234A and 235A. In some embodiments, the antibody comprises an Fc region comprising 327G, 330S, and 331S. In some embodiments, the antibody comprises an Fc region comprising 327G, 330S, and 331S. In some embodiments, the antibody comprises an Fc region comprising 233P, 234V, 235A, and 236-. In some embodiments, the antibody comprises an Fc region comprising 233P, 234V, and 235A. In some embodiments, the

antibody comprises an Fc region comprising 233P, 234V, 235A, 236-, 327G, 330S, and 331S. In some embodiments, the antibody comprises an Fc region comprising 233P, 234V, 235A, 327G, 330S, and 331S. In some embodiments, the antibody comprises an Fc region comprising 297A/G/Q. In some embodiments, the antibody comprises an Fc region comprising 242C, 297C, and 334C. In some embodiments, the antibody comprises an Fc region comprising 287C, 297G, and 306C. In some embodiments, the antibody comprises an Fc region comprising 292C, 297G, and 302C. In some embodiments, the antibody comprises an Fc region comprising 297G, 323C, and 332C. In some embodiments, the antibody comprises an Fc region comprising 259C, 297G, and 306C. In some embodiments, the antibody comprises an Fc region comprising 234F, 235Q, 322Q, 252Y, 254T, and 256E. In some embodiments, the antibody comprises an Fc region comprising 234A, 235A, and 329G. In some embodiments, the antibody comprises an Fc region comprising 330S and 331S. In some embodiments, the antibody comprises an Fc region comprising 234A, 237A, 238S, 268A, 309L, 330S, and 331S. In some embodiments, the antibody comprises an Fc region comprising 233P, 234V, 235A, and 236^{-}. In some embodiments, the antibody comprises an Fc region comprising 228P, 234V, and 235A. In some embodiments, the antibody comprises an Fc region comprising 228P and 235E/A.

[0107] In some embodiments, an anti-Siglec-7 antibody comprises an Fc region comprising a human IgG1 Fc region variant having decreased effector function. In some embodiments, the human IgG1 Fc region variant has at least 85%, identity to a native human IgG1 Fc region amino acid sequence. In some embodiments, the human IgG1 Fc region variant has at least 90% identity, or at least 95% identity, to a native human IgG1 Fc region amino acid sequence. In some embodiments, the Fc region comprises a human IgG1 Fc region variant having decreased effector function and modifications to the Fc region that increase serum half-life of the antibody. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications L234A and L235A. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications A327G, A330S, and P331S.. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications E233P, L234V, L235A, which may further comprise an amino acid modification G236-, amino acid modifications G236-, A327G, A330S, and P331S; or amino acid modifications A327G, A330S, and P331S. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising an amino acid modification N297A/G/Q. In some embodiments, an anti-

Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications L242C, N297C, and K334C. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications A287C, N297G, and L306C. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications R292C, N297G, and V302C. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications N297G, V323C, and I332C. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications V259C, N297G, and L306C. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications L234F, L235Q, K322Q, and M252Y, S254T, T256E. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising amino acid modifications L234A, L235A, and P329G. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG1 Fc region comprising at least one amino acid modification, or at least two amino acid modifications selected from the group consisting of N297A, N297G, N297Q, N297C, D265A, L234A, L235A, G237A, C226S, C229S, E233P, L234V, L234F, L235E, L235Q, P329G, P331S, P331G, S267E, L328F, A287C, L306C, R292C, V259C, V302C, K322Q, V323C, I332C, A330L, A327G, A330S, L242C, and K334C.

[0108] In some embodiments, an anti-Siglec-7 antibody comprises an Fc region comprising a human IgG2 Fc region variant having decreased effector function. In some embodiments, the human IgG2 variant Fc region has at least 85%, identity to a native human IgG2 Fc region amino acid sequence. In some embodiments, the human IgG2 variant Fc region has at least 90% identity, or at least 95% identity to a native human IgG2 Fc region amino acid sequence. In some embodiments, the Fc region comprises a human IgG2 Fc region variant having decreased effector function and modifications to the Fc region that increase serum half-life of the antibody. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG2 Fc region comprising amino acid modifications A330S and P331S. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG2 Fc region comprising amino acid modifications V234A, G237A, P238S, H268A, V309L, A330S, and P331S. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG2 Fc region comprising at least one amino acid modification V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, and T256E. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG2 Fc region comprising one or more modifications, or two or more

modifications at a position selected from the group consisting of V234A, G237A, P238S, H268Q, V309L, A330S, P331S S267E, S267E, and L328F.

[0109] In some embodiments, an anti-Siglec-7 antibody comprises an Fc region comprising a human IgG4 Fc region variant having decreased effector function. In some embodiments, the human IgG4 variant Fc region has at least 85%, identity to a native human IgG4 Fc region amino acid sequence. In some embodiments, the human IgG4 variant Fc region has at least 90% identity, or at least 95% identity to a native human IgG4 Fc region amino acid sequence. In some embodiments, the Fc region comprises a human IgG4 Fc region variant having decreased effector function and modifications to the Fc region that increase serum half-life of the antibody. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG4 Fc region comprising amino acid modifications E233P, F234V, L235A, and G236-. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG4 Fc region comprising amino acid modifications E233P, F234V, and L235A. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG4 Fc region comprising amino acid modifications S228P and L235E/A. In some embodiments, an anti-Siglec-7 antibody comprises a human IgG4 Fc region comprising at least one modification selected from the group consisting of E233P, L235A or L235E, G237A, L236E, S267E, E318A, and L328F.

[0110] In certain embodiments, the proline at position 329 of a wild-type human Fc region of an anti-Siglec-7 antibody of the present disclosure is substituted with glycine or arginine or an amino acid residue large enough to destroy the proline sandwich within the Fc/Fcγ receptor interface that is formed between the proline 329 of the Fc and tryptophan residues Trp 87 and Trp 110 of FcγRIII (Sondermann et al.: Nature 406, 267-273 (20 Jul. 2000)). In certain embodiments, the antibody comprises at least one further amino acid substitution. In one embodiment, the further amino acid substitution is S228P, E233P, L234A, L235A, L235E, N297A, N297D, or P331S. In some embodiments, the at least one further amino acid substitution is L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region (see e.g., US 2012/0251531). In another embodiments, the at least one further amino acid substitution is L234A and L235A and P329G of the human IgG1 Fc region.

[0111] In some embodiments, an anti-Siglec-7 antibody having reduced effector function includes one more amino acid substitutions at an Fc region positions selected from the group consisting of 238, 265, 269, 270, 297, 327 and 329 (U.S. Patent No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269,

270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581).

[0112] In some embodiments, an anti-Siglec-7 antibody having reduced effector function comprises CH domains from different human IgG isotypes. For examples, in some embodiments, an anti-Siglec-7 antibody may comprise an IgG2 CH1 domain and hinge sequence, such as the sequence ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP (SEQ ID NO:114), and an IgG1 CH2 and CH3 domain sequence that comprises an amino acid substitution S267E and/or L328F; and/or an N297A or N297Q substitution. In some embodiments, an anti-Siglec-7 antibody having reduced effector function comprises human IgG2 and IgG4 sequences. For example, such an antibody may comprise amino acids 117 to 260 of human IgG2 and amino acids 261 to 447 of human IgG4.

[0113] Reduced effector function or antibody half-life can be evaluated using any suitable assay. For example, *in vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm reduced CDC and/or ADCC activities. In some embodiments, Fc receptor binding assays can be conducted to determine reduced and/or undetectable binding to an FcγR. Non-limiting examples of *in vitro* assays to assess ADCC activity are described in U.S. Patent No. 5,500,362 (see, e.g. Hellstrom, I . et al. Proc. Nat'l Acad. Sci. USA 83:7059-7063 (1986)) and Hellstrom, I et al., Proc. Nat'l Acad. Sci. USA 82: 1499-1502 (1985); 5,821 ,337 (see Bruggemann, M. et al., J. Exp. Med. 166: 1351 -1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTI™ non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, Wl).

[0114] Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g. , in an animal model such as that disclosed in Clynes et al. Proc. Nat'l Acad. Sci. USA 95:652-656 (1998). C1 q binding assays may also be carried out to confirm that the antibody is unable, or has a reduced ability, to bind C q and hence lacks or has reduced CDC activity. See, e.g. , C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro et al., J. Immunol. Methods 202: 163 (1996);

Cragg, M.S. et al., Blood 101 : 1045-1052 (2003); and Cragg, M.S. and M.J. Glennie, Blood 103:2738-2743 (2004)).

[0115] In typical embodiments, a variant Fc region that has reduced effector function has at least a 30%, or 50% or greater, reduction in effector function compared to the widltype counterpart Fc region when the variant is compared to the wildtype using the same assay and antibody format.

[0116] An anti-Siglec-7 antibody comprising an Fc region having reduced effector function as described herein may also comprises modification to increase serum half-life. In ssome embodiments, FcRn binding ability, which typically correlates with serum half-life may also be evaluated. Antibodies with increased half-lives and improved binding to the neonatal Fc receptor (FcRn) are described in US2005/0014934A1 (Hinton et al.). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region 36, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328.$17, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, e.g., substitution of Fc region residue 434 (US Patent No. 7,371 ,826). See also Duncan & Winter, Nature 322:738-40 (1988); U.S. Patent No. 5,648,260; U.S. Patent No. 5,624,821 ; and WO 94/29351 concerning other examples of Fc region variants. Additional mutations that improve serum half-life include YTE mutations, i.e., amino acids Y, T, and E at positions 252, 254, and 256, respectively. FcRn binding and *in vivo* clearance/half-life determinations can be performed using methods known in the art (see, e.g. , Petkova, S.B. et al. , Int'l. Immunol. 18(12): 1759-1769 (2006)). In typical embodiments, a variant Fc region that confers increased stability, increases serum half-life by at least 5%, or at least 10%, at least 20%, or greater, when the variant is compared to the counterpart wild-type antibody.

[0117] In some embodiments, biological half-life can be increased by modifying the Fc region within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 region of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121 ,022 by Presta et al. In some embodiments, stabilizing mutations, *e.g.,* at cysteine positions C232 and C233 of human IgG2, are introduced to prevent disulfide bond exchange and stabilize the human IgG2 in the IgG2-A conformation.

[0118] In still another embodiment, the glycosylation of an antibody is modified. For example, an aglycoslated antibody or antibody having an altered glycosylation pattern can be made. Glycosylation can be altered, for example, to increase the affinity of the antibody for an

antigen or, if made in the Fc region, to influence effector function. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen.

Treatment of Cancer

[0119] Anti-Siglec-7 antibodies of the invention can be used to treat any number of cancers. In some aspects of the present disclosure antibodies are used to treat cancers that exhibit infiltration of immune cells, such as CD8+ T cells, with high levels of Siglec-7 expression. In some embodiments, anti-Siglec-7 antibodies of the invention can be used to treat cancers that exhibit infiltration of NK cells or monocytes that express Siglec-7.

[0120] In some aspects, the disclosure thus provides methods of identifying subjects who are candidates for treatment with an anti-Siglec-7 antibody. Thus, in one embodiment, the invention provides a method of identifying the level of infiltration of Siglec-7 expressing CD8+ T cells in a tumor sample obtained from a patient. In some embodiments, the tumor sample is from a primary tumor. In alternative embodiments, the tumor sample is a metastatic lesion. The level of expression of Siglec-7 on the surface of cells, *e.g.,* T cells, can be measured using any assay, such as immunohistochemistry or flow cytometry. In the context of the determination of levels of expression of Siglec-7 on tumor-infiltrating T cells, "overexpression" of Siglec-7 is considered to be where at least 10%, at least 20%, or at least 25%, or at least 30%, or greater, of the cells being analyzed, *e.g.,* CD8+ T cells, express detectable Siglec-7 on the cell surface. Thus, "overexpress" in this context refers to the percentage of T cells that express detectable Siglec-7. "Overexpression" in this context is synonymous with the term "elevated numbers" or "elevated levels" of T cells that express detectable Siglec-7 in referring to the percentage of T cells that express detectable Siglec-7.

[0121] The level of Siglec-7 ligand expressed by a tumor is also typically evaluated. A tumor is considered to express Siglec-7 ligand when detectable binding of Siglec-7 is observed on the surface of tumor cells. In some embodiments, expression of Siglec-7 ligand on at least 10%, at least 20%, at least 30%, at least 50%, or greater of the tumor cells in a sample that is evaluated may be used as a selection criteria for determining a patient to be treated with an anti-Siglec-7 antibody.

[0122] Any cancer can be treated with an anti-Siglec-7 antibody as described herein. In some embodiments, the cancer is a carcinoma or a sarcoma. In some embodiments, the cancer is a hematological cancer. In some embodiments, the cancer is breast cancer, prostate cancer, testicular cancer, renal cell cancer, bladder cancer, ovarian cancer, cervical cancer, endometrial cancer, lung cancer, colorectal cancer, anal cancer, pancreatic cancer, gastric cancer, esophageal cancer, hepatocellular cancer, head and neck cancer, glioblastoma, mesothelioma, melanoma, or a bone or soft tissue sarcoma. In some embodiments, the cancer is acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, basal-cell carcinoma, bile duct cancer, bladder cancer, bone tumor, brainstem glioma, brain cancer, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, visual pathway and hypothalamic glioma, breast cancer, bronchial adenomas, Burkitt's lymphoma, central nervous system lymphoma, cerebellar astrocytoma, cervical cancer, chondrosarcoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, cutaneous T-cell lymphoma, desmoplastic small round cell tumor, endometrial cancer, epitheliod hemangioendothelioma (EHE), esophageal cancer, Ewing's sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), germ cell tumor, gestational trophoblastic tumor, gastric carcinoid, hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular cancer, Hodgkin lymphoma, hypopharyngeal cancer, hypothalamic and visual pathway glioma, childhood, intraocular melanoma, islet cell carcinoma, Kaposi sarcoma, kidney cancer, laryngeal cancer, leukemias, lip and oral cavity cancer, liposarcoma, liver cancer, non-small cell lung cancer, small-cell lung cancer, lymphomas, macroglobulinemia, male breast cancer, malignant fibrous histiocytoma of bone, medulloblastoma, melanoma, Merkel cell cancer, mesothelioma, metastatic squamous neck cancer, mouth cancer, multiple endocrine neoplasia syndrome, multiple myeloma, myelodysplastic syndromes, myelogenous leukemia, myeloid leukemia, adult acute, myeloproliferative disorders, chronic, myxoma, nasal cavity and paranasal sinus cancer, nasopharyngeal carcinoma, neuroblastoma, non-Hodgkin lymphoma, oligodendroglioma, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma,

pineal astrocytoma, pineal germinoma, pineoblastoma, pituitary adenoma, plasma cell neoplasia, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, Ewing sarcoma, Kaposi sarcoma, soft tissue sarcoma, uterine sarcoma, Sézary syndrome, non-melanoma skin cancer, melanoma Merkel cell skin carcinoma, small intestine cancer, squamous cell carcinoma, squamous neck cancer, stomach cancer, cutaneous T-Cell lymphoma, testicular cancer, throat cancer, thymoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, gestational, urethral cancer, uterine cancer, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, or Wilms tumor.

[0123] In one aspect, methods of the disclosure comprise administering an anti-Siglec-7 antibody as a pharmaceutical composition to a cancer patient in a therapeutically effective amount using a dosing regimen suitable for treatment of the cancer. The composition can be formulated for use in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the compositions for proper formulation. Suitable formulations for use in the present invention are found, *e.g.*, in Remington: The Science and Practice of Pharmacy, 21st Edition, Philadelphia, PA. Lippincott Williams & Wilkins, 2005.

[0124] The anti-Siglec-7 antibody is provided in a solution suitable for administration to the patient, such as a sterile isotonic aqueous solution for injection. The antibody is dissolved or suspended at a suitable concentration in an acceptable carrier. In some embodiments the carrier is aqueous, e.g., water, saline, phosphate buffered saline, and the like. The compositions may contain auxiliary pharmaceutical substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, and the like.

[0125] The pharmaceutical compositions are administered to a patient in an amount sufficient to cure or at least partially arrest the disease or symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose." A therapeutically effective dose is determined by monitoring a patient's response to therapy. Typical benchmarks indicative of a therapeutically effective dose include amelioration of symptoms of the disease in the patient. Amounts effective for this use will depend upon the severity of the disease and the general state of the patient's health, including other factors such as age, weight, gender, administration route, etc. Single or multiple

administrations of the antibody may be administered depending on the dosage and frequency as required and tolerated by the patient. In any event, the methods provide a sufficient quantity of anti-Siglec-7 antibody to effectively treat the patient.

[0126] An anti-Siglec-7 antibody can be administered by any suitable means, including, for example, parenteral, intrapulmonary, and intranasal, administration, as well as local administration, such as intratumor administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In some embodiments, the antibody may be administered by insufflation. In an illustrative embodiment, the antibody may be stored at 10 mg/ml in sterile isotonic aqueous saline solution for injection at 4°C and is diluted in either 100 ml or 200 ml 0.9% sodium chloride for injection prior to administration to the patient. In some embodiments, the antibody is administered by intravenous infusion over the course of 1 hour at a dose of between 0.01 and 25 mg/kg. In other embodiments, the antibody is administered by intravenous infusion over a period of between 15 minutes and 2 hours. In still other embodiments, the administration procedure is via sub-cutaneous bolus injection.

[0127] The dose of antibody is chosen in order to provide effective therapy for the patient and is in the range of less than 0.01 mg/kg body weight to about 25 mg/kg body weight or in the range 1 mg – 2 g per patient. Preferably the dose is in the range 0.1 – 10 mg/kg or approximately 50 mg – 1000 mg / patient. The dose may be repeated at an appropriate frequency which may be in the range once per day to once every three months, or every six months, depending on the pharmacokinetics of the antibody (e.g., half-life of the antibody in the circulation) and the pharmacodynamic response (e.g., the duration of the therapeutic effect of the antibody). In some embodiments, the in vivo half-life of between about 7 and about 25 days and antibody dosing is repeated between once per week and once every 3 months or once every 6 months. In other embodiments, the antibody is administered approximately once per month.

[0128] An anti-Siglec-7 antibody of may be administered with one or more additional therapeutic agents, e.g., chemotherapeutic agents and/or additional immunotherapies.

[0129] In some embodiments, an anti-Siglec-7 antibody can be administered in conjunction with another checkpoint inhibitor. In one aspect, the checkpoint inhibitor is a biologic therapeutic or a small molecule. In another aspect, the checkpoint inhibitor is a monoclonal antibody, a humanized antibody, a fully human antibody, a fusion protein or a combination

thereof. In certain embodiments, the checkpoint inhibitor inhibits a checkpoint protein which may be CTLA-4, PDLl, ICOS, PDL2, IDO1, IDO2, PDl, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, GITR, HAVCR2, LAG3, KIR, LAIR1, LIGHT, MARCO, OX-40, SLAM, , 2B4, CD2, CD27, CD28, CD30, CD40, CD70, CD80, CD86, CD137, CD160, CD39, VISTA, TIGIT, CGEN-15049, 2B4, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In some embodiments, the immune checkpoint inhibitor is an inhibitor of PD-Ll . In some embodiments, the immune checkpoint inhibitor is an inhibitor of PD-1. In some embodiments, the immune checkpoint inhibitor is an inhibitor of CTLA-4. In some embodiments, the immune checkpoint inhibitor is an inhibitor of LAG3. In some embodiments, the immune checkpoint inhibitor is an inhibitor of TIM3. In some embodiments, the immune checkpoint inhibitor is ICOS.

[0130] In some embodiments, an anti-Siglec-7 antibody can be administered in conjunction with a therapeutic antibody, such as an antibody that targets a tumor cell antigen. Examples of therapeutic antibodies include as rituximab, trastuzumab, tositumomab, ibritumomab, alemtuzumab, epratuzumab, bevacizumab, elotuzumab, necitumumab, blinatumomab, brentuximab, cetuximab, daratumumab, denosumab, dinutuximab, gemtuzumab ibritumomab ipilimumab, nivolumab, obinutuzumab, ofatumumab, ado-trastuzumab, panitumumab, pembrolizumab, pertuzumab, ramucirumab, and ranibizumab.

[0131] In some embodiments, an anti-Siglec-7 antibody is administered with a chemotherapeutic agent. Examples of cancer chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic

acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; antimetabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside; cyclophosphamide; thiotepa; taxoids, e.g. paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; docetaxel, platinum; etoposide (VP- 16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-1 1 ; topoisomerase inhibitor RFS 2000; difluoromethylomithine (DMFO); retinoic acid derivatives such as bexarotene, alitretinoin; denileukin diftitox; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, mifepristone, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 1 17018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Further cancer therapeutic agents include sorafenib and other protein kinase inhibitors such as afatinib, axitinib, crizotinib, dasatinib, erlotinib, fostamatinib, gefitinib, imatinib, lapatinib, lenvatinib, mubritinib, nilotinib, pazopanib, pegaptanib, ruxolitinib, vandetanib, vemurafenib, and sunitinib; sirolimus (rapamycin), everolimus and other mTOR inhibitors. Examples of additional chemotherapeutic agents include topoisomerase I inhibitors (e.g., irinotecan,

topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin); topoisomerase II inhibitors (e.g., etoposide, teniposide, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics (e.g., 5-fluorouracil, capecitibine, gemcitabine, fludarabine, cytarabine, mercaptopurine, thioguanine, pentostatin, and hydroxyurea). Illustrative chemotherapeutic agents additionally include paclitaxel, docetaxel, and related analogs; vincristine, vinblastin, and related analogs; thalidomide, lenalidomide, and related analogs (e.g., CC-5013 and CC-4047); protein tyrosine kinase inhibitors (e.g., imatinib mesylate and gefitinib); proteasome inhibitors (e.g., bortezomib); NF-κB inhibitors, including inhibitors of IκB kinasel and other inhibitors of proteins or enzymes known to be upregulated, over-expressed or activated in cancers, the inhibition of which down regulates cell replication. Additional agents include asparaginase and a Bacillus Calmete-Guérin preparation.

[0132] An anti-Siglec-7 antibody may also be administered to a cancer patient in conjunction with a cell based therapy, such as NK or T cell therapy, or a cancer vaccine. In some instances, a cancer vaccine is a peptide-based vaccine, a nucleic acid based vaccine, a cell-based vaccine, a virus-based or viral fragment based vaccine or an antigen presenting cell (APC) based vaccine (e.g. dendritic cell based vaccine). Cancer vaccines include Gardasil®, Cervarix®, sipuleucel-T (Provenge®), NeuVax™, HER-2 ICD peptide-based vaccine, HER-2/neu peptide vaccine, AdHER2/neu dendritic cell vaccine, HER-2 pulsed DC1 vaccine, Ad-sig-hMUC-l/ecdCD40L fusion protein vaccine, MVX-ONCO-1, hTERT/survivin/CMV multipeptide vaccine, E39, J65, PlOs-PADRE, rV-CEA-Tricom, GVAX®, Lucanix®, HER2 VRP, AVX901, ONT-10, ISAlOl, ADXSl 1-001, VGX-3100, INO-9012, GSK1437173A, BPX-501, AGS-003, IDC-G305, HyperAcute®-Renal (HAR) immunotherapy, Prevenarl3, MAGER-3.A1, NA17.A2, DCVax-Direct, latent membrane protein-2 (LMP2)-loaded dendritic cell vaccine (NCT02115126), HS410-101 (NCT02010203, Heat Biologies), EAU RF 2010-01 (NCT01435356, GSK), 140036 (NCT02015104, Rutgers Cancer Institute of New Jersey), 130016 (NCTO 1730118, National Cancer Institute), MVX-201101 (NCT02193503, Maxivax SA), ITL-007-ATCR-MBC (NCT01741038, Immunovative Therapies, Limited), CDR0000644921 (NCT00923143, Abramson cancer center of the University of Pennsylvania), SuMo-Sec-01 (NCT00108875, Julius Maximilians Universitaet Hospital), or MCC-15651 (NCT01176474, Medarex, Inc, BMS).

[0133] In the context of the present invention a therapeutic agent that is administered in conjunction with an anti-Siglec-7 antibody of the present invention can be administered prior to administrations of the anti-Siglec-7 antibody or after administration of the anti-Siglec-7 antibody. In some embodiments, an anti-Siglec-7 antibody may be administered at the same time as the additional therapeutic agent.

[0134] The following examples are offered for illustrative purposes, and are not intended to limit the invention. Those of skill in the art will readily recognize a variety of non-critical parameters that can be changed or modified to yield essentially the same results.

EXAMPLES

Example 1. Siglec-7 detection on tumor-infiltrating T cells.

[0135] Samples comprising cells from primary human tumor specimens were prepared using the Mylteni GentleMACS instrument according to the manufacturer's instructions. Cells were analyzed by fluorescent-activated cell sorting to determine immune cell surface markers including CD3, CD8, CD16, CD45 and 7-AAD as a viability marker. CD8+ T cells were identified and gated as 7-AAD- CD45+ CD3+ CD8+. Anti-Siglec-7-PE (clone S7.7 Biolegend) was used to detect Siglec-7 levels. The results demonstrated that both the percentage (Figure 4) and the level (Figure 5) of Siglec-7 expression is enhanced on CD8+ tumor-infiltrating T cells in a subset of tumors.

Example 2. Siglec-7 ligand detection on tumor cells

[0136] Ligand levels on tumor cells were also evaluated. Specific binding of recombinant Siglec-7-Fc fusion protein was used to assess Siglec-7 ligand levels on cells isolated form fresh primary tumors. As a specificity control, cells were treated with sialidase/neuraminidase (Roche) at 0.1U/mL to remove sialic acids from the cell surface. The results demonstrated that Siglec-7 ligands are detected on tumor cells from various subsets of tumors (Figure 6). Sialidase treatment of cells (i.e. "stripping" of sialoglycans from the cell membrane) eliminatedbinding.

Example 3. Antibodies with Improved K_D

[0137] A panel of antibodies was evaluated for binding to Siglec-7. The results identified anti-Siglec-7 antibodies that have improved K_D values compared to commercially available anti-Siglec-7 antibodies (Figure 7).

Example 4. Antibodies with Siglec-7 ligand blocking activity

[0138] Recombinant Siglec-7-Fc was added to A375 cells in the presence of anti-Siglec-7 antibodies at increasing concentrations and binding of the complex was detected on the cell surface. The results showed that anti-Siglec-7 antibodies blocked the interaction of Siglec-7 with ligands present on the surface of A375 melanoma human cells with various potencies (Figure 8) and demonstrated antibodies that have improved ligand blocking activity relative to commercially available anti-Siglec-7 antibodies.

Example 5. Antibodies with Siglec-7 internalization activity

[0139] Primary human peripheral blood mononuclear cells (PBMC) were incubated with increasing concentrations of anti-Siglec-7 antibodies for 24 hours and remaining Siglec-7 in the cell surface of NK cells was detected using a non-competing anti-Siglec-7 antibody. The results showed that anti-Siglec-7 antibodies caused internalization of Siglec-7 on primary human NK cells with various potencies (Figure 9) and demonstrated antibodies that have improved internalization activity compared to commercially available, or previously described, anti-Siglec-7 antibodies. Rapid, concentration-dependent antibody-induced internalization of Siglec-7 on human NK cells was further evaluated using monoclonal antibody 3F1. 3F1 showed more potent internalization activity compared to commercially available S7.7 antibody (Figure 10)

[0140] Evaluation of monoclonal antibody 8A2 (Figure 11) demonstrated that the antibody did not block Siglec-7/ligand interaction (left panel), but caused internalization (right panel) of Siglec-7 on primary human immune cells.

Example 6. Humanized sequences

[0141] Humanized antibodies were generated using monoclonal antibodies 16H11 and 8A2 to obtain humanized internalizing anti-Siglec 7 antibodies.

[0142] Humanized antibodies derived from 16H11 were evaluated for binding to Siglec 7. Antibody binding results (measured in the form of a monovalent Fab) are shown in Table 1. Antibodies having the following heavy and light chain variable regions demonstrated K_D values (monovalent Fab) of about 75 nM or lower: VH438-4 and VL418-2; VH440-2 and VL418-2; VH441-2 and VL418-2; VH443-1 and VL418-2; VH444-2 and VL418-2, VH445-3 and VL418-2; VH449-4 and VL448-3; VH449-6 and VL418-2; VH387-11 and VL418-2;

VH446-7 and VL418-2; VH 446-7 and VL448-3; VH463-2 and VL418-2; Vh463-2 and VL448-3; FH465-17 and VL418-2; VH484-6 and VL418-2; VH484-6 and VL448-3; and VH484-7 and VL448-3. The ligand blocking activity of the 16H11 anti-Siglec-7 antibody is preserved, as indicated by analysis of selected antibodies (indicated by the VH/VL pairs in Table 1): AK410-1/AK418-2, AK446-7/AK418-2, and AK446-7/AK448-3.

Table 1. K_D values of humanized antibodies derived from 16H11 measured as monovalent Fabs:

No.	VH	VL	KD (pM)
1	AK410-1 (SEQ ID NO:44)	AK418-2 (SEQ ID NO:69)	250-500
2	AK417-17 (SEQ ID NO:42)	AK418-2 (SEQ ID NO:69)	250-500
3	AK417-8(SEQ ID NO:41)	AK421-3 (SEQ ID NO:71)	>500
4	AK417-8 (SEQ ID NO:41)	AK419-2 (SEQ ID NO:70)	>500
5	AK417-17 (SEQ ID NO:42)	AK421-3 (SEQ ID NO:71)	250-500
6	AK417-17 (SEQ ID NO:42)	AK419-2 (SEQ ID NO:70)	>500
7	AK417-17 (SEQ ID NO:42)	AK424-1 (SEQ ID NO:72)	>500
8	AK417-17 (SEQ ID NO:42)	AK425-3 (SEQ ID NO:73)	>500
9	AK417-17 (SEQ ID NO:42)	AK426-2 (SEQ ID NO:74)	>500
10	AK417-17 (SEQ ID NO:42)	AK427-1 (SEQ ID NO:75)	>500
12	AK417-17 (SEQ ID NO:42)	AK418-2 (SEQ ID NO:69)	>500
13	AK417-17 (SEQ ID NO:42)	AK419-2 (SEQ ID NO:70)	>500
14	AK417-17 (SEQ ID NO:42)	AK435-7 (SEQ ID NO:76)	>500
15	AK417-8 (SEQ ID NO:41)	AK419-2 (SEQ ID NO:70)	>500
16	AK417-8 (SEQ ID NO:41)	AK435-7 (SEQ ID NO:76)	>500
17	AK438-4 (SEQ ID NO:45)	AK418-2 (SEQ ID NO:69)	<75
18	AK440-2 (SEQ ID NO:46)	AK418-2 (SEQ ID NO:69)	<100
19	AK441-2 SEQ ID NO:47)	AK418-2 (SEQ ID NO:69)	<75
20	AK417-17 (SEQ ID NO:42)	AK435-7 (SEQ ID NO:76)	250-500
21	AK417-17 (SEQ ID NO:42)	AK439-5 (SEQ ID NO:77)	250-500
22	AK417-8 (SEQ ID NO:41)	AK439-5 (SEQ ID NO:77)	250
23	AK443-1 (SEQ ID NO:48)	AK418-2 (SEQ ID NO:69)	<75
24	AK444-2 (SEQ ID NO:49)	AK418-2 (SEQ ID NO:69)	<75
25	AK445-3 (SEQ ID NO:50)	AK418-2 (SEQ ID NO:69)	<75
26	AK447-2 (SEQ ID NO:52)	AK418-2 (SEQ ID NO:69)	75-150
27	AK447-2 (SEQ ID NO:52)	AK448-3 (SEQ ID NO:78)	75-150
28	AK449-4 (SEQ ID NO:53)	AK418-2 (SEQ ID NO:69)	75-150
29	AK449-4 (SEQ ID NO:53)	AK448-3 (SEQ ID NO:78)	<100
30	AK449-6 (SEQ ID NO:54)	AK418-2 (SEQ ID NO:69)	<100
31	AK449-6 (SEQ ID NO:54)	AK448-3 (SEQ ID NO:78)	50-100
32	AK387-11 (SEQ ID NO:43)	AK418-2 (SEQ ID NO:69)	<75
33	AK446-7 (SEQ ID NO:51)	AK418-2 (SEQ ID NO:69)	<75
34	AK446-7 (SEQ ID NO:51)	AK448-3 (SEQ ID NO:78)	<75
35	AK463-2 (SEQ ID NO:55)	AK418-2 (SEQ ID NO:69)	<75
36	AK463-2 (SEQ ID NO:55)	AK448-3 (SEQ ID NO:78)	<75
37	AK446-7 (SEQ ID NO:51)	AK419-2 (SEQ ID NO:70)	>500

38	AK463-2 (SEQ ID NO:55)	AK419-2 (SEQ ID NO:70)	>500
39	AK465-17 (SEQ ID NO:57)	AK418-2 (SEQ ID NO:69)	<75
40	AK465-17 (SEQ ID NO:57)	AK419-2 (SEQ ID NO:70)	150-250
41	AK465-17 (SEQ ID NO:57)	AK448-3 (SEQ ID NO:78)	100-150
42	AK484-6 (SEQ ID NO:58)	AK418-2 (SEQ ID NO:69)	<100
43	AK484-6 (SEQ ID NO:58)	AK448-3 (SEQ ID NO:78)	<75
44	AK484-7 (SEQ ID NO:59)	AK448-3 (SEQ ID NO:78)	<75
45	AK485-5 (SEQ ID NO:61)	AK418-2 (SEQ ID NO:69)	>500
46	AK485-5 (SEQ ID NO:61)	AK448-3 (SEQ ID NO:78)	>500
47	AK485-4 (SEQ ID NO:60)	AK448-3 (SEQ ID NO:78)	>500

Methods

K_D measurements

[0143] Antibody binding analysis was carried out by bio-layer interferometry (ForteBio). The assay was conducted at 25°C in 1x ForteBio Kinetics buffer (ForteBio18-132) in ultrapure water. Antibodies were captured on anti-mouse kinetic sensors at 0.5 ug/mL; Siglec-7-ECD was used as analyte and diluted in assay buffer from 50 nM to 1.56 nM with 2x dilutions. Two-minute associations were conducted, followed by 10-minute dissociations. Results were determined relative to a control empty reference AHC sensor, and analyzed using ForteBio analysis software with 1:1 global fit parameters.

Antibody competition using Fortebio

[0144] Siglec-7-ECD-huFc was captured on anti-human IgG kinetic sensors at 0.5 ug/ml under saturating conditions (15 min at 1 ug/ml), after which the competing antibody was tested for binding. Each anti-Siglec-7 antibody was tested both ways (i.e. as saturating antibody and as competing antibody) against all other antibodies. When the antibody on the sensor competes with the antibody in solution, no additional binding to the antigen is observed. When a binding signal is observed, the two antibodies bind to the antigen in a non-competitive manner.

Ligand blocking assay

[0145] Human melanoma cell line A375, which expresses high level of ligands for Siglec-7, was used to determine the blocking activity of anti-Siglec-7 antibodies in a cell based assay. Two-fold serial dilutions of anti-Siglec-7 antibodies (40 nM to 40 pM) were combined with 10nM Siglec-7-ECD-Fc in FACS buffer (PBS/2% BSA) and incubated on ice for 30 minutes.

2.5x10e4 A375 cells per well were added to round bottom 96-well tissue culture plates in FACS buffer, plates were centrifuged at 400g for 2 min, supernatant was removed and cells were re-suspended in 100 ul of the antibody-Siglec-7 complexes. After a 1 hour incubation on ice, cells were washed twice and incubated for 30 minutes with goat anti-human $F(ab')_2$ fragment conjugated to AF647 (Jackson IR labs) at 1ug/ml in FACS buffer. After two more washes, cells were fixed in PBS/2%PFA and acquired on a Novocyte flow cytometer (ACEA biosciences). IC_{50} values for blocking were determined based on plotting mean fluorescence in the APC channel and analysis using Prism Graphpad software.

Internalization assay

[0146] Healthy donor peripheral blood mononuclear monocytes (PBMC) were used to determine internalization activity of anti-Siglec-7 antibodies. Previously cryopreserved PBMC were thawed and incubated for 90 minutes at 37°C in complete medium (RPMI medium supplemented with 10% fetal bovine serum). Five-fold serial dilutions of anti-Siglec-7 antibodies (100 nM-0.01 pM) were prepared in complete medium. Cells (5x10e4 per well) and antibody dilutions were combined in 96-well tissue culture plates and incubated at 37°C for 24 hours. Cells were re-suspended in huFc block (Becton Dickinson) in FACS buffer and stained with an antibody cocktail containing CD3-FITC, CD16-PE and anti-Siglec-7 antibody 4B12-AF647 for 1 hour on ice. After two washes, cells were fixed in PBS/2%PFA and acquired on a Novocyte flow cytometer. IC_{50} values for internalization were determined based on plotting mean fluorescence in the APC channel on NK cells (gated as CD3-CD16+) and analysis using Prism Graphpad software.

Primary tumor analysis

[0147] Single cells from primary human tumor specimens were prepared using the Mylteni GentleMACS instrument according to the manufacturer's instructions. Cells were re-suspended in huFc block (Becton Dickinson) in FACS buffer and staining was performed using cocktails containing conjugated antibodies against immune cell surface markers, including CD3, CD8, CD16, CD45 and 7-AAD as a viability marker. CD8+ T cells were identified and gated as 7-AAD- CD45+ CD3+ CD8+. Anti-Siglec-7-PE (clone S7.7 Biolegend) was used to detect Siglec-7 levels. Cells were fixed in PBS/2%PFA and acquired on a Novocyte cytometer. Gating and analysis was performed using Flowjo software (Tristar).

[0148] Ligand levels on tumor cells were detected using Siglec-7-ECD-Fc as described under Ligand blocking assay above. As a specificity control, cells were treated with sialidase/neuraminidase (Roche) at 0.1U/mL to remove sialic acids from the cell surface.

[0149] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, accession numbers, and patent applications cited herein are hereby incorporated by reference for the purposes in the context of which they are cited.

Table of illustrative sequences

SEQ ID NO:1 heavy chain variable region sequence (16H11); CDRs as defined by Kabat: underline; CDRs as defined by Chothia: bold, italics

QVQLHQSGAELVKPGASVKISCKGS***GYDFSNF***WMNWVKQRPGKGLEWIGQI***YPGDGE***IKYNGKFKGKATLTA
DESSSTAYIHLSSLTSEDSAVYFCAR***DDYLRAMDY***WGQGTSVTVSS

SEQ ID NO:2 heavy chain variable region sequence (2G12); CDRs as defined by Kabat: underlined; CDRs as defined by Chothia: bold, italics

QVQLQQPGAELVKPGASVKLSCKAS***GYTFTSY***WMQWVKQRPGQGLEWIGEI***DPSVSY***TEYNQKFKGKAT
LTVDTSSSTAYMQLSSLTSEDSAVYFCAR***WSKDYYGMDY***WGQGTSVTVSS

SEQ ID NO:3 heavy chain variable region sequence (5D1); CDRs as defined by Kabat: underlined; CDRs as defined by Chothia: bold, italics

QVQLQQPGAELVKPGASVKMSCKAS***GYTFTSS***WITWVKDRPGQGLEWIGDI***YPGNGN***TNYNEKFKSKAT
LTVDTSSNTVYMQLSSLTSEDSAVHYCAR***DGRGYFDY***WGPGTTLTVSS

SEQ ID NO:4 heavy chain variable region sequence (8A2); CDRs as defined by Kabat: underlined; CDRs as defined by Chothia: bold, italics

QVQLKESGPGLVAPSQSLSITCTVS***GFSLTTY***GVDWVRQFPGKGLEWLGVI***WGGGN***TNYNSALMSRLSI
SKDTSKSQVFLKMNSLQTDDTAMYYCAK***HKGTSHAMEY***WGQGTSVTVSS

SEQ ID NO:11 heavy chain variable region sequence (4B12); CDRs as defined by Kabat: underlined; CDRs as defined by Chothia: bold, italics

EVQLQQSGPELVKPGASVKIPCKAS***GYTFTDY***NMDWVKQSHEKSLEWIGDI***DPHNGV***TLYNQKFKDKAT
LTIDKSSNTAYMELRSLTSEDSAVYYCAL***TGSTY***WGQGTLVTVSA

SEQ ID NO:15 light chain variable region sequence (16H11); CDRs as defined by both Kabat and Chothia are underlined

DIQMTQSPASLSASVGETVTITCRASGNIHNYLAWFQQKQGKSPHFLVYSAKALADGVPSRFSGSGSGT
QYSLKINSLQPEDFGTYYCQHFWSSPYTFGGGTKLEIK

SEQ ID NO:16 light chain variable region sequence (2G12); CDRs as defined by both Kabat and Chothia are underlined.

DIVLTQSHKFMSTSVGDRVTITCKASQDVSTAVAWYQQKPGQSPKLLIYWTSTRHTGVPDRFTGSGSGT
DHTLTISSVQAEDLALYYCHQQYSTPPTFGGGTKLEIK

SEQ ID NO:18 light chain variable region sequence (8A2); CDRs as defined by both Kabat and Chothia are underlined.

QIVLTQSPAIMSASPGEKVTMTCSASSRVIFMYWYQQKPGSSPRLLIYDTSNLASGVPVRFSGGGSGTS
YSLTISRMEAEDAATYYCQQWSSYPPTFGAGTKLELK

SEQ ID NO:17 light chain variable region sequence (5D1); CDRs as defined by both Kabat and Chothia are underlined.

DIQMTQTTSSLSASLGDRVTIICRASQDISNFLNWYQQKPDGTVKLLMYDTSILQSGVPSRFSGRGSGA
DYSLTINNLEQEDLATYFCQQGKTLPYTFGGGTKLEIK

SEQ ID NO:25 light chain variable region sequence (4B12); CDRs as defined by both Kabat and Chothia are underlined.

DIVMTQSQKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKAVIYSASYRNSGVPDRFTGSGSGT DFTLTISNVQSEDLTEYFCQQYNNYPYTFGGGTKLEIK

SEQ ID NOS:29-78—humanized variable region sequences derived from 16A11:

SEQ ID NO:29 Humanized V_H region 386-1 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWISWVRQAPGQGLEWMGGIYPGDG EINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL VTVSS

SEQ ID NO:30 Humanized V_H region 392-3 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSNFWISWVRQAPGQGLEWMGGIYPGDG EINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL VTVSS

SEQ ID NO:31 Humanized V_H region 392-4 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGGDFSNFWISWVRQAPGQGLEWMGGIYPGDG EINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL VTVSS

SEQ ID NO:32 Humanized VH region 393-4 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWISWVRQAPGQGLEWMGGIIPGDGE INYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL VTVSS

SEQ ID NO:33 Humanized V_H region 393-8 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWISWVRQAPGQGLEWMGGIYPIDGE INYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL VTVSS

SEQ ID NO:34 Humanized V_H region 394-2 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWISWVRQAPGQGLEWMGGIYPGDG TINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL VTVSS

SEQ ID NO:35 Humanized V_H region 394-4 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWISWVRQAPGQGLEWMGGIYPGDG EANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGT LVTVSS

SEQ ID NO:36 Humanized V_H region 400-5 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSSYAISWVRQAPGQGLEWMGGIYPGDG EINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL VTVSS

SEQ ID NO:37 Humanized V_H region 400-7 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSSFWISWVRQAPGQGLEWMGGIYPGDG
EINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL
VTVSS

SEQ ID NO:38 Humanized V_H region 400-9 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSSYWISWVRQAPGQGLEWMGGIYPGDG
EINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL
VTVSS

SEQ ID NO:39 Humanized V_H region 400-14 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNYAISWVRQAPGQGLEWMGGIYPGDG
EINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL
VTVSS

SEQ ID NO:40 Humanized V_H region 401-1 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWISWVRQAPGQGLEWMGGIYPGFG
EINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQGTL
VTVSS

SEQ ID NO:41 Humanized V_H region 417-8 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGGIYPGD
GEINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDVWGQG
TMVTVSS

SEQ ID NO:42 Humanized V_H region 417-17 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGGIYPGD
GEINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:43 Humanized V_H region 387-11 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKGSGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTLTADESTSTAYMELSSLRSEDTAVYFCARDDYLRAMDYWGQG
TLVTVSS

SEQ ID NO:44 Humanized V_H region 410-1 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGGIYPGD
GEINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQG
TLVTVSS

SEQ ID NO:45 Humanized V_H region 438-4 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTLTADESTSTAYMELSSLRSEDTAVYFCARDDYLRAMDYWGQG
TLVTVSS

SEQ ID NO:46 Humanized V_H region 440-2 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKGSGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYFCARDDYLRAMDYWGQGT
LVTVSS

SEQ ID NO:47 Humanized V_H region 441-2 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKGSGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTLTADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:48 Humanized V_H region 443-1 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKGSGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:49 Humanized V_H region 444-2amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYFCARDDYLRAMDYWGQGT
LVTVSS

SEQ ID NO:50 Humanized V_H region 445-3 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTLTADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:51 Humanized V_H region 446-7 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:52 Humanized V_H region 447-2 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEINYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:53 Humanized V_H region 449-4 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGGIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:54 Humanized V_H region 449-6 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKGSGYDFSNFWMNWVRQAPGQGLEWMGGIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:55 Humanized V_H region 463-2 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQG
TLVTVSS

SEQ ID NO:56 Humanized V_H region 465-2 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEINYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:57 Humanized V_H region 465-17 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFWMNWVRQAPGQGLEWMGQIYPGD
GEIKYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:58 Humanized V_H region 484-6 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNYWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:59 Humanized V_H region 484-7 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNYWMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQG
TLVTVSS

SEQ ID NO:60 Humanized V_H region 485-4 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFAMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDYWGQG
TLVTVSS

SEQ ID NO:61 Humanized V_H region 485-5 amino acid sequence; CDRs as defined by Chothia are underlined

QVQLVQSGAEVKKPGSSVKVSCKASGYDFSNFAMNWVRQAPGQGLEWMGQIYPGD
GEIKYNQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDDYLRAMDIWGQGT
MVTVSS

SEQ ID NO:62 Humanized V_L region 381-1 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAPKLLLYSAKRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:63 Humanized V_L region 390-8 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGNIHNSLAWYQQKPGKAPKLLLYSAKRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:64 Humanized V_L region 391-1 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAPKLLLYAASRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:65 Humanized V_L region 391-8 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAPKLLLYSASRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:66 Humanized V_L region 395-1 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGGIHNYLAWYQQKPGKAPKLLLYSAKRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:67 Humanized V_L region 395-4 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASQNIHNYLAWYQQKPGKAPKLLLYSAKRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:68 Humanized V_L region 396-2 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGNISNYLAWYQQKPGKAPKLLLYSAKRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:69 Humanized V_L region 418-2 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAPKFLLYSAKRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:70 Humanized V_L region 419-2 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASQNIHNYLAWYQQKPGKAPKFLLYSAKRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:71 Humanized V_L region 421-3 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAPKFLLYSAKRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGQGTKLEIK

SEQ ID NO:72 Humanized V_L region 424-1 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAPKLLLYSAKRLASGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:73 Humanized V_L region 425-3 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAPKLLLYSAKRLEDGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:74 Humanized V_L region 426-2 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASQNIHNYLAWYQQKPGKAPKLLLYSAKRLASGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:75 Humanized V_L region 427-1 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASQNIHNYLAWYQQKPGKAPKLLLYSAKRLEDGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:76 Humanized V_L region 435-7 amino acid sequence; CDRs as defined by Chothia are underlined

DIQMTQSPSSLSASVGDRVTITCRASQNIHNYLAWYQQKPGKAPKFLLYSAKRLEDGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGGGTKVEIK

SEQ ID NO:77 Humanized V_L region 439-5 amino acid sequence

DIQMTQSPSSLSASVGDRVTITCRASQNIHNYLAWYQQKPGKAPKFLLYSAKRLEDGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGQGTKLEIK

SEQ ID NO:78 Humanized V_L region 448-3 amino acid sequence

DIQMTQSPSSLSASVGDRVTITCRASQNIHNYLAWYQQKPGKAPKFLLYSAKRLESGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWSSPYTFGQGTKLEIK

SEQ ID NOS:104-107 humanized variable region sequences derived from 8A2:

SEQ ID NO:104 humanized heavy chain variable region sequence RHA; CDRs as defined by Chothia are underlined

QVQLQESGPGLVKPSETLSLTCTVSGFSLTTYGWSWIRQPPGKGLEWIGYIWGGGNTN
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAKHKGTSHAMEYWGQGTMV
TVSS

SEQ ID NO:105: humanized light chain variable region sequence RKA; CDRs as defined by Chothia are underlined

EIVLTQSPATLSLSPGERATLSCRASSRVIFLAWYQQKPGQAPRLLIYDTSNKATGVPA
RFSGSGSGTDFTLTISSLEPEDFAVYYCQQWSSYPPTFGGGTKVEIK

SEQ ID NO:106 humanized heavy chain variable region sequence RHB; CDRs as defined by Chothia are underlined

QVQLQESGPGLVKPSETLSLTCTVSGFSLTTYGVDWVRQPPGKGLEWIGVIWGGGNT
NYNSSLKSRVTISKDTSKNQVFLKLSSVTAADTAVYYCAKHKGTSHAMEYWGQGTM
VTVSS

SEQ ID NO:107 humanized light chain variable region sequence RKB; CDRs as defined by Chothia are underlined

QIVLTQSPATLSLSPGERATLSCRASSRVIFMYWYQQKPGQSPRLLIYDTSNLATGVPA
RFSGGGSGTDYTLTISSLEPEDFAVYYCQQWSSYPPTFGGGTKVEIK

WHAT IS CLAIMED IS:

1. An anti-Siglec-7 antibody that competes with an antibody having a variable heavy chain sequence of SEQ ID NO:1 and a variable light chain sequence of SEQ ID NO:15 for binding to Siglec-7; wherein the antibody comprises a variant Fc region that comprises at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region.

2. The anti-Siglec-7 antibody of claim 1, wherein the variant Fc region has at least 80%, or at least 90%, amino acid sequence identity to a native human Fc region.

3. The anti-Siglec-7 antibody of claim 1 or 2, wherein the antibody has internalization activity and does not block ligand binding to Siglec-7.

4. The anti-Siglec-7 antibody of claim 1, 2, or 3, wherein the variant Fc region comprises at least one amino acid modification, or at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of 232, 233, 234, 235, 236, 237, 238, 242, 252, 254, 256, 259, 267, 268, 287, 292, 297, 302, 306, 309, 322, 323, 327, 328, 329, 330, 331, 332, and 334.

5. The anti-Siglec-7 antibody of claim 1, 2, or 3, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 328, 330, and 331 that reduces effector function.

6. The anti-Siglec-7 antibody of claim 5, wherein the variant Fc region comprises at least two amino acid modifications, or at least three modifications, at positions selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328.

7. The anti-Siglec-7 antibody of claim 1, 2, or 3, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 234A/V, 235A, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

8. The anti-Siglec-7 antibody of claim 7, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from the group

consisting of 234A/V/F, 235A/Q, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

9. The anti-Siglec-7 antibody of claim 1, 2, or 3, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

10. The anti-Siglec-7 antibody of claim 9, wherein the variant Fc region comprises at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

11. The anti-Siglec-7 antibody of claim 1, 2, or 3, wherein the variant Fc region comprises at least one amino acid, or at least two amino acid, or at leaset three amino acids, selected from the group consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C.

12. The anti-Siglec-7 antibody of any one of claims 5, 6, 7, or 8, wherein the variant Fc region comprises at least one amino acid modification, or at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

13. The anti-Siglec-7 antibody of any one of claims 5, 6, 7, or 8, wherein the variant Fc region comprises at least one amino acid, or at least two amino acid, or at leaset three amino acids, selected from the group consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C.

14. The anti-Siglec-7 antibody of any one of claims 1 to 8, or wherein the variant Fc region further comprises at least one amino acid selected from the group consisting of 252Y, 254T, 256E, 232S and 233S.

15. The anti-Siglec-7 antibody of claim 14, wherein the variant Fc region comprises amino acids 252Y, 254T, and 256E.

16. The anti-Siglec-7 antibody of claim 1, 2, or 3, wherein the variant Fc region is a human IgG1 region comprising amino acid modifications:

(i) L234A and L235A;
(ii) A327G, A330S, and P331S;
(iii) E233P, L234V, L235A, and G236-;
(iv) E233P, L234V, and L235A;
(v) E233P, L234V, L235A, G236-, A327G, A330S, and P331S;
(vi) E233P, L234V, L235A, A327G, A330S, and P331S;
(vii) N297A, N297G, or N297Q;
(viii) L242C, N297C, and K334C;
(ix) A287C, N297G, and L306C;
(x) R292C, N297G, and V302C;
(xi) N297G, V323C, and I332C;
(xii) V259C, N297G, and L306C
(xiii) L234F, L235Q, K322Q, M252Y, S254T,and T256E; or
(xiv) L234A, L235A, and P329G.

17. The anti-Siglec-7 antibody of claim 1, 2, or 3, wherein the variant Fc region is a human IgG2 region comprising amino acid modifications:
(i) A330S and P331S;
(ii) V234A, G237A, P238S, H268A, V309L, A330S, and P331S; or
(iii) V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, or T256E.

18. The anti-Siglec-7 antibody of claim 1, 2, or 3, wherein the variant Fc region is a human IgG4 region comprising amino acid modifications:
(i) E233P, F234V, L235A, and G236-;
(ii) E233P, F234V,and L235A; or
(iii) S228P and L235E/A.

19. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the antibody comprises a heavy chain variable region comprising a CDR3 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which 1, 2, or 3 amino acids are substituted.

20. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the anti-Siglec-7 antibody comprises a heavy chain variable region comprising a CDR3 as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61.

21. The anti-Siglec-7 antibody of claim 19 or 20, where the heavy chain variable region comprises a CDR1 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which 1, 2, or 3 amino acids are substituted; and/or a CDR2 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 in which 1, 2, or 3 amino acids are substituted.

22. The anti-Siglec-7 antibody of claim 19 or 20, where the heavy chain variable region comprises a CDR1 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61 and a CDR2 having a sequence as set forth in any one of SEQ ID NOS:29-31, 33, and 35-61.

23. The anti-Siglec-7 antibody of any one of claims 1 to 22, wherein the anti-Siglec-7 antibody comprises a light chain variable region comprising a CDR3 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78 in which 1, 2, or 3 amino acids are substituted.

24. The anti-Siglec-7 antibody of any one of claims 1 to 22, wherein the anti-Siglec-7 antibody comprises a light chain variable region comprising a CDR3 as set forth in any one of SEQ ID NOS:62 and 64-78.

25. The anti-Siglec-7 antibody of claim 23 or 24, where the light chain variable region comprises a CDR1 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78 in which 1, 2, or 3 amino acids are substituted; and/or a CDR2 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78 in which 1, 2, or 3 amino acids are substituted.

26. The anti-Siglec-7 antibody of claim 23 or 24, where the light chain variable region comprises a CDR1 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78 and a CDR2 having a sequence as set forth in any one of SEQ ID NOS:62 and 64-78.

27. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the anti-Siglec-7 antibody comprises a heavy chain variable region having at least 80%, or at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of any one of SEQ ID NOS:29-31, 33, and 35-61.

28. The anti-Siglec-7 antibody of any one of claims 1 to 18, or 27, wherein the anti-Siglec-7 antibody comprises a light chain variable region having at least 80%, or at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a light chain variable region of any one of SEQ ID NOS:62 and 64-78.

29. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the anti-Siglec-7 antibody comprises a heavy chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a heavy chain variable region of any of SEQ ID NOS:41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, 58, 59, 60 or 61; and a light chain variable region having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of a light chain variable region of SEQ ID NO:69, 70, 71, 72, 73, 74, 75, 76, 77, or 78.

30. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the anti-Siglec-7 antibody comprises a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in a heavy chain variable region sequence selected from SEQ ID NO:43, 45, 46, 47, 48, 49, 50, 51, 54, 55, 57, and 58; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO:69.

31. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the anti-Siglec-7 antibody comprises a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in a heavy chain variable region sequence selected from SEQ ID NO:53, 54, 51, 55, 58, and 59; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO:78.

32. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the anti-Siglec-7 antibody comprises:

a) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:43, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(b) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:45, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(c) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:46, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(d) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:47, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(e) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:48, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(f) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:49, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(g) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:50, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(h) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:51, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(i) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in a heavy chain variable region sequence SEQ ID NO:54, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(j) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:55, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69;

(k) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:57, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69; or

(l) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:58, and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:69.

33. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the anti-Siglec-7 antibody comprises:

a) a heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:53; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(b) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:54; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(c) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:51; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(d) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:55; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78;

(e) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:58; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78; or

(f) heavy chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:59; and a light chain variable region comprising the CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:78.

34. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the anti-Siglec-7 antibody comprises:

a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:43 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:45 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:46 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(d) a heavy chain variable region comprising the amino acid sequence of ID NO:47 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:48 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:49 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:50 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(h) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:54 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69;

(j) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:55 and a light chain variable comprising the amino acid sequence of SEQ ID NO:69;

(k) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:57 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:69; or

(l) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:58 and a light chain variable comprising the amino acid sequence of SEQ ID NO:69.

35. The anti-Siglec-7 antibody of any one of claims 1 to 18, wherein the anti-Siglec-7 antibody comprises:

a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78;

(b) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:54 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78;

(c) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78;

(d) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:55 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78;

(e) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:58 and a light chain variable region comprising the amino acid sequence of ; or

(f) heavy chain variable region comprising the amino acid sequence of SEQ ID NO:59 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:78.

36. An anti-Siglec-7 antibody that blocks binding of ligand to Siglec-7 and competes with antibody QA79 produced from the hybridoma deposited under accession number ICLC PD99003 for binding to Siglec-7, but does not compete with antibody Z176 or antibody S7.7 for binding to Siglec-7; wherein the antibody comprises a variant Fc region comprising at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region.

37. The anti-Siglec-7 antibody of claim 36, wherein the variant Fc region has at least 80%, or least 90%, amino acid sequence identity to a native human Fc region sequence.

38. The anti-Siglec-7 antibody of claim 36 or 37, wherein the variant Fc region comprises at least one amino acid modification, or at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of the group consisting of 232, 233, 234, 235, 236, 237, 238, 242, 252, 254, 256, 259, 267, 268, 287, 292, 297, 302, 306, 309, 322, 323, 327, 328, 329, 330, 331, 332, and 334.

39. The anti-Siglec-7 antibody of claim 36 or 37, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group

consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328 that reduces effector function.

40. The anti-Siglec-7 antibody of claim 39, wherein the variant Fc region comprises at least two amino acid modifications, or at least three modifications, at positions selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328.

41. The anti-Siglec-7 antibody of claim 36 or 37, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 234A/V, 235A, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

42. The anti-Siglec-7 antibody of claim 41, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from the group consisting of 234A/V/F, 235A/Q, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

43. The anti-Siglec-7 antibody of claim 36, 37, or 39, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

44. The anti-Siglec-7 antibody of claim 43, wherein the variant Fc region comprises at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

45. The anti-Siglec-7 antibody of claim 36, 37, or 39, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C.

46. The anti-Siglec-7 antibody of claim 45, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from thegroup

consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C

47. The anti-Siglec-7 antibody of any one of claims 36 to 42, wherein the variant Fc region further comprises at least one amino acid selected from the group consisting of 252Y, 254T, 256E, 232S and 233S.

48. The anti-Siglec-7 antibody of claim 47, wherein the variant Fc region comprises amino acids 252Y, 254T, and 256E.

49. The anti-Siglec-7 antibody of claim 36 or 37, wherein the variant Fc region is a human IgG1 region comprising amino acid modifications:

(i) L234A and L235A;
(ii) A327G, A330S, and P331S;
(iii) E233P, L234V, L235A, and G236-;
(iv) E233P, L234V, and L235A;
(v) E233P, L234V, L235A, G236-, A327G, A330S, and P331S;
(vi) E233P, L234V, L235A, A327G, A330S, and P331S;
(vii) N297A, N297G, or N297Q;
(viii) L242C, N297C, and K334C;
(ix) A287C, N297G, and L306C;
(x) R292C, N297G, and V302C;
(xi) N297G, V323C, and I332C;
(xii) V259C, N297G, and L306C
(xiii) L234F, L235Q, K322Q, M252Y, S254T,and T256E; or
(xiv) L234A, L235A, and P329G.

50. The anti-Siglec-7 antibody of claim 36 or 37, wherein the variant Fc region is a human IgG2 region comprising amino acid modifications:

(i) A330S and P331S;
(ii) V234A, G237A, P238S, H268A, V309L, A330S, and P331S; or
(iii) V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, or T256E.

51. The anti-Siglec-7 antibody of claim 36 or 37, wherein the variant Fc region is a human IgG4 region comprising amino acid modifications:

(i) E233P, F234V, L235A, and G236-;
(ii) E233P, F234V,and L235A; or
(iii) S228P and L235E/A.

52. The anti-Siglec-7 antibody of any one of claims 36 to 51, wherein anti-Siglec-7 antibody competes with an antibody comprising a V_H sequence and V_L sequence designated as 2G12 in Figures 1 and 2.

53. The anti-Siglec-7 antibody of any one of claims 36 to 52, wherein the anti-Siglec-7 antibody has a V_H region that comprises at least one CDR, or at least two CDRs, of a heavy chain variable region sequence of SEQ ID NO:2.

54. The anti-Siglec-7 antibody of any one of claims 36 to 53, wherein the anti-Siglec-7 antibody has a V_H region that comprises a CDR3 of a heavy chain variable region sequence of SEQ ID NO:2.

55. The anti-Siglec-7 antibody of any one of claims 36 to 52, wherein the anti-Siglec-7 antibody has a V_H region that comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence of SEQ ID NO:2.

56. The anti-Siglec-7 antibody of any one of claims 36 to 55, wherein the anti-Siglec-7 antibody has a V_L region that comprises at least one CDR, or at least two CDRs, of a light chain variable region sequence of SEQ ID NO:16.

57. The anti-Siglec-7 antibody of any one of claims 36 to 55, wherein the anti-Siglec-7 antibody has a V_L region that comprises a CDR3 of a light chain variable region sequence of SEQ ID NO:16.

58. The anti-Siglec-7 antibody of any one of claims 36 to 55, wherein the anti-Siglec-7 antibody has a V_L region that comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence of SEQ ID NO:16.

59. An anti-Siglec-7 antibody that has internalization activity, does not block ligand binding to Siglec-7, and competes with antibody S7.7, but not with antibody QA79 or antibody Z176, for binding to Siglec-7; wherein the antibody comprises a variant Fc region comprising at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region.

60. The anti-Siglec-7 antibody of claim 59, wherein the variant Fc region has at least 80%, or at least 90%, amino acid sequence identity to a native human Fc region sequence.

61. The anti-Siglec-7 antibody of claim 59 or 60, wherein the variant Fc region comprises at least one amino acid modification, or at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of the group consisting of 232, 233, 234, 235, 236, 237, 238, 242, 252, 254, 256, 259, 267, 268, 287, 292, 297, 302, 306, 309, 322, 323, 327, 328, 329, 330, 331, 332, and 334.

62. The anti-Siglec-7 antibody of claim 59 or 60, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328 that reduces effector function.

63. The anti-Siglec-7 antibody of claim 62, wherein the variant Fc region comprises at least two amino acid modifications, or at least three modifications, at positions selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328.

64. The anti-Siglec-7 antibody of claim 59 or 60, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 234A/V, 235A, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

65. The anti-Siglec-7 antibody of claim 64, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from the group consisting of 234A/V/F, 235A/Q, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

66. The anti-Siglec-7 antibody of claim 59, 60, or 62, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

67. The anti-Siglec-7 antibody of claim 66, wherein the variant Fc region comprises at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

68. The anti-Siglec-7 antibody of claim 59, 60, or 62, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C.

69. The anti-Siglec-7 antibody of claim 68, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from thegroup consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C

70. The anti-Siglec-7 antibody of any one of claims 59 to 65, wherein the variant Fc region further comprises at least one amino acid selected from the group consisting of 252Y, 254T, 256E, 232S and 233S.

71. The anti-Siglec-7 antibody of claim 70, wherein the variant Fc region comprises amino acids 252Y, 254T, and 256E.

72. The anti-Siglec-7 antibody of claim 59 or 60, wherein the variant Fc region is a human IgG1 region comprising amino acid modifications:

(i) L234A and L235A;
(ii) A327G, A330S, and P331S;
(iii) E233P, L234V, L235A, and G236-;
(iv) E233P, L234V, and L235A;
(v) E233P, L234V, L235A, G236-, A327G, A330S, and P331S;
(vi) E233P, L234V, L235A, A327G, A330S, and P331S;
(vii) N297A, N297G, or N297Q;
(viii) L242C, N297C, and K334C;
(ix) A287C, N297G, and L306C;
(x) R292C, N297G, and V302C;
(xi) N297G, V323C, and I332C;

(xii) V259C, N297G, and L306C

(xiii) L234F, L235Q, K322Q, M252Y, S254T,and T256E; or

(xiv) L234A, L235A, and P329G.

73. The anti-Siglec-7 antibody of claim 59 or 60, wherein the variant Fc region is a human IgG2 region comprising amino acid modifications:

(i) A330S and P331S;

(ii) V234A, G237A, P238S, H268A, V309L, A330S, and P331S; or

(iii) V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, or T256E.

74. The anti-Siglec-7 antibody of claim 59 or 60, wherein the variant Fc region is a human IgG4 region comprising amino acid modifications:

(i) E233P, F234V, L235A, and G236-;

(ii) E233P, F234V,and L235A; or

(iii) S228P and L235E/A.

75. The anti-Siglec-7 antibody of any one of claims 59 to 74, wherein the anti-Siglec-7 antibody competes for bindingto Siglec-7 with an antibody comprising a V_H sequence and V_L sequence designated as 8A2 in Figures 1 and 2.

76. The anti-Siglec-7 antibody of any one of claims 59 to 75, wherein the anti-Siglec-7 antibody has a V_H region that comprises at least one CDR, or at least two CDRs, of a heavy chain variable region sequence of SEQ ID NO:4, SEQ ID NO:104, or SEQ ID NO:106.

77. The anti-Siglec-7 antibody of any one of claims 59 to 76, wherein the anti-Siglec-7 antibody has a V_H region that comprises a CDR3 of a heavy chain variable region sequence of SEQ ID NO:4, SEQ ID NO:104, or SEQ ID NO:106.

78. The anti-Siglec-7 antibody of any one of claims 59 to 75, wherein the anti-Siglec-7 antibody has a V_H region that comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence of SEQ ID NO:4, SEQ ID NO:104, or SEQ ID NO:106.

79. The anti-Siglec-7 antibody of any one of claims 59 to 78, wherein the anti-Siglec-7 antibody has a V_L region that comprises at least one CDR, or at least two CDRs,

of a light chain variable region sequence of SEQ ID NO:18, SEQ ID NO:105, or SEQ ID NO:107.

80. The anti-Siglec-7 antibody of any one of claims 59 to 78, wherein the anti-Siglec-7 antibody has a V_L region that comprises a CDR3 of a light chain variable region sequence of SEQ ID NO:18, SEQ ID NO:105, or SEQ ID NO:107.

81. The anti-Siglec-7 antibody of any one of claims 59 to 78, wherein the anti-Siglec-7 antibody has a V_L region that comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence of SEQ ID NO:18, SEQ ID NO:105, or SEQ ID NO:107.

82. An anti-Siglec-7 antibody has internalization activity, does not block ligand binding to Siglec-7, and competes with antibody Z176, but not with antibody QA79 or antibody S7.7, for binding to Siglec-7; wherein the antibody comprises a variant Fc region comprising at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region.

83. The anti-Siglec-7 antibody of claim 82, wherein the Fc region has at least 80%, or at least 90%, amino acid sequence identity to a native human Fc region sequence.

84. The anti-Siglec-7 antibody of claim 82 or 83, wherein the variant Fc region comprises at least one amino acid modification, or at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of the group consisting of 232, 233, 234, 235, 236, 237, 238, 242, 252, 254, 256, 259, 267, 268, 287, 292, 297, 302, 306, 309, 322, 323, 327, 328, 329, 330, 331, 332, and 334.

85. The anti-Siglec-7 antibody of claim 82 or 83, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328 that reduces effector function.

86. The anti-Siglec-7 antibody of claim 85, wherein the variant Fc region comprises at least two amino acid modifications, or at least three modifications, at positions

selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328.

87. The anti-Siglec-7 antibody of claim 82 or 83, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 234A/V, 235A, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

88. The anti-Siglec-7 antibody of claim 87, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from the group consisting of 234A/V/F, 235A/Q, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

89. The anti-Siglec-7 antibody of claim 82, 83, or 85, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

90. The anti-Siglec-7 antibody of claim 89, wherein the variant Fc region comprises at least two amino acid modifications, or at least three amino acid modifications, at positions selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

91. The anti-Siglec-7 antibody of claim 82, 83, or 85, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C.

92. The anti-Siglec-7 antibody of claim 91, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from thegroup consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C

93. The anti-Siglec-7 antibody of any one of claims 82 to 88, wherein the variant Fc region further comprises at least one amino acid selected from the group consisting of 252Y, 254T, 256E, 232S and 233S.

94. The anti-Siglec-7 antibody of claim 93, wherein the variant Fc region comprises amino acids 252Y, 254T, and 256E.

95. The anti-Siglec-7 antibody of claim 82 or 83, wherein the variant Fc region is a human IgG1 region comprising amino acids modifications:

(i) L234A and L235A;

(ii) A327G, A330S, and P331S;

(iii) E233P, L234V, L235A, and G236-;

(iv) E233P, L234V, and L235A;

(v) E233P, L234V, L235A, G236-, A327G, A330S, and P331S;

(vi) E233P, L234V, L235A, A327G, A330S, and P331S;

(vii) N297A, N297G, or N297Q;

(viii) L242C, N297C, and K334C;

(ix) A287C, N297G, and L306C;

(x) R292C, N297G, and V302C;

(xi) N297G, V323C, and I332C;

(xii) V259C, N297G, and L306C

(xiii) L234F, L235Q, K322Q, M252Y, S254T,and T256E; or

(xiv) L234A, L235A, and P329G.

96. The anti-Siglec-7 antibody of claim 82 or 83, wherein the variant Fc region is a human IgG2 region comprising amino acid modifications:

(i) A330S and P331S;

(ii) V234A, G237A, P238S, H268A, V309L, A330S, and P331S; or

(iii) V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, or T256E.

97. The anti-Siglec-7 antibody of claim 82 or 83, wherein the variant Fc region is a human IgG4 region comprising amino acid modifications:

(i) E233P, F234V, L235A, and G236-;

(ii) E233P, F234V,and L235A; or

(iii) S228P and L235E/A.

98. The anti-Siglec-7 antibody of any one of claims 82 to 97, wherein the anti-Siglec-7 antibody competes with an antibody comprising a V_H sequence and V_L sequence designated as 5D1 in Figures 1 and 2.

99. The anti-Siglec-7 antibody of any one of claims 82 to 98, wherein the anti-Siglec-7 antibody has a V_H region that comprises at least one CDR, or at least two CDRs, of a heavy chain variable region sequence of SEQ ID NO:3.

100. The anti-Siglec-7 antibody of any one of claims 82 to 99 wherein the anti-Siglec-7 antibody has a V_H region that comprises a CDR3 of a heavy chain variable region sequence of SEQ ID NO:3.

101. The anti-Siglec-7 antibody of any one of claims 82 to 98, wherein the anti-Siglec-7 antibody has a V_H region that comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence of SEQ ID NO:3.

102. The anti-Siglec-7 antibody of any one of claims 82 to 101, wherein the anti-Siglec-7 antibody has a V_L region that comprises at least one CDR, or at least two CDRs, of a light chain variable region sequence of SEQ ID NO:17.

103. The anti-Siglec-7 antibody of any one of claims 82 to 101, wherein the anti-Siglec-7 antibody has a V_L region that comprises a CDR3 of a light chain variable region sequence of SEQ ID NO:17.

104. The anti-Siglec-7 antibody of any one of claims 82 to 101, wherein the anti-Siglec-7 antibody has a V_L region that comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence of SEQ ID NO:17.

105. An anti-Siglec-7 antibody that has internalization activity, does not block ligand binding to Siglec-7, and does not compete with antibody Z176, antibody QA79, or antibody S7.7 for binding to Siglec-7; wherein the antibody comprises a variant Fc region comprising at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region.

106. The anti-Siglec-7 antibody of claim 105, wherein the Fc region has at least 80%, or at least 90%, amino acid sequence identity to a native human Fc region sequence.

107. The anti-Siglec-7 antibody of claim 105 or 106, wherein the variant Fc region comprises at least one amino acid modification, or at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of the group consisting of 232, 233, 234, 235, 236, 237, 238, 242, 252, 254, 256, 259, 267, 268, 287, 292, 297, 302, 306, 309, 322, 323, 327, 328, 329, 330, 331, 332, and 334.

108. The anti-Siglec-7 antibody of claim 105 or 106, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328.

109. The anti-Siglec-7 antibody of claim 108, wherein the variant Fc region comprises at least two amino acid modifications, or at least three modifications, at positions selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328.

110. The anti-Siglec-7 antibody of claim 105 or 106, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 234A/V, 235A, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

111. The anti-Siglec-7 antibody of claim 110, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from the group consisting of 234A/V/F, 235A/Q, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

112. The anti-Siglec-7 antibody of claim 105, 106, or 108, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

113. The anti-Siglec-7 antibody of claim 112, wherein the variant Fc region comprises at least two amino acid modifications, or at least three amino acid modifications, at positions selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

114. The anti-Siglec-7 antibody of claim 105, 106, or 108, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C.

115. The anti-Siglec-7 antibody of claim 115, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from thegroup consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C

116. The anti-Siglec-7 antibody of any one of claims 105 to 111, wherein the variant Fc region further comprises at least one amino acid selected from the group consisting of 252Y, 254T, 256E, 232S and 233S.

117. The anti-Siglec-7 antibody of claim 116, wherein the variant Fc region comprises amino acids 252Y, 254T, and 256E.

118. The anti-Siglec-7 antibody of claim 105 or 106, wherein the variant Fc region is a human IgG1 region comprising amino acidmodifications:

(i) L234A and L235A;
(ii) A327G, A330S, and P331S;
(iii) E233P, L234V, L235A, and G236-;
(iv) E233P, L234V, and L235A;
(v) E233P, L234V, L235A, G236-, A327G, A330S, and P331S;
(vi) E233P, L234V, L235A, A327G, A330S, and P331S;
(vii) N297A, N297G, or N297Q;
(viii) L242C, N297C, and K334C;
(ix) A287C, N297G, and L306C;
(x) R292C, N297G, and V302C;
(xi) N297G, V323C, and I332C;

(xii) V259C, N297G, and L306C

(xiii) L234F, L235Q, K322Q, M252Y, S254T,and T256E; or

(xiv) L234A, L235A, and P329G.

119. The anti-Siglec-7 antibody of claim 105 or 106, wherein the variant Fc region is a human IgG2 region comprising amino acid modifications:

(i) A330S and P331S;

(ii) V234A, G237A, P238S, H268A, V309L, A330S, and P331S; or

(iii) V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, or T256E.

120. The anti-Siglec-7 antibody of claim 105 or 106, wherein the variant Fc region is a human IgG4 region comprising amino acid modifications:

(i) E233P, F234V, L235A, and G236-;

(ii) E233P, F234V,and L235A; or

(iii) S228P and L235E/A.

121. The anti-Siglec-7 antibody of any one of claims 105 to 120 wherein the anti-Siglec-7 antibody competes with an antibody comprising a V_H sequence and V_L sequence designated as 4B12 in Figures 1 and 2.

122. The anti-Siglec-7 antibody of any one of claims 105 to 121, wherein the anti-Siglec-7 antibody has a V_H region that comprises at least one CDR, or at least two CDRs, of a heavy chain variable region sequence of SEQ ID NO:11.

123. The anti-Siglec-7 antibody of claim 122, wherein the anti-Siglec-7 antibody has a V_H region that comprises a CDR3 of a heavy chain variable region sequence of SEQ ID NO:11.

124. The anti-Siglec-7 antibody of any one of claims 105 to 121, wherein the anti-Siglec-7 antibody has a V_H region that comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence of SEQ ID NO:11.

125. The anti-Siglec-7 antibody of any one of claims 105 to 124, wherein the anti-Siglec-7 antibody has a V_L region that comprises at least one CDR, or at least two CDRs, of a light chain variable region sequence of SEQ ID NO:25.

126. The anti-Siglec-7 antibody of any one of claims 105 to 124, wherein the anti-Siglec-7 antibody has a V_L region that comprises a CDR3 of a light chain variable region sequence of SEQ ID NO:25.

127. The anti-Siglec-7 antibody of any one of claims 105 to 124, wherein the anti-Siglec-7 antibody has a V_L region that comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence of SEQ ID NO:25.

128. An anti-Siglec-7 antibody having a V_H region that comprises at least one CDR, or at least two CDRs, of a V_H region sequence set forth in Figure 1; wherein the antibody comprises a variant Fc region comprising at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region.

129. An anti-Siglec-7 antibody of claim 128, wherein the V_H region comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence set forth in Figure 1.

130. The anti-Siglec-7 antibody of claim 129, wherein the V_H region comprises a heavy chain variable region sequence set forth in Figure 1.

131. An anti-Siglec-7 antibody having a V_L region that comprises at least one CDR, or at least two CDRs, of a V_L region sequence set forth in Figure 2; wherein the antibody comprises a variant Fc region comprising at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region.

132. The anti-Siglec-7 antibody of claim 131, wherein the V_L region comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence set forth in Figure 2..

133. The anti-Siglec-7 antibody of claim 132, where the V_L region comprises a light chain variable region sequence set forth in Figure 2.

134. An anti-Siglec-7 antibody having a V_H region that comprises at least one CDR, or at least two CDRs, of a V_H region sequence set forth in Figure 1; and a V_L

region that comprises at least one CDR, or at least two CDRs, of a V_L region sequence set forth in Figure 2; wherein the antibody comprises a variant Fc region comprising at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region.

135. The anti-Siglec-7 antibody of claim 134, wherein the V_H region comprises a CDR1, CDR2, and CDR3 of a heavy chain variable region sequence set forth in Figure 1; and the V_L region comprises a CDR1, CDR2, and CDR3 of a light chain variable region sequence set forth in Figure 2..

136. The anti-Siglec-7 antibody of claim 134, wherein the V_H region that comprises a heavy chain variable region sequence set forth in Figure 1; and the V_L region comprises a light chain variable region sequence set forth in Figure 2.

137. An anti-Siglec-7 antibody that competes for binding to Siglec-7 with antibody QA79; wherein the antibody comprises a variant Fc region comprising at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region.

138. The anti-Siglec-7 antibody of any one of claims 128 to 137, wherein the Fc region has at least 80%, or at least 90%, amino acid sequence identity to a native human Fc region sequence.

139. The anti-Siglec-7 antibody of any one of claims 128 to 138, wherein the variant Fc region comprises at least one amino acid modification, or at least two amino acid modifications, or at least three amino acid modifications, at a position selected from the group consisting of the group consisting of 232, 233, 234, 235, 236, 237, 238, 242, 252, 254, 256, 259, 267, 268, 287, 292, 297, 302, 306, 309, 322, 323, 327, 328, 329, 330, 331, 332, and 334.

140. The anti-Siglec-7 antibody of any one of claims 128 to 138, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328 that reduces effector function relative to a native Fc region.

141. The anti-Siglec-7 antibody of claim 140, wherein the variant Fc region comprises at least two amino acid modifications, or at least three modifications, at positions selected from the group consisting of 234, 235, 236, 237, 238, 267, 268, 297, 309, 322, 327, 330, 331, and 328.

142. The anti-Siglec-7 antibody of any one of claims 128 to 138, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 234A/V, 235A, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

143. The anti-Siglec-7 antibody of claim 142, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from the group consisting of 234A/V/F, 235A/Q, 236-, 237A, 238S, 236-, 267E, 268Q, 297A/G/Q, 327G, 309L, 322Q, 327G, 328F, 330S, and 331S.

144. The anti-Siglec-7 antibody of any one of claims 128 to 140, wherein the variant Fc region comprises at least one amino acid modification at a position selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

145. The anti-Siglec-7 antibody of claim 144, wherein the variant Fc region comprises at least two amino acid modifications, or at least three amino acid modifications, at positions selected from the group consisting of 232, 233, 242, 252, 254, 256, 259, 287, 292, 302, 306, 323, 329, 332, and 334.

146. The anti-Siglec-7 antibody of claim any one of claims 128 to 140, wherein the variant Fc region comprises at least one amino acid selected from the group consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C.

147. The anti-Siglec-7 antibody of claim 146, wherein the variant Fc region comprises at least two amino acids, or at least three amino acids, selected from thegroup consisting of 232S, 233S, 242C, 252Y, 254T, 256E, 259C, 287C, 292C, 302C, 306C, 323C, 329G, 332C, and 334C

148. The anti-Siglec-7 antibody of any one of claims 128 to 144143, wherein the variant Fc region further comprises at least one amino acid selected from the group consisting of 252Y, 254T, 256E, 232S and 233S.

149. The anti-Siglec-7 antibody of claim 148, wherein the variant Fc region comprises amino acids 252Y, 254T, and 256E.

150. The anti-Siglec-7 antibody of any one of claims 128 to 138, wherein the variant Fc region is a human IgG1 region comprising amino acid modifications:

(i) L234A and L235A;

(ii) A327G, A330S, and P331S;

(iii) E233P, L234V, L235A, and G236-;

(iv) E233P, L234V, and L235A;

(v) E233P, L234V, L235A, G236-, A327G, A330S, and P331S;

(vi) E233P, L234V, L235A, A327G, A330S, and P331S;

(vii) N297A, N297G, or N297Q;

(viii) L242C, N297C, and K334C;

(ix) A287C, N297G, and L306C;

(x) R292C, N297G, and V302C;

(xi) N297G, V323C, and I332C;

(xii) V259C, N297G, and L306C

(xiii) L234F, L235Q, K322Q, M252Y, S254T,and T256E; or

(xiv) L234A, L235A, and P329G.

151. The anti-Siglec-7 antibody of any one of claims 128 to 138, wherein the variant Fc region is a human IgG2 region comprising amino acid modifications:

(i) A330S and P331S;

(ii) V234A, G237A, P238S, H268A, V309L, A330S, and P331S; or

(iii) V234A, G237A, H268Q, V309L, A330S, P331S, C232S, C233S, S267E, L328F, M252Y, S254T, or T256E.

152. The anti-Siglec-7 antibody of any one of claims 128 to 138, wherein the variant Fc region is a human IgG4 region comprising amino acid modifications:

(i) E233P, F234V, L235A, and G236-;

(ii) E233P, F234V,and L235A; or

153. A bispecific or multi-specific antibody that comprises an antibody of any one of claims 1 to 152.

154. A method of inhibiting proliferation of tumor cells, the method comprising administering a therapeutically effective amount of an antibody of any one of claims 1 to 152, or a bispecific or multi-specific antibody of claim 153, to a patient that has a tumor that expresses sialylated Siglec-7 ligands.

155. The method of claim 154, wherein the tumor has an elevated number of CD8+ infiltrating T cells that express Siglec-7.

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16H11    1 QVQLHQSGAELVKPGASVKISCKGSGYDFSNFWMNWVKQRPGKGLEWIGQIYPGDGEIKYNGKFKGKATLTADESSSTAYIHLSSL
2G12     1 QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMQWVKQRPGQGLEWIGEIDPSVSYTEYNQKFKGKATLTVDTSSSTAYMQLSSL
5D1      1 QVQLQQPGAELVKPGASVKMSCKASGYTFTSSWITWVKDRPGQGLEWIGDIYPGNGNTNYNEKFKSKATLTVDTSSNTVYMQLSSL
8A2      1 QVQLKESGPGLVAPSQSLSITCTVSGFSLTTYGVDWVRQFPGKGLEWLGVIWGGGNTNYNSALMSRLSISKDTSKSQVFLKMNSL
9D4      1 QVTLKESGPGILQPSQTLSLTCSFSGFSLSTFGMGVGWIRQPSGKGLEWLAHIWWDDDKYYHPALKSRLTISKDTSNNQVFLKIANV
13D2     1 DVQLQESGPGMVKPSQSLSLTCTVTGYSITSDYDWHWIRHFPGNKLEWMGYISYSGSTKYNPSLKSRISITHDTSKNHFFLKLNSV
5215-2   1 DVQLQESGPGLVKPSQSLSLTCTVTGYSITSDYVWTWIRQFPGNKLEWMGYITYSDSTNYNPSLKSRLSITRDTSKNQFFLQLSSV
5G10     1 EVKLEESGGGLVQPGGSMKVSCVASGFTFSNYWMNWVRQSPEKGLEWVAQIRLKSDNYATHYAESVKGRFTISRDDSKSSVYLQMNNL
9H11     1 EVQLQQSGPELVKPGASVKISCKASGYTFTDYYINWVKQSHGKSLEWIGDNNPNNGGASYNQSFKGKATMTVDQSSRTAYLELRSL
10E11    1 EVQLQQSGPELVKPGDSVKISCKASGYSSTGYFMNWVMQSHGKSLEWIGRIIPYNGDTFYNQKFKDKATLTVDKSSNTAHLELRSL
4B12     1 EVQLQQSGPELVKPGASVKIPCKASGYTFTDYNMDWVKQSHEKSLEWIGDIDPHNGVTLYNQKFKDKATLTIDKSSNTAYMELRSL
3F1      1 EFQLQQSGPEMVKPGASVKMSCKASGDSFTDYKINWVKQNNGKSLEWIGVINPDSGTTSYNQIFEGKATLTVDQSSSTAYMQVNRL
5215-13  1 EVQLQQSGAELVKPGASVKLSCTVSGFNFKDTYIHWVKQRPEQGLEWIGRIDPANGNTKYASKFQDKATITADTSSNTVYMQLSSL
5215-9   1 EVQLQQSGAELVKSGASVKLSCTASGFNIKDTYMHWVKQRPEKGLEWIGWIDPADGHTKYDPKFQGKATITADTSSNTAYLHLSSL

16H11   87 TSEDSAVYFCARDDYLRAMDYWGQGTSVTVSS (SEQ ID NO:1)
2G12    87 TSEDSAVYFCARWSKDYYGMDYWGQGTSVTVSS (SEQ ID NO:2)
5D1     87 TSEDSAVHYCARDGRGYFDYWGPGTTLTVSS (SEQ ID NO:3)
8A2     86 QTDDTAMYYCAKHKGTSHAMEYWGQGTSVTVSS (SEQ ID NO:4)
9D4     88 DTAETATFYCARVERGYPLDHWGQGTTLRVSS (SEQ ID NO:5)
13D2    87 TAEDTATYYCARENDFPGFWYFDVWGTGTTVTVSS (SEQ ID NO:6)
5215-2  87 TTEDTATYFCARSLTGNYFDYWGQGTTLTVSS (SEQ ID NO:7)
5G10    89 RAEDTGIYYCTEGDYDIFAYWGQGTLVTVSA (SEQ ID NO:8)
9H11    87 TSEDSAVYYCARPERYWYFDAWGTGTTVTVSS (SEQ ID NO:9)
10E11   87 TSEDSVVYYCAGPRIGGDYDGGSWLAYWGQGTLVTVSA (SEQ ID NO:10)
4B12    87 TSEDSAVYYCALTGSTYWGQGTLVTVSA (SEQ ID NO:11)
3F1     87 TSEDSAVYYCTTWDDYSFYAMDYWGQGTSVTVSS (SEQ ID NO:12)
5215-13 87 TSEDTAVYYCTRGWDGYYFDCWGQGTTLTVSS (SEQ ID NO:13)
5215-9  87 TSEDAAVYYCPRGGSSPYFDYWGQGTTLTVSS (SEQ ID NO:14)
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FIG. 1

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16H11    1 QVQLHQSGAELVKPGASVKISCKGSGYDFSNFWMNWVKQRPGKGLEWIGQIYPGDGEIKYNGKFKGKATLTADESSSTAYIHLSSL
2G12     1 QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMQWVKQRPGQGLEWIGEIDPSVSYTEYNQKFKGKATLTVDTSSSTAYMQLSSL
5D1      1 QVQLQQPGAELVKPGASVKMSCKASGYTFTSSWITWVKDRPGQGLEWIGDIYPGNGNTNYNEKFKSKATLTVDTSSNTVYMQLSSL
8A2      1 QVQLKESGPGLVAPSQSLSITCTVSGFSLTTYGVDWVRQFPGKGLEWLGVIWGGGNTNYNSALMSRLSISKDTSKSQVFLKMNSL
9D4      1 QVTLKESGPGILQPSQTLSLTCSFSGFSLSTFGMGVGWIRQPSGKGLEWLAHIWWDDDKYYHPALKSRLTISKDTSNNQVFLKIANV
13D2     1 DVQLQESGPGMVKPSQSLSLTCTVTGYSITSDYDWHWIRHFPGNKLEWMGYISYSGSTKYNPSLKSRISITHDTSKNHFFLKLNSV
5215-2   1 DVQLQESGPGLVKPSQSLSLTCTVTGYSITSDYVWTWIRQFPGNKLEWMGYITYSDSTNYNPSLKSRLSITRDTSKNQFFLQLSSV
5G10     1 EVKLEESGGGLVQPGGSMKVSCVASGFTFSNYWMNWVRQSPEKGLEWVAQIRLKSDNYATHYAESVKGRFTISRDDSKSSVYLQMNNL
9H11     1 EVQLQQSGPELVKPGASVKISCKASGYTFTDYYINWVKQSHGKSLEWIGDNNPNNGGASYNQSFKGKATMTVDQSSRTAYLELRSL
10E11    1 EVQLQQSGPELVKPGDSVKISCKASGYSSTGYFMNWVMQSHGKSLEWIGRIIPYNGDTFYNQKFKDKATLTVDKSSNTAHLELRSL
4B12     1 EVQLQQSGPELVKPGASVKIPCKASGYTFTDYNMDWVKQSHEKSLEWIGDIDPHNGVTLYNQKFKDKATLTIDKSSNTAYMELRSL
3F1      1 EFQLQQSGPEMVKPGASVKMSCKASGDSFTDYKINWVKQNNGKSLEWIGVINPDSGTTSYNQIFEGKATLTVDQSSSTAYMQVNRL
5215-13  1 EVQLQQSGAELVKPGASVKLSCTVSGFNFKDTYIHWVKQRPEQGLEWIGRIDPANGNTKYASKFQDKATITADTSSNTVYMQLSSL
5215-9   1 EVQLQQSGAELVKSGASVKLSCTASGFNIKDTYMHWVKQRPEKGLEWIGWIDPADGHTKYDPKFQGKATITADTSSNTAYLHLSSL

16H11   87 TSEDSAVYFCARDDYLRAMDYWGQGTSVTVSS (SEQ ID NO:1)
2G12    87 TSEDSAVYFCARWSKDYYGMDYWGQGTSVTVSS (SEQ ID NO:2)
5D1     87 TSEDSAVHYCARDGRGYFDYWGPGTTLTVSS (SEQ ID NO:3)
8A2     86 QTDDTAMYYCAKHKGTSHAMEYWGQGTSVTVSS (SEQ ID NO:4)
9D4     88 DTAETATFYCARVERGYPLDHWGQGTTLRVSS (SEQ ID NO:5)
13D2    87 TAEDTATYYCARENDFPGFWYFDVWGTGTTVTVSS (SEQ ID NO:6)
5215-2  87 TTEDTATYFCARSLTGNYFDYWGQGTTLTVSS (SEQ ID NO:7)
5G10    89 RAEDTGIYYCTEGDYDIFAYWGQGTLVTVSA (SEQ ID NO:8)
9H11    87 TSEDSAVYYCARPERYWYFDAWGTGTTVTVSS (SEQ ID NO:9)
10E11   87 TSEDSVVYYCAGPRIGGDYDGGSWLAYWGQGTLVTVSA (SEQ ID NO:10)
4B12    87 TSEDSAVYYCALTGSTYWGQGTLVTVSA (SEQ ID NO:11)
3F1     87 TSEDSAVYYCTTWDDYSFYAMDYWGQGTSVTVSS (SEQ ID NO:12)
5215-13 87 TSEDTAVYYCTRGWDGYYFDCWGQGTTLTVSS (SEQ ID NO:13)
5215-9  87 TSEDAAVYYCPRGGSSPYFDYWGQGTTLTVSS (SEQ ID NO:14)
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FIG. 2

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16H11   1 DIQMTQSPASLSASVGETVTITCRASGNIHNYLAWFQQKQGKSPHFLVYSAKALADGVPSRFSGSGSGTQYSLK
9D4     1 DIVLTQSPASLAVSLGQRATISCRASQSVSSSSYSYMHWYQQKPGQPPKLLIKYASNLKSGVPARFSGSGSGTDFTLT
SL2     1 VIVLTQSPASLEVSLGQRATISCRASQTVRISSYSYMNWYQQKPGQPPKLLIKYASNLESGVPARFSGSGSGTDFTLN
SL13    1 DIVLTQSPASLVVSLGLRATISCRASQSVSTSSHSYLHWYQQKPGQPPKLLIKYASNLASGVPARFSGSGSGADFTLN
SL9     1 DIVLTQSPASLTISLGQRATISCRASQSVSTSTYSYIHWYQQKPGQPPKLLIKYASNLASGVPARFSGSGSGTDFSLS
8A2     1 QIVLTQSPAIMSASPGEKVTMTCSASSRVIFMYWYQQKPGSSPRLLIYDTSNLASGVPVRFSGGGSGTSYSLT
2G12    1 DIVLTQSHKFMSTSVGDRVTITCKASQDVSTAVAWYQQKPGQSPKLLIYWTSTRHTGVPDRFTGSGSGTDFTLT
10E11   1 DIVMTQSQKFMSTTVGDRVSITCKASQNVGTAVAWYQQKPGHSPKLLIYSASNRYTGVPDRFTGSGYGTDFTLT
4B12    1 DIVMTQSQKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKAVIYSASYRNSGVPDRFTGSGSGTDFTLT
13D2    1 DIVMSQSPSSQVVSVGEKVTVTCTSSQSLLYGTNQKNYLAWYQQKPGQSPKLLIYWASIRESGVPDRFTGSGSGTDFTLT
3F1     1 DVLMTQTPLSLPVSLGDQASISCRSSQNIVHSNGNTYLEWFLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLK
5D1     1 DIQMTQTTSSLSASLGDRVTIICRASQDISNFLNWYQQKPDGTVKLLMYDTSILQSGVPSRFSGRGSGADYSLT
5G10    1 DIQMTQTTSSLSASLGDRVTISCSASQGITNYLNWYQQKPDGTVKLLIYYTSILHSGVPSRFSGSGSGTDYSLT
9H11    1 DIVLTQSPVTLSVTPGDSVSLSCRASQSIRNNLHWYQQKSHESPRLLINYASQSISGIPSRFSGSGSGTDFILS

16H11  75 INSLQPEDFGTYYCQHFWSSPYTFGGGTKLEIK (SEQ ID NO:15)
9D4    79 IHPVEEEDTATYYCQHSWEIPPTFGGGTKLEIK (SEQ ID NO:19)
SL2    79 IHPVEEEDTATYYCQHSWKIPTFGGGTKLEIK (SEQ ID NO:20)
SL13   79 IHPVEEEDTATYYCQHSWEIPYTFGGGTKLEIK (SEQ ID NO:21)
SL9    79 IHPMEEEDTATYYCQHSWKIPFTFGSGTKLEIK (SEQ ID NO:22)
8A2    74 ISRMEAEDAATYYCQQWSSYPPTFGAGTKLELK (SEQ ID NO:18)
2G12   75 ISSVQAEDLALYYCHQQYSTPPTFGGGTKLEIK (SEQ ID NO:16)
10E11  75 ISNMQSEDLADYFCQQYNSYPLTFGAGTKLELK (SEQ ID NO:23)
4B12   75 ISNVQSEDLTEYFCQQYNNYPYTFGGGTKLEIK (SEQ ID NO:25)
13D2   81 ISSVKAEDLAVYYCQQYYSYPLTFGAGTKLELK (SEQ ID NO:28)
3F1    80 ISRVEAEDLGVYYCFQGSHIPWTFGGGTKLEIK (SEQ ID NO:24)
5D1    75 INNLEQEDLATYFCQQGKTLPYTFGGGTKLEIK (SEQ ID NO:17)
5G10   75 ISNLEPEDIATYYCQQYSKPPYTFGGGTKLEIK (SEQ ID NO:26)
9H11   75 INSVETEDFGMYFCQQSNNWPRTFGGGTLLQIKR (SEQ ID NO:27)
```

FIG. 3

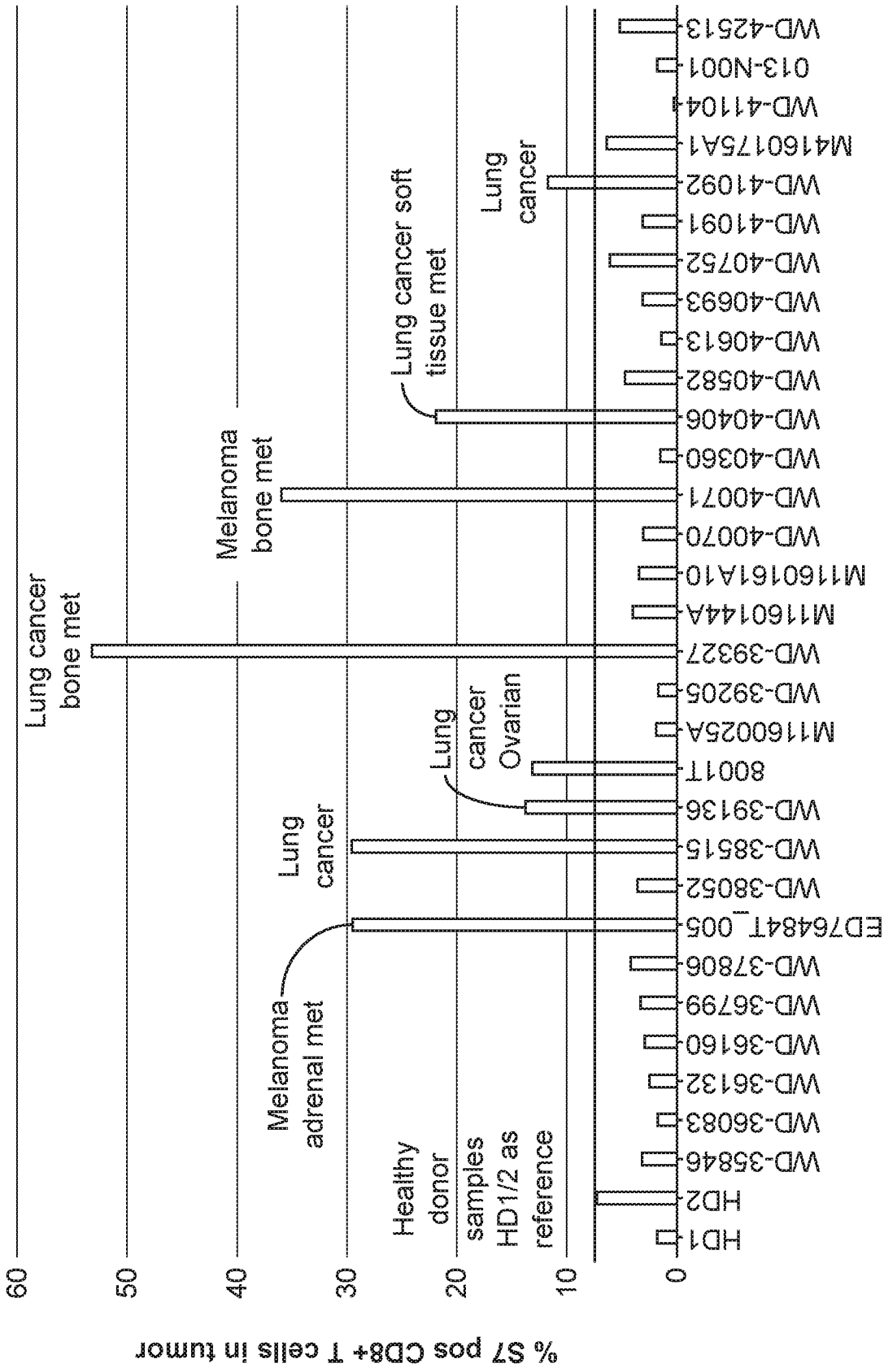

% S7 pos CD8+ T cells in tumor
0
10
20
30
40
50
60
Healthy donor samples HD1/2 as reference
Melanoma adrenal met
Lung cancer
Lung cancer Ovarian
Lung cancer soft tissue met
Melanoma bone met
Lung cancer bone met
HD1
HD2
WD-35846
WD-36083
WD-36132
WD-36160
WD-36799
WD-37806
ED76484T_005
WD-38052
WD-38515
WD-39136
80011T
M11600254
WD-39205
WD-39327
M11601444
M11601614A10
WD-40070
WD-40071
WD-40360
WD-40406
WD-40582
WD-40613
WD-40693
WD-40752
WD-41091
WD-41092
M41601754A1
WD-41104
013-N001
WD-42513

FIG. 4

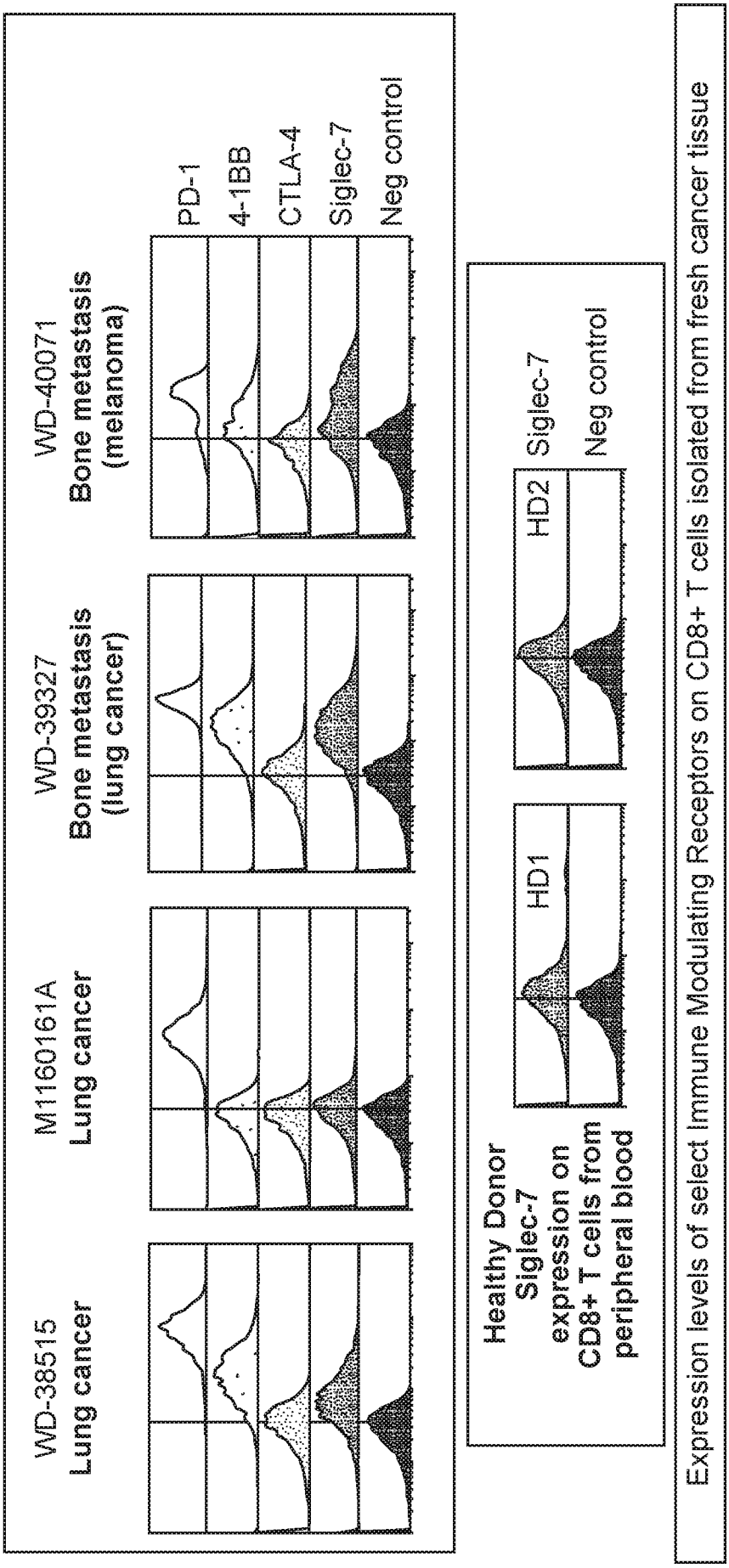

WD-38515
Lung cancer
M1160161A
Lung cancer
WD-39327
Bone metastasis
(lung cancer)
WD-40071
Bone metastasis
(melanoma)
PD-1
4-1BB
CTLA-4
Siglec-7
Neg control
Healthy Donor
Siglec-7
expression on
CD8+ T cells from
peripheral blood
HD1
HD2
Siglec-7
Neg control
Expression levels of select Immune Modulating Receptors on CD8+ T cells isolated from fresh cancer tissue

FIG. 5

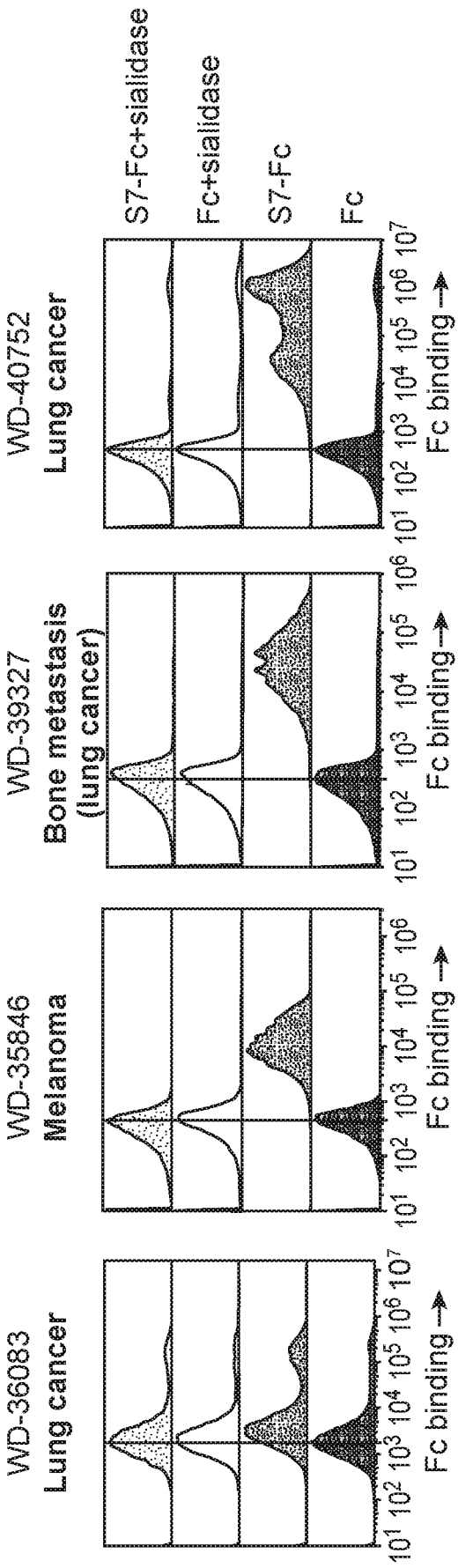
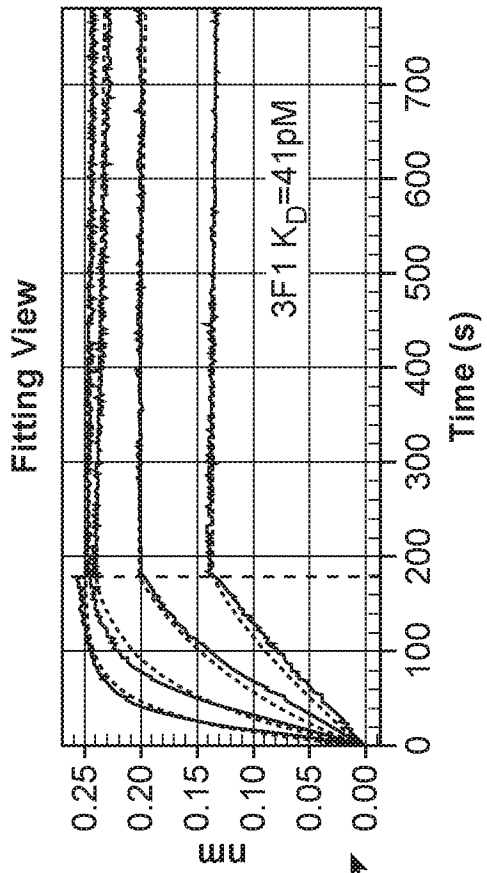
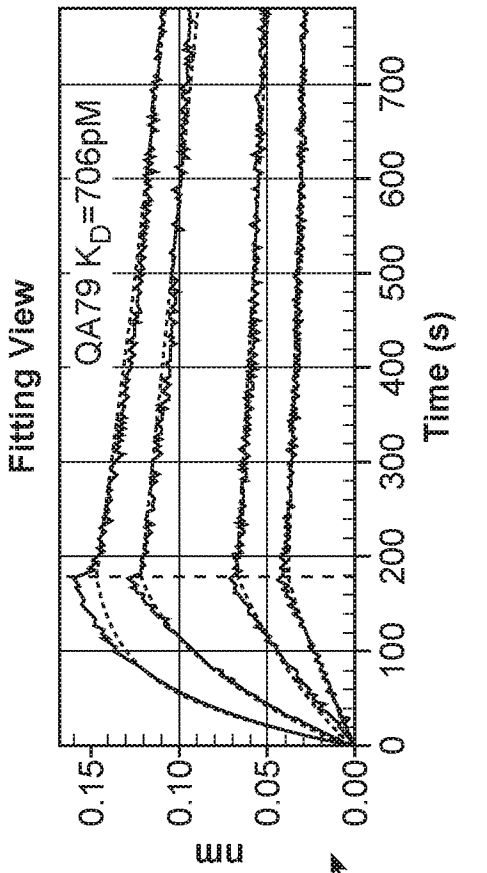

S7-Fc+sialidase
Fc+sialidase
S7-Fc
Fc
WD-40752
Lung cancer
WD-39327
Bone metastasis
(lung cancer)
WD-35846
Melanoma
WD-36083
Lung cancer
Fc binding
10^1 10^2 10^3 10^4 10^5 10^6 10^7

FIG. 6





mAb	KD (pM)*
5215-9	1
8A2	1
5D1	1
5215-21	1
5G10	1
5215-28	1
16H11/21B2	35
3F1	41
Z176	86
5215-2	149
5215-11	159
2G12	205
4B12	260
5215-7	273
S7.7	422
10E11	522
13D2	536
QA79	706
9D4hu	760
9D4	760
5215-13	990
5215-18	3500

FIG. 7

mAb	blocking IC50 (pM)
5215-18	543
5215-13	1324
9D4	1412
5215-7	1546
9D4hu	1760
5215-11	3050
5G10	3068
5215-28	3508
5215-21	3824
5215-2	4119
S7.7	4259
5215-9	5334
10E11	6232
16H11/21B2	7418
QA79	7492
3F1	8498
13D2	11893
2G12	19841
Z176	13000000
8A2	DNB
5D1	DNB
4B12	DNB
	DNB=does not block

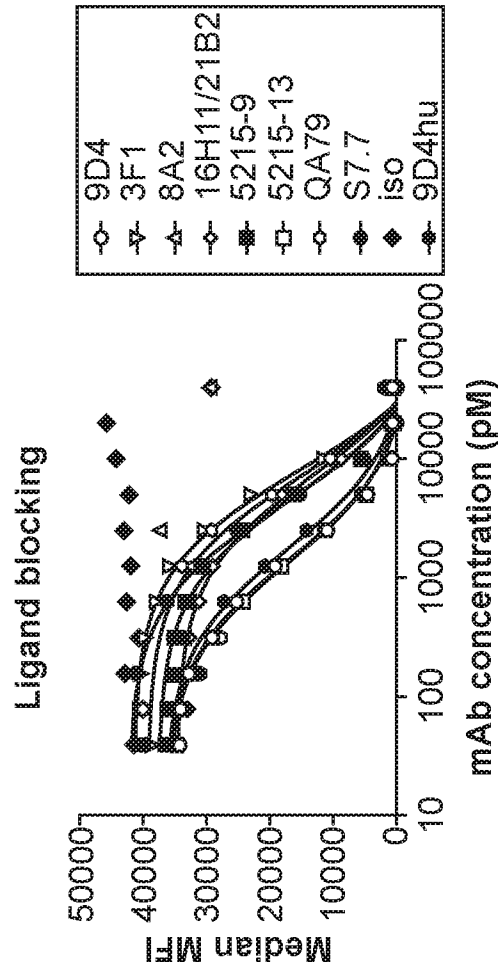


FIG. 8

mAb	Internalization IC50 (pM)
16H11/21B2	10.58
5215-9	12.77
3F1	12.97
8A2	14.9
5215-2	16.87
13D2	17.52
5D1	20.65
5215-21	22.88
10E11	49.26
9D4hu	52.55
2G12	67.29
Z176	76.65
9D4	87.51
5215-11	122.8
5G10	206
5215-28	228.1
QA79	325.8
5215-7	374.3
S7.7	468.9
5215-13	1888
5215-18	14120

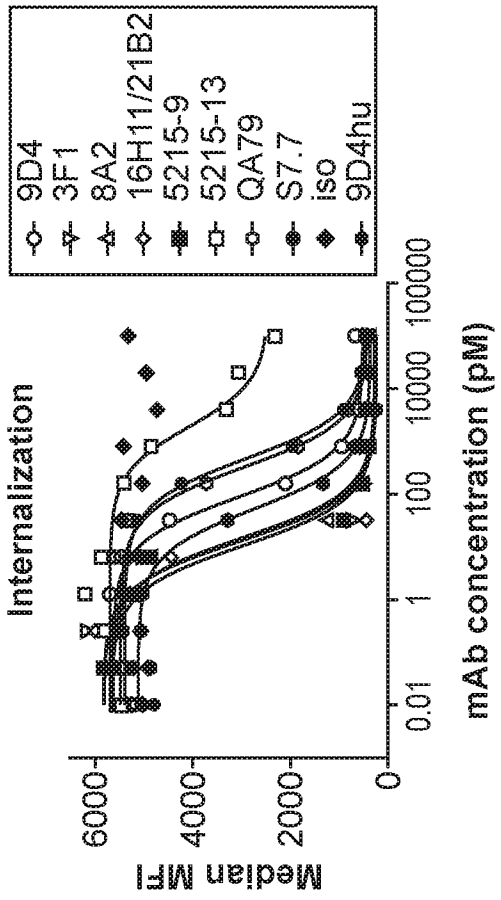


FIG. 9

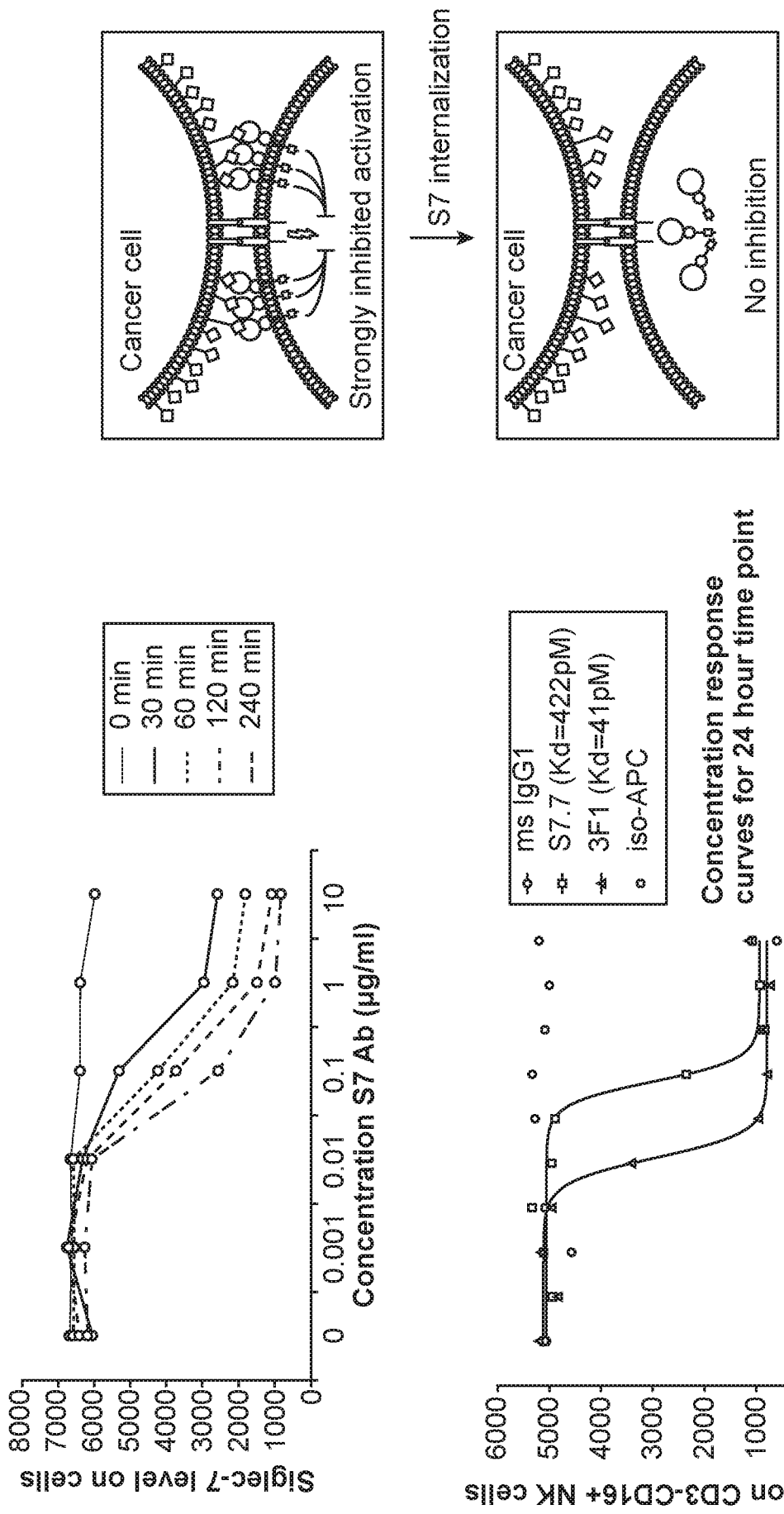

Cancer cell
Strongly inhibited activation
S7 internalization
Cancer cell
No inhibition
Siglec-7 level on cells
Concentration S7 Ab (µg/ml)
0 min
30 min
60 min
120 min
240 min
MFI on CD3-CD16+ NK cells
ug/ml
Concentration response curves for 24 hour time point
ms IgG1
S7.7 (Kd=422pM)
3F1 (Kd=41pM)
iso-APC

FIG. 10

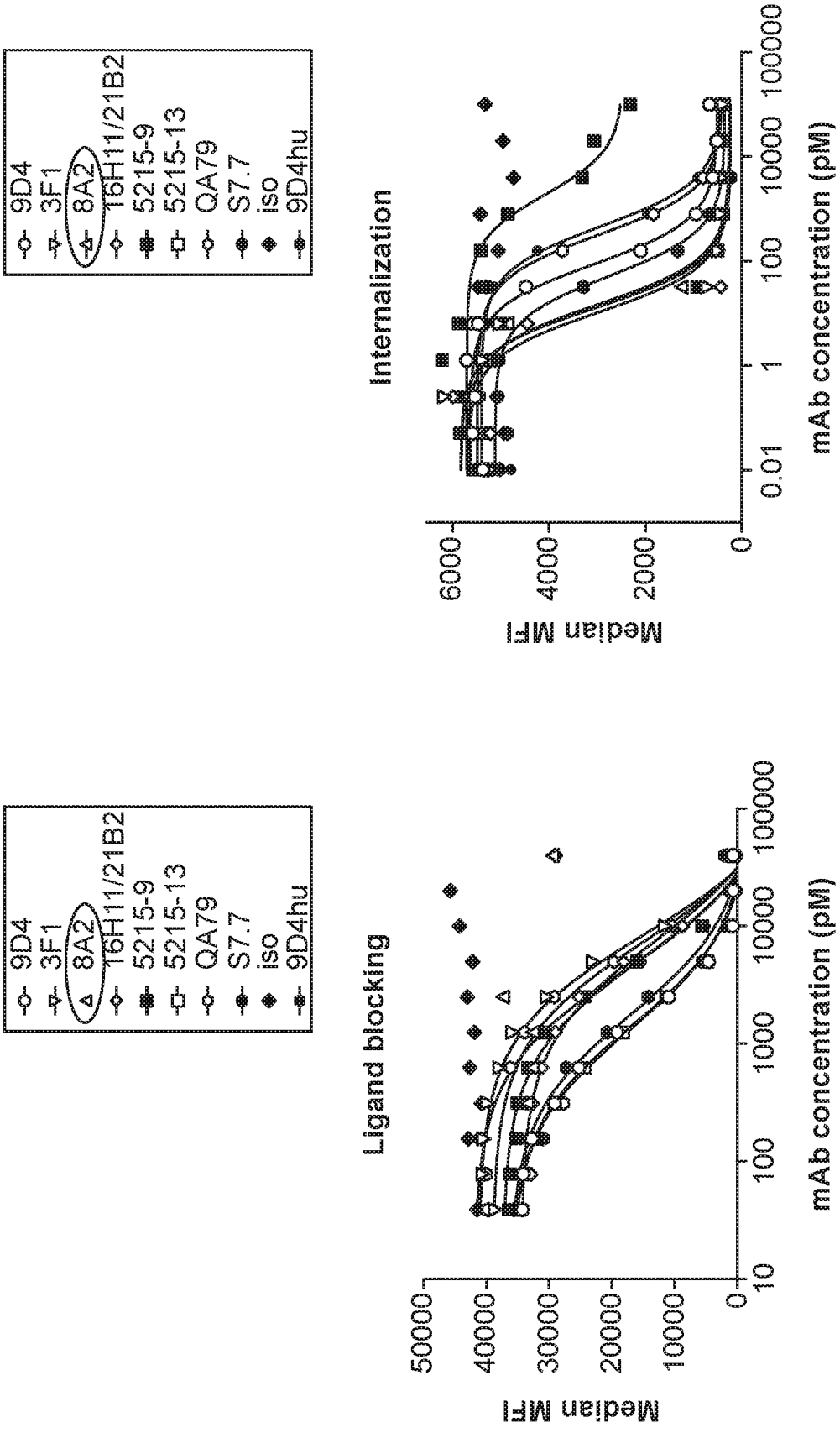

9D4
3F1
8A2
16H11/21B2
5215-9
5215-13
QA79
S7.7
iso
9D4hu
Internalization
Median MFI
6000
4000
2000
0
0.01
1
100
10000
100000
mAb concentration (pM)
Ligand blocking
Median MFI
50000
40000
30000
20000
10000
0
10
100
1000
10000
100000
mAb concentration (pM)

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/13316

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. ☒ forming part of the international application as filed:

      ☒ 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/US19/13316

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.: 4-35, 43-48, 52-58, 66-71, 75-81, 89-94, 98-104, 112-117, 121-127, 139-155
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:

-***-Please See Supplemental Page-***-

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 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.:

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.:
1-2, 3/1-2, 128-136; SEQ ID NOs.: 1, 15

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/13316

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 39/00; A61P 25/00, 35/00; C07K 16/28 (2019.01)

CPC - A61K 39/00, 39/39558, 45/06; A61P 25/00, 35/00, 37/02; C07K 16/28, 16/2803

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017/040301 A1 (ALECTOR LLC) 09 March 2017; paragraphs [0003], [0017], [0022], [0025], [0080], [0099], [0122], [0225], [0256], [0297], [0305], [0306]	1-2, 3/1-2, 128-136
A	US 2010/0240872 A1 (NAKANO) 23 September 2010; paragraph [0028]	1-2, 3/1-2, 128-130, 134-136
A	US 2014/0193427A1 (AVEO PHARMACEUTICALS INC.) 10 July 2014; paragraph [0370]	1-2, 3/1-2, 131-136
A	US 2017/0226203 A1 (DAIICHI SANKYO CO LTD) 10 August 2017; paragraph [0463]	128-130
A	US 2014/0363826 A1 (STEM CENTRX, INC.) 11 December 2014; paragraph [0010]	131-133

☐ Further documents are listed in the continuation of Box C. ☐ 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
29 May 2019 (29.05.2019)	21 JUN 2019
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US19/13316

-***-Continued from Box No. III Observations where unity of invention is lacking: -***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, Claims 1-3, 128-136 (each in-part), are directed toward an anti-Siglec-7 antibody that competes with an antibody having a variable heavy chain sequence of SEQ ID NO: 1 and a variable light chain sequence of SEQ ID NO: 15 for binding to Siglec-7.

Group II, Claims 36-42, 49-51, 128-136 (each in-part), 137 and 138 are directed toward an anti-Siglec-7 antibody that blocks binding of ligand to Siglec-7 and competes with antibody QA79 produced from the hybridoma deposited under accession number ICLC PD99003 for binding to Siglec-7, but does not compete with antibody Z176 or antibody S7.7 for binding to Siglec-7

Group III, Claims 59-65, 72-74, 128-136 (each in-part) are directed toward an anti-Siglec-7 antibody that has internalization activity, does not block ligand binding to Siglec-7, and competes with antibody S7.7, but not with antibody QA79 or antibody Z176, for binding to Siglec-7;

Group IV, Claims 82-88, 95-97, 128-136 (each in-part) are directed toward an anti-Siglec-7 antibody has internalization activity, does not block ligand binding to Siglec-7, and competes with antibody Z176, but not with antibody QA79 or antibody S7.7, for binding to Siglec-7.

Group V, Claims 105-111, 118-120, 128-136 (each in-part) are directed toward an anti-Siglec-7 antibody that has internalization activity, does not block ligand binding to Siglec-7, and does not compete with antibody Z176, antibody QA79, or antibody S7.7 for binding to Siglec-7

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include SEQ ID NO: 1, not present in any other Group; the special technical features of Group II include an anti-Siglec-7 antibody that blocks binding of ligand to Siglec-7 and competes with antibody QA79, not present in any other Group; the special technical features of Group III include an anti-Siglec-7 antibody that competes with antibody S7.7, not present in any other Group; the special technical features of Group IV include an anti-Siglec-7 antibody that competes with antibody Z176, not present in any other Group; the special technical features of Group V include an anti-Siglec-7 antibody that does not compete with antibody Z176, antibody QA79, or antibody S7.7 for binding to Siglec-7, not present in any other Group.

Groups I-V share the technical features including: an anti-Siglec-7 antibody that comprises a variant Fc region that comprises at least one amino acid amino acid modification that reduces effector function or increases antibody stability compared to the corresponding native Fc region. Groups II, III and V share the technical features including: an anti-Siglec-7 antibody that does not compete with antibody Z176. Groups II, IV and V share the technical features including: an anti-Siglec-7 antibody that does not compete with antibody S7.7. Groups III, IV and V share the technical features including: an anti-Siglec-7 antibody that has internalization activity, does not block ligand binding to Siglec-7, and does not compete with antibody QA79.

However, these shared technical features are previously disclosed by WO 2017/040301 A1 to Alector LLC (hereinafter 'Alector) in view of the article 'SOCS3 Targets Siglec 7 for Proteasomal Degradation and Blocks Siglec 7-mediated Responses' by Orr et al. (hereinafter 'Orr'); and the article 'Engagement of Siglec-7 Receptor Induces a Pro-Inflammatory Response Selectively in Monocytes' by Varchetta et al. (hereinafter 'Varchetta').

Alector discloses an anti-Siglec-7 antibody (paragraphs [0003], [0017]) that competes with an antibody (anti-Siglec-7 antibody competing with other antibodies; paragraphs [0022], [0122]) having a specified variable heavy chain sequence (paragraphs [0022], [0025]) and a specified variable light chain sequence (paragraphs [0022], [0025]) for binding to Siglec-7 (abstract; paragraph [0022]); wherein the antibody comprises a variant Fc region (paragraph [0099]) that comprises at least one amino acid amino acid modification (paragraph [0099]) that reduces effector function (modified effector function associated with variant; paragraphs [0256], [0297]) or increases antibody stability (improved stability from amino acid substitutions; paragraphs [0080], [0305], [0306]) compared to the corresponding native Fc region (relative to wild-type Fc regions; paragraph [0225]); wherein the antibody has internalization activity (wherein the antibody has internalization activity; paragraph [0021]), and do not block binding of Siglec-7 to a ligand (do not block binding of Siglec-7 to a ligand; paragraph [0019]); and reference antibody S7.7 (reference antibody S7.7; paragraph [0525]).

Alector does not disclose competition or lack thereof to any of reference antibodies S7.7, QA79, or Z176.

Orr discloses antibody QA79 (antibody QA79; page 3419, first column, second paragraph).

Varchetta discloses antibody Z176 (antibody Z176; page 2, first column, fourth paragraph).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Alector to have used any one or more known antibodies as references for competition, as disclosed by Alector, including antibody S7.7, as disclosed by Alector, antibody QA79, as disclosed by Orr, and antibody Z176, as disclosed by Varchetta, in order to establish, generally, the epitopes bound or not bound by the antibodies disclosed by Alector, and whether the modified antibody disclosed by Alector would or would not serve as a useful replacement for any of the antibodies with which it does or does not compete.

Since none of the special technical features of the Groups I-V inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the combination of the Alector, Orr and Varchetta references, unity of invention is lacking.