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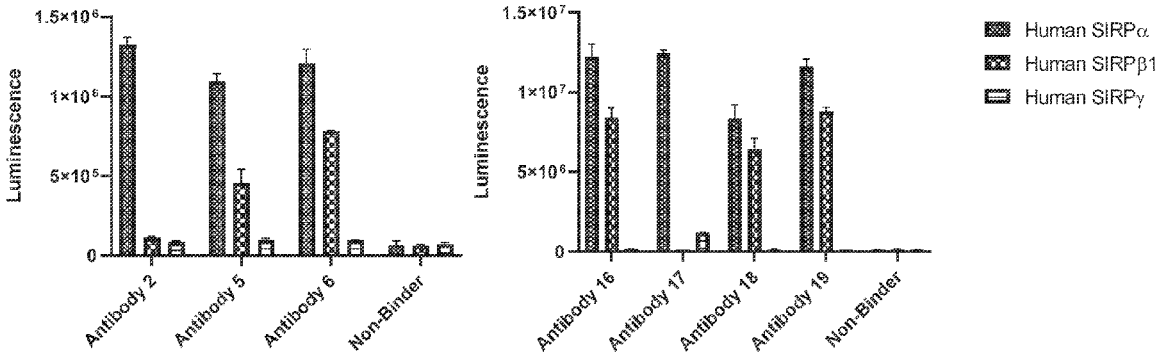
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(54) Title: SIRP ALPHA AND SIRP BETA 1 ANTIBODIES AND USES THEREOF

FIG. 1B



(57) **Abstract:** Provided herein are antibodies that bind signal regulatory protein SIRPα, SIRPβ1, or a combination of SIRPα and SIRPβ1, and methods of using such antibodies. In some embodiments, the antibodies are human monoclonal antibodies that bind human SIRPα and/or SIRPβ1. In some embodiments, the antibodies provided herein are useful for treating a disease or condition associated with overactivation and/or hyperproliferation of myeloid cells, or a disease or condition associated with SIRPα and/or SIRPβ1 activity.

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SIRP ALPHA AND SIRP BETA 1 ANTIBODIES AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional patent application number 63/022,309, filed on May 8, 2020, the contents of which are incorporated by reference herein in their entirety.

BACKGROUND

[0002] Signal regulatory proteins (SIRPs) are a family of immune receptors with Ig-like extracellular domains. The SIRP family contains three inhibitory, activating, and non-signaling members, which have closely related extracellular regions, but differ in their cytoplasmic domains. SIRPα and SIRPβ1 family members are expressed mainly by myeloid cells, and play a role in immune regulation. Signal regulatory protein alpha (also known as SIRPα, SIRP alpha, CD172a, BIT, MFR, MYD-1, P84, PTPNS1, SHPS1) is a transmembrane glycoprotein and one member of the signal regulatory SIRP family of cell-surface receptors. SIRPα delivers an inhibitory signal via immunoreceptor tyrosine-based inhibition motifs (ITIMs) located in the cytoplasmic domain of the protein that downregulates myeloid cell phagocytic and pro-inflammatory activity. SIRPα on phagocytes interacts with CD47, also known as integrin-associated protein (IAP), a ubiquitously expressed cell surface protein that serves, among other things, as a marker of "self" on viable cells. Thus, CD47/SIRPα signaling acts as a "do not eat me" immune check point to negatively control innate immune cell phagocytosis. SIRPβ1 (also known as SIRPβ, SIRPB1, and CD172b) delivers an activating signal through association with the DNA polymerase III subunit tau (DNAX) activation protein of 12 kDa (DAP12, also known as transmembrane immune signaling adaptor TYROBP, or TYROBP), a transmembrane adaptor protein with an immunoreceptor tyrosine-based activation motif (ITAM). SIRPα and SIRPβ1 are expressed on myeloid cells of the immune system, as well as other cell types. There is a need for agents that bind to SIRPα and SIRPβ1 expressing cells for the treatment of a variety of diseases and conditions.

SUMMARY

[0003] The disclosure provides Fc-containing antibodies that are specific for one or more of SIRPα and SIRPβ1, wherein binding of the antibody to one or more of SIRPα and SIRPβ1 on a cell induces depletion of the cell.

[0004] The disclosure provides antibodies that are specific for one or more of SIRPα and SIRPβ1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, and wherein the heavy chain variable region comprises: (i) a complementarity determining region 1 (CDR-H1) sequence selected from the group consisting of SEQ ID NOS: 55, 57-58 and 66-69; (ii) a CDR-H2 sequence selected from the group consisting of SEQ ID NOS: 71, 73-74 and 82-85; and (iii) a CDR-H3 sequence selected from the group consisting of SEQ ID NOS: 87, 90-91 and 100-103; and/or wherein the light chain variable region comprises: (i) a light chain CDR 1 (CDR-L1) sequence selected from the group consisting of SEQ ID NOS: 6, 9-10, and 19-22; (ii) a CDR-L2 sequence selected from the group consisting of SEQ ID NOS: 23, 25-26, 32 and 34-35; and (iii) a CDR-L3 sequence selected from the group consisting of SEQ ID NOS: 37, 40-41 and 50-53.

[0005] In some embodiments of the antibodies of the disclosure, the antibody comprises the heavy and light variable chain CDR sequence combination selected from the group consisting of: (a) SEQ ID NO: 6, SEQ ID NO: 23, SEQ ID NO: 37, SEQ ID NO: 55, SEQ ID NO: 71, and SEQ ID NO: 87; (b) SEQ ID NO: 9, SEQ ID NO: 25, SEQ ID NO: 40, SEQ ID NO: 57, SEQ ID NO: 73, and SEQ ID NO: 90; (c) SEQ ID NO: 10, SEQ ID NO: 26, SEQ ID NO: 41, SEQ ID NO: 58, SEQ ID NO: 74, and SEQ ID NO: 91; (d) SEQ ID NO: 19, SEQ ID NO: 32, SEQ ID NO: 50, SEQ ID NO: 66, SEQ ID NO: 82, and SEQ ID NO: 100; (e) SEQ ID NO: 20, SEQ ID NO: 34, SEQ ID NO: 51, SEQ ID NO: 67, SEQ ID NO: 83, and SEQ ID NO: 101; (f) SEQ ID NO: 21, SEQ ID NO: 34, SEQ ID NO: 52, SEQ ID NO: 68, SEQ ID NO: 84, and SEQ ID NO: 102; and (g) SEQ ID NO: 22, SEQ ID NO: 35, SEQ ID NO: 53, SEQ ID NO: 69, SEQ ID NO: 85, and SEQ ID NO: 103.

[0006] In some embodiments of the antibodies of the disclosure, the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NOS: 105, 108-109, 119-122. In some embodiments, the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NOS: 124, 127-128, 138-141. In some embodiments, in the

heavy chain variable region sequence and the light chain variable region sequence are selected from the group consisting of: (a) SEQ ID NO: 105 and SEQ ID NO: 124; (b) SEQ ID NO: 108 and SEQ ID NO: 127; (c) SEQ ID NO: 109 and SEQ ID NO: 128; (d) SEQ ID NO: 119 and SEQ ID NO: 138; (e) SEQ ID NO: 120 and SEQ ID NO: 139; (f) SEQ ID NO: 121 and SEQ ID NO: 140; and (g) SEQ ID NO: 122 and SEQ ID NO: 141.

[0007] In some embodiments of the antibodies of the disclosure, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 105 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 124, or an amino acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 108 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 127, or an amino acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 109 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 128, or an amino acid sequence with at least 80%, sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 119 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 120 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 139, or an amino acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 121 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 140, or an amino acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 122 or an amino acid sequence

with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 141, or an amino acid sequence with at least 80% sequence identity thereto.

[0008] In some embodiments of the antibodies of the disclosure, the antibody comprises an Fc domain. In some embodiments, the antibody is an Fc-containing antibody, and the binding of the antibody to one or more of SIRPα and SIRPβ1, on a cell induces depletion of the cell. In some embodiments, the cell depletion involves antibody dependent cellular phagocytosis (ADCP). In some embodiments, the cell depletion involves antibody dependent cellular cytotoxicity (ADCC). In some embodiments, the cell depletion involves depletion of SIRPα positive cells. In some embodiments, the cell depletion involves depletion of SIRPβ1 positive cells. In some embodiments, the cell depletion involves depletion of SIRPα positive cells and depletion of SIRPβ1 positive cells.

[0009] In some embodiments of the antibodies of the disclosure, the SIRPα positive cells are myeloid cells or myeloid progenitor cells. In some embodiments, the SIRPα positive cells are selected from the group consisting of monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, and mast cells. In some embodiments, the SIRPβ1 positive cells are myeloid cells. In some embodiments, the SIRPβ1 positive cells are selected from the group consisting of monocytes, macrophages, dendritic cells, eosinophils, basophils and neutrophils.

[0010] In some embodiments of the antibodies of the disclosure, the antibody is a monoclonal antibody. In some embodiments, the antibody is an antibody fragment. In some embodiments, the antibody is a human antibody. In some embodiments, the antibody is a humanized antibody. In some embodiments, the antibody is a chimeric antibody. In some embodiments, the antibody is a full-length antibody.

[0011] In some embodiments of the antibodies of the disclosure, the Fc domain is selected from the group consisting of human IgG1, IgG2, IgG3, and IgG4. In some embodiments, the Fc domain comprises SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 16. In some embodiments, the Fc domain comprises one or more amino acid substitutions relative to SEQ ID NO: 3, SEQ ID NO: 4, or SEQ ID NO: 16. In some embodiments, the Fc domain of the antibody is human IgG1 and comprises at least one amino acid substitution at a position selected from the group consisting of: 214, 215, 221, 222, 228, 234, 235, 236, 239, 240, 241, 243, 244, 245, 247, 250,

252, 254, 256, 262, 263, 264, 265, 266, 267, 268, 269, 270, 292, 296, 297, 298, 299, 300, 305, 313, 324, 325, 326, 327, 328, 329, 330, 332, 333, 334, 345, 356, 358, 396, 428, 430, 433, 434, and 440 wherein the position numbers of the amino acid residues are of the EU numbering scheme. In some embodiments, the IgG1 Fc comprises a sequence selected from the group consisting of (a) SEQ ID NO: 11; (b) SEQ ID NO: 12, wherein X1 is V or A; (c) SEQ ID NO: 13, wherein X1 is V or A; X2 is G or A; X3 is S or D; and X4 is I or E; (d) SEQ ID NO: 14, wherein X1 is V or A; (e) SEQ ID NO: 15, wherein X1 is V or A; X2 is M or L; and X3 is N or S; and (f) SEQ ID NO: 16, wherein X1 is K or R; X2 is D or E; and X3 is L or M. In some embodiments, the IgG4 Fc comprises a sequence of SEQ ID NO: 17, 18 or 24, wherein X1 in SEQ ID NO: 24 is S or P; and X2 in SEQ ID NO: 24 is L or E.

[0012] In some embodiments of the antibodies of the disclosure, the binding of the antibody does not disrupt the interaction between CD47 and SIRPα. In some embodiments of the antibodies of the disclosure, the binding of the antibody disrupts the interaction between CD47 and SIRPα. In some embodiments, the antibody binds SIRPα and exhibits little or no binding to SIRPβ1 and SIRPγ. In some embodiments, the antibody binds SIRPβ1 and exhibits little or no binding to SIRPα and SIRPγ. In some embodiments, antibody binds SIRPα and SIRPβ1, and exhibits little or no binding to SIRPγ.

[0013] In some embodiments of the antibodies of the disclosure, the antibody comprises a binding affinity to SIRPα of about 100 pM, about 1 nM, about 5 nM, about 10 nM, about 50 nM, about 100 nM, about 500 nM, or about 1 μM. In some embodiments, the antibody comprises a binding affinity for SIRPβ1 of about 0.05 nM about 0.1 nM, about 5 nM, about 10 nM, about 50 nM, about 100 nM, about 500 nM, or about 1 μM, or about 5 μM.

[0014] The disclosure provides a pharmaceutical composition comprising an antibody of the disclosure, and optionally a pharmaceutically acceptable carrier.

[0015] The disclosure provides a nucleic acid encoding for the antibody of the disclosure. In some embodiments, the nucleic acid comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOS: 143, 146-147, 157-160, 162, 165-166, and 176-179. In some embodiments, the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 143, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO:

162, or a nucleic acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 146, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 165, or a nucleic acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 147, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 166, or a nucleic acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 157, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 176, or a nucleic acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 158, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 177, or a nucleic acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 159, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 178, or a nucleic acid sequence with at least 80% sequence identity thereto. In some embodiments, the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 160, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 179, or a nucleic acid sequence with at least 80% sequence identity thereto.

[0016] The disclosure provides vectors comprising the nucleic acid of the disclosure.

[0017] The disclosure provides methods of inducing the depletion of a population of cells, the methods comprising contacting the population of cells with the antibody of the disclosure.

[0018] In some embodiments of the methods of the disclosure, at least a subset of the population of cells expresses SIRPα. In some embodiments, the population of cells that express SIRPα comprise myeloid cells or myeloid progenitor cells. In some embodiments, the population of

cells that express SIRPα comprise monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, or mast cells. In some embodiments, at least a subset of the population of cells expresses SIRPβ1. In some embodiments, the population of cells that express SIRPβ1 comprise myeloid cells or myeloid progenitor cells. In some embodiments, the population of cells that express SIRPβ1 comprise monocytes, macrophages, dendritic cells, eosinophils, basophils, neutrophils or mast cells. In some embodiments, at least a subset of the population of cells expresses SIRPα and SIRPβ1. In some embodiments the population of cells whose depletion is induced comprises a first population of cells expressing SIRPα and a second population of cells expressing SIRPβ1.

[0019] In some embodiments of the methods of the disclosure, the method is in vitro. In some embodiments, the method is in vivo. In some embodiments, the population of cells comprises tissue-resident cells. In some embodiments, the population of cells comprises circulating cells.

[0020] In some embodiments of the methods of the disclosure, the cell depletion involves ADCC. In some embodiments, the cell depletion involves ADCP. In some embodiments, the cell depletion involves ADCC and ADCP.

[0021] The disclosure provides methods of treating a disease or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibody or the pharmaceutical composition of the disclosure.

[0022] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or condition is characterized by overactivation and/or hyperproliferation of myeloid cells, and the antibody induces depletion of myeloid cells. In some embodiments, the myeloid cells comprise monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, or mast cells.

[0023] In some embodiments of the methods of treating a disease or condition of the disclosure, the myeloid cells comprise eosinophils, and wherein the disease or condition comprises acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, eosinophilic cardiomyopathy/Loeffler endocarditis, Löffler syndrome or episodic angioedema with eosinophilia/Gleich syndrome. In some embodiments, the myeloid cells comprise mast cells, and

wherein the disease or condition comprises cutaneous mastocytosis, mastocytic enterocolitis, systemic mastocytosis, mast cell activation syndrome, hereditary alpha tryptasemia syndrome, or chronic urticaria. In some embodiments, the myeloid cells comprise neutrophils, and wherein the disease or condition comprises neutrophilic dermatoses, psoriatic arthritis, generalized pustular psoriasis, pyoderma gangrenosum, Sweet's syndrome, subcorneal pustular dermatosis, neutrophilic eccrine hidradenitis, bowel-associated dermatosis-arthritis syndrome (BADAS), rheumatoid neutrophilic dermatitis, or Behçet's disease.

[0024] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or condition comprises an autoimmune disorder or an inflammatory disorder. In some embodiments, the autoimmune disorder comprises presentation of self antigens by antigen presenting cells in germinal centers of secondary lymphoid tissue of the subject.

[0025] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or condition comprises systemic mastocytosis, hyper IgE syndrome, systemic inflammatory response syndrome, acute respiratory distress syndrome, autoimmune hemolytic anemia, immune/idiopathic thrombocytopenia purpura, epidermolysis bullosa acquisita, pemphigus foliaceus, pemphigus vulgaris, anti-glomerular basement membrane disease (Goodpasture Syndrome), anti-glomerular basement membrane disease (Goodpasture Syndrome), antiphospholipid syndrome, catastrophic antiphospholipid syndrome, anti-glomerular basement membrane disease (Goodpasture Syndrome), antiphospholipid syndrome, catastrophic antiphospholipid syndrome, antibody-mediated rejection (AMR), cutaneous mastocytosis, mastocytic enterocolitis, mast cell activation syndrome, eosinophilic cardiomyopathy/Loeffler endocarditis, coronary artery disease (CAD)/ peripheral artery disease (PAD), myelofibrosis, Löffler syndrome, chronic neutrophilic leukemia, hereditary alpha tryptasemia syndrome, or chronic urticaria.

[0026] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or condition comprises a hematological malignancy. In some embodiments, the hematological malignancy comprises acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic eosinophilic leukemia, or chronic neutrophilic leukemia.

[0027] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or condition is selected from the group consisting of cytokine release syndrome (CRS), systemic mastocytosis, hypereosinophilic syndrome (including primary, secondary, and idiopathic), hyper IgE syndrome, systemic inflammatory response syndrome, acute respiratory distress syndrome, autoimmune neutropenia , acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic eosinophilic leukemia, secondary hemophagocytic lymphohistiocytosis (sHLH) or cytokine release syndrome (CRS) associated with associated with T cell therapy, sHLH or CRS associated with chimeric antigen receptor (CAR) T cell therapy, sHLH or CRS associated with T cell activating bispecific monoclonal antibody therapy, autoimmune hemolytic anemia, immune/idiopathic thrombocytopenia purpura, epidermolysis bullosa acquisita, pemphigus foliaceus, pemphigus vulgaris, anti-glomerular basement membrane disease (Goodpasture Syndrome), antiphospholipid syndrome, catastrophic antiphospholipid syndrome, antibody-mediated rejection (AMR), acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, cutaneous mastocytosis, mastocytic enterocolitis, mast cell activation syndrome, eosinophilic cardiomyopathy/Loeffler endocarditis, acute kidney injury, chronic kidney disease, coronary artery disease (CAD)/peripheral artery disease (PAD), myelofibrosis, IgG4-related disease, Löffler syndrome, chronic neutrophilic leukemia, episodic angioedema with eosinophilia/Gleich syndrome, hereditary alpha tryptasemia syndrome, and chronic urticaria, and hyperthyroidism.

[0028] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or condition the subject is human.

[0029] The disclosure provides cells expressing SIRPα, wherein the cells are bound to an antibody of the disclosure, wherein the antibody is bound to SIRPα.

[0030] The disclosure provides cells expressing SIRPβ1, wherein the cells are bound to an antibody of the disclosure, wherein the antibody is bound to SIRPβ1.

[0031] The disclosure provides cells expressing SIRPα and SIRPβ1, wherein the cells are bound to an antibody of the disclosure, wherein the antibody is bound to SIRPα and SIRPβ1.

[0032] The disclosure provides kits or articles of manufacture comprising an antibody of pharmaceutical composition of the disclosure.

[0033] The disclosure provides antibodies or pharmaceutical compositions of the disclosure, for use in the treatment of a disease or disorder in a subject in need thereof.

[0034] The disclosure provides antibodies or pharmaceutical compositions of the disclosure, for use in the manufacture of a medicament for the treatment of a disease or disorder in a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] FIG. 1A shows binding of selected antibodies of the disclosure to human and cynomolgus monkey (Cyno) SIRPα by enzyme-linked immunosorbent assay (ELISA).

[0036] FIG. 1B shows binding of selected antibodies of the disclosure to human SIRPα, human SIRPβ1 and lack of binding to human SIRPγ by ELISA.

[0037] FIG. 2A shows binding curves of selected antibodies to human and cynomolgus monkey SIRPα by ELISA.

[0038] FIG. 2B shows binding curves of selected antibodies to human and cynomolgus monkey SIRPα (top row) and SIRPβ1 (bottom row) by ELISA.

[0039] FIG. 2C shows binding curves of selected antibodies to human and cynomolgus monkey SIRPγ by ELISA, indicating little or no binding.

[0040] FIG. 2D shows binding curves of selected antibodies to human and cynomolgus monkey SIRPα (top row) and SIRPβ1 (bottom row) by ELISA.

[0041] FIG. 2E shows binding curves of selected antibodies to human and cynomolgus monkey SIRPγ by ELISA, indicating little or no binding.

[0042] FIG. 3A shows binding curves of Antibody 22 to human and cynomolgus monkey SIRPα by ELISA.

[0043] FIG. 3B shows binding curves of Antibody 27 to human and cynomolgus monkey SIRPα (top row) and human and cynomolgus monkey SIRPβ1 (bottom row) by ELISA.

[0044] FIG. 3C shows binding curves of Antibody 27 to human and cynomolgus monkey SIRPγ by ELISA, indicating little or no binding to human SIRPγ.

[0045] FIG. 4A shows the binding curves of selected antibodies of the disclosure to human monocytes and neutrophils (top), and to human CD4+ T cells and CD8+ T cells (bottom) in human whole blood by flow cytometry.

[0046] FIG. 4B shows binding curves of selected antibodies of the disclosure to human CD20+ B cells in human whole blood by flow cytometry.

[0047] FIG. 4C shows binding curves of selected antibodies of the disclosure to human platelets in platelet-rich plasma by flow cytometry.

[0048] FIG. 4D shows binding of selected antibodies of the disclosure to cynomolgus monkey (Cyno) monocytes and granulocytes in cynomolgus monkey whole blood by flow cytometry.

[0049] FIG. 4E shows binding curves of selected antibodies of the disclosure to cynomolgus monkey (Cyno) CD20+ B cells in cynomolgus monkey whole blood by flow cytometry.

[0050] FIG. 4F shows binding curves of selected antibodies of the disclosure to cynomolgus monkey (Cyno) platelets cells in cynomolgus platelet-rich plasma by flow cytometry.

[0051] FIG. 4G shows binding of selected antibodies of the disclosure to human SIRPα-expressing CHO cells (top) and human SIRPβ1-expressing CHO cells (bottom) by flow cytometry.

[0052] FIG. 4H binding curves of selected antibodies of the disclosure to human SIRPγ-expressing CHO cells by flow cytometry.

[0053] FIG. 4I shows binding of Antibody 27 to human SIRPα-expressing CHO cells and human SIRPβ1-expressing CHO cells (top), and human SIRPγ-expressing CHO cells (bottom).

[0054] FIG. 5A shows the effect of Antibody 27 on ADCC of human monocytes (top) and cynomolgus monkey monocytes (bottom) *in vitro*.

[0055] FIG. 5B shows the effect of Antibody 27 on ADCC of human CD4+ T cells *in vitro*.

[0056] FIG. 5C shows the effect of Antibody 27 on ADCC of human CD8+ T cells *in vitro*.

[0057] FIG. 6 shows the effect of Antibody 27 on ADCP of human monocytes (top) and cynomolgus monkey monocytes (bottom) *in vitro*.

[0058] FIG. 7 is a graph depicting the results of an ELISA experiment assessing the ability of Antibody 6 to compete with CD47 for binding to human SIRPα.

DETAILED DESCRIPTION

[0059] Provided herein are antibodies that bind to SIRPα and/or SIRPβ1. Also provided are methods of making and using such antibodies. The antibodies may be useful for treating diseases or conditions involving cells expressing SIRPα and/or SIRPβ1. For example, in some embodiments, the antibodies may be used for treating diseases or conditions involving overactivation and/or hyperproliferation of SIRPα or SIRPβ1 expressing cells (e.g. myeloid cells) as a part of the pathology.

[0060] Where elements are presented in a list format (e.g., in a Markush group), it should be understood that each possible subgroup of the elements is also disclosed, and that any one or more elements can be removed from the list or group.

[0061] It should be understood that, unless clearly indicated, in any method described or disclosed herein that includes more than one act, the order of the acts is not necessarily limited to the order in which the acts of the method are recited, but the disclosure encompasses exemplary embodiments in which the order of the acts is so limited.

[0062] The terms used throughout the specification are defined as follows unless otherwise limited in specific instances. As used in the specification and the claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. All technical and scientific terms, acronyms, and abbreviates used in the specification and claims have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains, unless defined or stated otherwise. All numerical ranges are inclusive of the values defining the range as well as all integer values in between, unless indicated or defined otherwise.

[0063] The terms "individual," "subject," and "patient" are used interchangeably herein and refer to any subject for whom treatment or therapy is desired. The subject may be a mammalian subject. Mammalian subjects include, e. g., humans, non-human primates, rodents, (e.g., rats, mice), lagomorphs (e.g., rabbits), ungulates (e.g., cows, sheep, pigs, horses, goats, and the like), etc. In some embodiments, the subject is a human. In some embodiments, the subject is a non-human primate, for example a cynomolgus monkey. In some embodiments, the subject is a companion animal (e.g. cats, dogs).

[0064] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

I. Antibodies

A. SIRP Antibodies

[0065] Provided herein are antibodies that bind to SIRPα, SIRPβ1, or both SIRPα and SIRPβ1 (referred to interchangeably herein as SIRP antibodies or anti-SIRP antibodies).

[0066] The skilled artisan will appreciate that, depending on context, a SIRP antibody of the disclosure will encounter a binding surface (e.g. a cell) that may express only a subset of the targets to which the antibody is capable of binding. For example, an antibody that can bind SIRPα and SIRPβ1 can bind to a cell expressing only SIRPα, or a cell expressing only SIRPβ1, as well as a cell expressing both SIRPα and SIRPβ1. In any of these situations the antibody is expected to bind that surface. Thus, although some of the SIRP antibodies of the disclosure bind SIRPα and SIRPβ1, the binding of all of the targets simultaneously is not required for activity.

[0067] The term antibody as used herein throughout is used in the broadest sense and includes a monoclonal antibody, polyclonal antibody, human antibody, humanized antibody, non-human antibody, chimeric antibody, a monovalent antibody, and an antibody fragment.

[0068] In exemplary embodiments, the SIRP antibodies provided herein are monoclonal antibodies (mAbs). In exemplary embodiments, the SIRP antibodies provided herein are human antibodies. In exemplary embodiments, the SIRP antibodies provided herein are humanized antibodies. In exemplary embodiments, the SIRP antibodies provided herein are monoclonal

human antibodies. In exemplary embodiments, the SIRP antibodies provided herein are chimeric antibodies. In exemplary embodiments, the SIRP antibodies provided herein are monoclonal chimeric antibodies.

[0069] In some embodiments, the SIRP antibodies provided herein are antibody fragments, retaining SIRP antigen binding specificity. In some embodiments, the antibody fragments are antigen-binding fragments (Fab), variable fragments (Fv) containing VH and VL sequences, single chain variable fragments (scFv) containing VH and VL sequences linked together in one chain, single chain antibody fragments (scAb) or other antibody variable region fragments, such as Fab', F(ab')2, dsFv diabody, and Fd polypeptide fragments.

[0070] Also provided herein are SIRP antibody-drug conjugates, bispecific antibodies comprising at least one arm specific for SIRP, and multispecific antibodies that exhibit binding for SIRPα.

[0071] The SIRPα protein has been characterized to be highly polymorphic, but does not appear to affect ligand binding properties. At least thirteen variants (polymorphs) have been characterized in humans, Variants 1-13, with V1 and V2 the most common. (Hatherley et al. JBC 289: 10024-10028, 2014). SIRPα also has at least three isoforms. Accordingly the term "SIRPα" as used herein is inclusive of all variants and isoforms of SIRPα.

[0072] The amino acid sequence of human SIRPα (hSIRPα) isoform 1, variant 1 (V1) is provided in SEQ ID NO: 1 and referred to herein as hSIRPα V1.

```
  1  MEPAGPAPGR LGPLLCLLLA ASCAWSGVAG EEELQVIQPD KSVLVAAGET ATLRCTATSL
 61  IPVGPIQWFR GAGPGRELIY NQKEGHFPRV TTVSDLTKRN NMDFSIRIGN ITPADAGTYY
121 CVKFRKGSPD DVEFKSGAGT ELSVRAKPSA PVVSGPAARA TPQHTVSFTC ESHGFSPRDI
181 TLKWFKNGNE LSDFQTNVDP VGESVSYSIH STAKVVLTRE DVHSQVICEV AHVTLQGDPL
241 RGTANLSETI RVPPTLEVTQ QPVRAENQVN VTCQVRKFYP QRLQLTWLEN GNVSRTETAS
301 TVTENKDGTY NWMSWLLVNV SAHRDDVKLT CQVEHDGQPA VSKSHDLKVS AHPKEQGSNT
361 AAENTGSNER NIYIVVGVVC TLLVALLMAA LYLVRIRQKK AQGSTSSTRL HEPEKNAREI
421 TQDTNDITYA DLNLPKGKKP APQAAEPNNH TEYASIQTSP QPASEDTLTY ADLDMVHLNR
481 TPKQPAPKPE PSFSEYASVQ VPRK (SEQ ID NO: 1)
```

[0073] The amino acid sequence of hSIRPα isoform 1, variant 2 (V2) is provided in SEQ ID NO: 2 and referred to herein as hSIRPα V2.

```
  1 MEPAGPAPGR LGPLLCLLLA ASCAWSGVAG EEELQVIQPD KSVSVAAGES AILHCTVTSL
 61 IPVGPIQWFR GAGPARELIY NQKEGHFPRV TTVSESTKRE NMDFSISISN ITPADAGTYY
121 CVKFRKGSPD TEFKSGAGTE LSVRAKPSAP VVSGPAARAT PQHTVSFTCE SHGFSPRDIT
181 LKWFKNGNEL SDFQTNVDPV GESVSYSIHS TAKVVLTRED VHSQVICEVA HVTLQGDPLR
241 GTANLSETIR VPPTLEVTQQ PVRAENQVNV TCQVRKFYPQ RLQLTWLENG NVSRTETAST
301 VTENKDGTYN WMSWLLVNVS AHRDDVKLTC QVEHDGQPAV SKSHDLKVSA HPKEQGSNTA
361 AENTGSNERN IYIVVGVVCT LLVALLMAAL YLVRIRQKKA QGSTSSTRLH EPEKNAREIT
421 QVQSLDTNDI TYADLNLPKG KKPAPQAAEP NNHTEYASIQ TSPQPASEDT LTYADLDMVH
481 LNRTPKQPAP KPEPSFSEYA SVQVPRK (SEQ ID NO: 2)
```

[0074] The amino acid sequence of hSIRPα isoform 2 is provided herein as SEQ ID NO: 5.

```
  1 MEPAGPAPGR LGPLLCLLLA ASCAWSGVAG EEELQVIQPD KSVLVAAGET ATLRCTATSL
 61 IPVGPIQWFR GAGPGRELIY NQKEGHFPRV TTVSDLTKRN NMDFSIRIGN ITPADAGTYY
121 CVKFRKGSPD DVEFKSGAGT ELSVRAKPSA PVVSGPAARA TPQHTVSFTC ESHGFSPRDI
181 TLKWFKNGNE LSDFQTNVDP VGESVSYSIH STAKVVLTRE DVHSQVICEV AHVTLQGDPL
241 RGTANLSETI RVPPTLEVTQ QPVRAENQVN VTCQVRKFYP QRLQLTWLEN GNVSRTETAS
301 TVTENKDGTY NWMSWLLVNV SAHRDDVKLT CQVEHDGQPA VSKSHDLKVS AHPKEQGSNT
361 AAENTGSNER NIYIVVGVVC TLLVALLMAA LYLVRIRQKK AQGSTSSTRL HEPEKNAREI
421 TQVQSLDTND ITYADLNLPK GKKPAPQAAE PNNHTEYASI QTSPQPASED TLTYADLDMV
481 HLNRTPKQPA PKPEPSFSEY ASVQVPRK (SEQ ID NO: 5)
```

[0075] The amino acid sequence of human SIRPα (hSIRPα) isoform 4 is provided in SEQ ID NO: 25.

```
  1 MEPAGPAPGR LGPLLCLLLA ASCAWSGVAG EEELQVIQPD KSVLVAAGET ATLRCTATSL
 61 IPVGPIQWFR GAGPGRELIY NQKEGHFPRV TTVSDLTKRN NMDFSIRIGN ITPADAGTYY
121 CVKFRKGSPD VEFKSGAGTE LSVRAKPSAP VVSGPAARAT PQHTVSFTCE SHGFSPRDIT
181 LKWFKNGNEL SDFQTNVDPV GESVSYSIHS TAKVVLTRED VHSQVICEVA HVTLQGDPLR
241 GTANLSETIR VPPTLEVTQQ PVRAENQVNV TCQVRKFYPQ RLQLTWLENG NVSRTETAST
301 VTENKDGTYN WMSWLLVNVS AHRDDVKLTC QVEHDGQPAV SKSHDLKVSA HPKEQGSNTA
361 AENTGSNERN IYIVVGVVCT LLVALLMAAL YLVRIRQKKA QGSTSSTRLH EPEKNAREIT
421 QDTNDITYAD LNLPKGKKPA PQAAEPNNHT EYASIQTSPQ PASEDTLTYA DLDMVHLNRT
481 PKQPAPKPEP SFSEYASVQV PRK (SEQ ID NO: 25)
```

[0076] In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of a SIRPα of a single species. In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of a SIRPα of more than one species. In some embodiments, the SIRP

antibodies bind to one or more variants or isoforms of human SIRPα. In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of a non-human primate SIRPα, e.g. a cynomolgus monkey SIRPα.

[0077] In some embodiments, the SIRP antibodies bind to a plurality of SIRPα variants found in a particular species, e.g. the SIRP antibodies bind to more than one of SIRPα human variants 1-13. In some embodiments the SIRP antibodies bind to hSIRPα V1. In some embodiments, the SIRP antibodies bind to hSIRPα V2. In some embodiments, the SIRP antibodies bind to hSIRPα V1 and V2. In some embodiments, the SIRP antibodies bind the extracellular domain of SIRPα, e.g. hSIRPα V1 (e.g. Met1-Arg370 of V1, Gly27-Arg370 of V1, or Glu31-Arg370 of V1), or e.g. hSIRPα V2 (Met1-Arg369).

[0078] In some embodiments, the SIRP antibodies of the disclosure bind a plurality of SIRPα isoforms. For example, the SIRP antibodies of the disclosure may bind to two or more SIRPα isoforms, or all SIRPα isoforms. In some embodiments, the SIRP antibodies bind to isoform 1, 2 and 4 of SIRPα.

[0079] In some embodiments, the SIRP antibodies bind specifically to hSIRPα V1. In some embodiments, the SIRP antibodies bind specifically to hSIRPα V2. In some embodiments, the SIRP antibodies bind specifically to hSIRPα V1 and hSIRPα V2. In some embodiments, the SIRP antibodies bind specifically to one or more variants of SIRPα but show little or no binding to other SIRP family members such as SIRPγ.

[0080] Human SIRPβ1 has at least 3 isoforms. The amino acid sequence of hSIRPβ1 isoform 1 is provided in SEQ ID NO: 7.

```
  1 MPVPASWPHL PSPFLLMTLL LGRLTGVAGE DELQVIQPEK SVSVAAGESA TLRCAMTSLI
 61 PVGPIMWFRG AGAGRELIYN QKEGHFPRVT TVSELTKRNN LDFSISISNI TPADAGTYYC
121 VKFRKGSPDD VEFKSGAGTE LSVRAKPSAP VVSGPAVRAT PEHTVSFTCE SHGFSPRDIT
181 LKWFKNGNEL SDFQTNVDPA GDSVSYSIHS TARVVLTRGD VHSQVICEIA HITLQGDPLR
241 GTANLSEAIR VPPTLEVTQQ PMRAENQANV TCQVSNFYPR GLQLTWLENG NVSRTETAST
301 LIENKDGTYN WMSWLLVNTC AHRDDVVLTC QVEHDGQQAV SKSYALEISA HQKEHGSDIT
361 HEAALAPTAP LLVALLLGPK LLLVVGVSAI YICWKQKA (SEQ ID NO: 7)
```

[0081] In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of a SIRPβ1 of a single species. In some embodiments, the SIRP antibodies bind to one or more

variants or isoforms of a SIRPβ1 of more than one species. In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of human SIRPβ1. In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of a non-human primate SIRPβ1, e.g. a cynomolgus monkey SIRPβ.

[0082] In some embodiments, the SIRP antibodies bind to a plurality of SIRPβ1 variants or isoforms found in a particular species, e.g. the SIRP antibodies bind to more than one of SIRPβ1 human isoforms 1-3. In some embodiments, the SIRP antibodies bind the extracellular domain of SIRPβ1 (e.g. amino acids 1-371 of SEQ ID NO: 7). In some embodiments, the SIRP antibodies bind specifically to one or more variants or isoforms of SIRPα, in addition to binding to SIRPβ1.

[0083] In some embodiments, the SIRP antibodies exhibit little or no binding to SIRPγ. For example, the binding of the SIRP antibodies to SIRPγ is not detectable, or detectable only at a low level, using the methods described herein and that are known to a person skilled in the art, and without being bound to theory or mechanism, may be non-specific.

[0084] The skilled artisan will recognize that antibodies that exhibit little or no binding to a target antigen can be described as having a low affinity, and a high equilibrium dissociation constant (KD) for the target antigen, for example a KD of about 10 μM or greater, about 100 μM or greater, about 1 mM or greater, or about 10 mM or greater.

[0085] In some embodiments, provided herein are SIRP antibodies comprising a binding affinity (KD) to SIRPα of about 0.05 nM, about 0.1 nM, about 0.5 nM, about 1 nM, about 5 nM, about 10 nM, about 50 nM, about 100 nM, about 500 nM, or about 1 μM.

[0086] In some embodiments, provided herein are SIRP antibodies comprising a binding affinity (KD) to SIRPα of between about 0.05 nM and 1 μM, between about 0.5 nM and 1 μM, between about 1 nM and 1 μM, between about 5 nM and 1 μM, between about 0.05 nM and 500 nM, between about 0.5 nM and 500 nM, between about 1 nM and 500 nM, between about 5 nM and 500 nM, between about 0.05 nM and 50 nM, between about 0.5 nM and 50 nM, between about 1 nM and 50 nM, or between about 5 nM and 50 nM.

[0087] In some embodiments, provided herein are SIRP antibodies comprising a binding affinity (KD) to SIRPβ1 of about 0.05 nM, about 0.1 nM, about 0.5nM, about 1 nM, about 5 nM, about 10 nM, about 50 nM, about 100 nM, about 500 nM, about 1 μM, or about 5 μM.

[0088] In some embodiments, provided herein are SIRP antibodies comprising a binding affinity (KD) to SIRPβ1 of between about 0.05 nM and 5 μM, between about 0.5 nM and 5 μM, between about 1 nM and 5 μM, between about 5 nM and 5 μM, between about 0.05 nM and 1 μM, between about 0.5 nM and 1 μM, between about 1 nM and 1μM, between about 5 nM and 1 μM, between about 0.05 nM and 500 nM, between about 0.5 nM and 500 nM, between about 1 nM and 500 nM, between about 5 nM and 500 nM, between about 0.05 nM and 50 nM, between about 0.5 nM and 50 nM, between about 1 nM and 50 nM, or between about 5 nM and 50 nM.

[0089] In some embodiments, the SIRP antibodies provided herein compete with CD47 for binding to SIRPα. In other embodiments, the SIRP antibodies provided herein do not compete with CD47 for binding to SIRPα. Exemplary antibodies of the disclosure that do not compete with CD47 binding of SIRPα include Antibodies 6 and 17, referring to Table 11.

[0090] In some embodiments, the constant region of a SIRP antibody (referred to interchangeably as a Fc domain, a Fc sequence or simply as a Fc) is a human Fc domain. In some embodiments, the Fc domain of a SIRP antibody is human IgG1, human IgG2, human IgG3, or human IgG4. In some embodiments, the Fc domain of a SIRP antibody is that of a mouse. In some embodiments, the Fc domain of a SIRP antibody is mouse IgG1 or mouse IgG2a. In some embodiments, the Fc domain of a SIRP antibody is that of a rat. In some embodiments, the Fc domain of a SIRP antibody is rat IgG1 or rat IgG2b. In some embodiments, the Fc domain of a SIRP antibody is rat IgG2b. In embodiments, the Fc domain of a SIRP antibody is that of a non-human primate, e.g. it is a cynomolgus monkey Fc domain.

[0091] In some embodiments, the SIRP antibodies provided herein are full-length antibodies. In some embodiments, the constant region of a full-length antibody (referred to interchangeably as a Fc domain, a Fc sequence or simply as a Fc) of the full-length SIRP antibodies is a human Fc domain. In some embodiments, the Fc domain of a full-length SIRP antibody is human IgG1, human IgG2, human IgG3, or human IgG4. In some embodiments, the Fc domain of a full-length SIRP antibody is that of a mouse. In some embodiments, the Fc domain of a full-length SIRP antibody is mouse IgG1 or mouse IgG2a. In some embodiments, the Fc domain of a full-

length SIRP antibody is that of a rat. In some embodiments, the Fc domain of a full-length SIRP antibody is rat IgG1 or rat IgG2b. In some embodiments, the Fc domain of a full-length SIRP antibody is rat IgG2b. In embodiments, the Fc domain of a full-length SIRP antibody is that of a non-human primate, e.g. it is a cynomolgus monkey Fc domain.

[0092] In some embodiments, the SIRP antibody contains an Fc domain, and the Fc domain of a SIRP antibody is a human IgG1 Fc. Exemplary, but non-limiting, human IgG1 Fc domain sequences are provided as SEQ ID NOS: 3-4, 11-16, 27-31, 33, 36, 38-=39 and 42-47.

```
1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 3)

1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 4)

1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLAG
121 PDVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 11)

ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLAG
121 PDVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 27)

1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
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121 PDVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 28)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 29)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
121 PDVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 30)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 31)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV LHEALHNHYT QKSLSLSPGK (SEQ ID NO: 33)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW

301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 36)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV LHEALHNHYT QKSLSLSPGK (SEQ ID NO: 38)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 39)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 42)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 43)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 44)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG

121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 45)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 46)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 47)

[0093] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 12, wherein X_1 is V or A.

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX_1EP KSCDKTHTCP PCPAPELLAG
121 PDVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 12)

[0094] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 13, wherein X_1 is V or A; X_2 is G or A; X_3 is S or D; and X_4 is I or E.

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX_1EP KSCDKTHTCP PCPAPELLX_2G
121 PX_3VFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPX_4EKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 13)

[0095] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 14, wherein X_1 is V or A.

```
  1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
 61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX1EP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV LHEALHSHYT QKSLSLSPGK (SEQ ID NO: 14)
```

[0096] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 15, wherein X_1 is V or A; X_2 is M or L; and X_3 is N or S.

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  1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
 61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX1EP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV X2HEALHX3HYT QKSLSLSPGK (SEQ ID NO: 15)
```

[0097] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 16, wherein X_1 is K or R; X_2 is D or E; and X_3 is L or M.

```
1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKX1VEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRX2E
241 X3TKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 16)
```

[0098] In some embodiments, the SIRP antibody contains an Fc domain, and the Fc domain of a SIRP antibody is a human IgG4 Fc. Exemplary human IgG4 heavy chain Fc domain sequences are provided as SEQ ID NO: 17-18, 24 and 59-63.

```
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
```

PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 17)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 18)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 59)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 60)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEALGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 61)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQID NO: 62)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 63)

[0099] In some embodiments, the human IgG4 Fc domain sequence is SEQ ID NO: 37, wherein X_1 is S or P; AND X_2 is L or E.

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPX$_1$CPAPEFX$_2$GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV
QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT
LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV
MHEALHNHYTQKSLSLSLGK (SEQ ID NO: 24)

[00100] In some embodiments, the SIRP antibodies provided herein are chimeric and comprise a variable region from one species, and a constant region from another species, e.g. comprise a human variable region and a rat constant region. In some embodiments, the rat constant region is rat IgG2b. In some embodiments, the antibodies comprise a human variable region and a mouse constant region. In some embodiments, the mouse constant region is mouse IgG1 or mouse IgG2a. In some embodiments, the antibodies comprise a human variable region and a human constant region. In exemplary embodiments, the human constant region is human IgG1 or human IgG4.

[00101] The EU numbering scheme is one of many available antibody numbering schemes based on the residue numbers assigned to a canonical antibody sequence. Accordingly, a skilled artisan would understand that reference to a particular residue using the EU numbering scheme may or may not be exactly the residue in one of the SIRP antibodies of the disclosure. For example, if a SIRP antibody of the disclosure comprises a V215A substitution in the FC, wherein the position number of the amino acid residue is of the EU numbering scheme, the residue may not be the actual residue 215 in that particular SIRP antibody. It may be actual residue number 213, or 214, or 215, or 216, or others. Accordingly, a skilled artisan will understand how to correspond the recited residue using the EU numbering scheme, to the actual residue in a SIRP antibody of the disclosure. The EU numbering system for antibodies is known in the art and is described, for example, at imgt.org/IMGTScientificChart/Numbering/Hu_IGHGnber.html.

[00102] In some embodiments, the Fc domain of a SIRP antibody is an IgG1 Fc domain (e.g. SEQ ID NOS: 3-4, or 11-16) or IgG4 human Fc domain (e.g. SEQ ID NOS: 17-18 or 24), and comprises at least one amino acid substitution at a position selected from the group consisting of: 214, 215, 221, 222, 228, 234, 235, 236, 239, 240, 241, 243, 244, 245, 247, 250, 252, 254, 256, 262, 263, 264, 265, 266, 267, 268, 269, 270, 292, 296, 297, 298, 299, 300, 305, 313, 324,

325, 326, 327, 328, 329, 330, 332, 333, 334, 345, 356, 358, 396, 428, 430, 433, 434, and 440 wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[00103] In some embodiments, the Fc domain of a SIRP antibody comprises SEQ ID NOS: 3-4, or 11-16, optionally with one or more Fc amino acid substitutions, for example at least one amino acid substitution at a position selected from the group consisting of: 214, 215, 221, 222, 228, 234, 235, 236, 239, 240, 241, 243, 244, 245, 247, 250, 252, 254, 256, 262, 263, 264, 265, 266, 267, 268, 269, 270, 292, 296, 297, 298, 299, 300, 305, 313, 324, 325, 326, 327, 328, 329, 330, 332, 333, 334, 345, 356, 358, 396, 428, 430, 433, 434, and 440 wherein the position numbers of the amino acid residues are of the EU numbering scheme. Exemplary substitutions include one or more of K214R, V215A, G236A, S239D, I332E, D356E, L358M, M428L, N434S, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[00104] In some embodiments, the Fc domain of a SIRP antibody is a human IgG1 (e.g. SEQ ID NOS: 3-4, or 11-16), and substitutions are introduced to increase effector function, selected from the group consisting of V215A, G236A, S239D, I332E, G236A/S239D, G236A/I332E, S239D/I332E, G236A/S239D,/I332E, K326W/E333S, S267E/H268F/S324T, and E345R/E430G/S440Y, F243L/R292P/Y300L/V305I/P396L, S239D/I332E, S298A/E333A/K334A, L234Y/L235Q/G236W/S239M/H268D/D270E/S298A, and D270E/K326D/A330M/K334E wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[00105] In some embodiments, the Fc domain of a SIRP antibody is a human IgG1 (e.g. SEQ ID NOS: 3-4, or 11-16), and substitutions are introduced to reduce effector function, including one or more of N297A, N297Q, N297G, L235E, L234A, L235A, K214R, D356E, and L358M, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[00106] In some embodiments, the Fc domain of a SIRP antibody is human IgG4 (e.g. SEQ ID NOS: 17-18 or 24), and substitutions are introduced to reduce effector function, including one or more of L235E, and F234A/L235A, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[00107] In some embodiments, the Fc domain of a SIRP antibody is human IgG2, and substitutions are introduced to reduce effector function, including H268Q/V309L/A330S/P331S and V234A/G237A/P238S/H268A/V309L/A330S/P331S, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[00108] In some embodiments, the Fc domain of a SIRP antibody is an IgG4 human Fc domain (e.g. SEQ ID NOS: 17-18 or 24), and the antibody is prone to the dynamic process of Fab-arm exchange. Accordingly, in some embodiments the IgG4 Fc domain comprises a S228P substitution, resulting in the reduction of this process, wherein the position number of the amino acid residues are of the EU numbering scheme.

[00109] In some embodiments, the Fc domain of a SIRP antibody is human IgG4 (e.g. SEQ ID NOS: 17-18 or 24), and one or more of the following substitution are introduced: L235A, L235E, S228P, L235E/S228P, S228P/F234A, S228P/F234A/L235A, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[00110] In other embodiments, the Fc domain of a SIRP antibody is altered to increase its serum half-life. Such alterations include substitutions of a human IgG1, IgG2, IgG3, or IgG4 such as M428L, N343S, T250Q/M428L, M252Y/S254T/T256E, M428L/N434S, S267E/L328F, N325S/L328F, and H433K/N434F, wherein the position number of the amino acid residues are of the EU numbering scheme.

i. SIRP Antibody-Mediated Cell Depletion

[00111] The SIRP antibodies that contain Fc domains provided herein are capable of targeting a variety of cell types for depletion and inducing the depletion of those cells.

[00112] In some embodiments, the SIRP antibodies containing Fc domains provided herein are capable of inducing the depletion of SIRPα- and/or SIRPβ1-expressing cells such as myeloid cells and myeloid progenitor cells, and include, but are not limited to, monocytes, macrophages, dendritic cells, mast cells, eosinophils, basophils, and neutrophils. In some embodiments, the SIRP antibodies provided herein are capable of inducing the depletion of non SIRPα-expressing cells, for example SIRPβ1 expressing cells.

[00113] Without being held to any theory, it is envisioned that the SIRP antigen binding domain allows for the antigen-binding fragments (Fab) of the antibody to bind to the SIRP expressing cell, and that the Fc portion of the antibody induces depletion. Accordingly in some embodiments, the antibody is a full-length antibody and the cell depletion involves antibody dependent cellular cytotoxicity (ADCC). In some embodiments, the antibody is a full-length antibody and the cell depletion involves antibody dependent cellular phagocytosis (ADCP). In some embodiments, the antibody is a full-length antibody and the cell depletion involves ADCC and ADCP. An Fc-containing SIRP antibody of the disclosure includes a full-length antibody, or an antibody fragment that is linked to a Fc domain, e.g. a VH-VL-Fc single chain antibody.

ii. Exemplary SIRP Antibodies – Complementarity Determining Region (CDR) Sequences

[00114] Provided herein are sequences for exemplary SIRP antibodies of the disclosure. Exemplary CDR-L1, L2, L3, H1, H2, and H3 sequences that make up the SIRP antigen binding domain are presented below in Tables 1-6. As referred below, a light chain variable (VL) domain CDR1 region is referred to as CDR-L1; a VL CDR2 region is referred to as CDR-L2; a VL CDR3 region is referred to as CDR-L3; a heavy chain variable (VH) domain CDR1 region is referred to as CDR-H1; a VH CDR2 region is referred to as CDR-H2; and a VH CDR3 region is referred to as CDR-H3. Tables 7 and 8 provide exemplary CDR triplets for the light chains and heavy chains of SIRP antibodies of the disclosure. Table 9 provides exemplary CDR combinations of antibodies of the disclosure.

Table 1: Exemplary SIRP Antibody CDR-L1 Sequences

CDR-L1	SEQ ID NO:
QSLLHSNGYNY	6
QSISSW	9
TGAVTTSNY	10
QSLLYSTNQKNY	19
QSIVHSNGNTY	20
QSLVHSNGNTY	21
QSVSND	22

Table 2: Exemplary SIRP Antibody CDR-L2 Sequences

CDR-L2	SEQ ID NO:
LGS	23
KAS	25
GTN	26
WAS	32
KVS	34
YAS	35

Table 3: Exemplary SIRP Antibody CDR-L3 Sequences

CDR-L3	SEQ ID NO:
MQALQTPRT	37
QQYNSYSWT	40
ALWYSNHWV	41
QQYYSYPWT	50
FQGSHFPYT	51
SQSTHVPFT	52
QQDYSSPWT	53

Table 4: Exemplary SIRP Antibody CDR-H1 Sequences

CDR-H1	SEQ ID NO:
GYTFTGYY	55
GFTFSNYG	57
GFTLSSYA	58
GYTFTSYW	66
GFAFSSYD	67
GYTFTSYY	68
GYTFTDYE	69

Table 5: Exemplary SIRP Antibody CDR-H2 Sequences

CDR-H2	SEQ ID NO:
INPNSGGT	71
IWYDGSYK	73
SSGSGANT	74
IDPSTGYT	82

CDR-H2	SEQ ID NO:
ISSGGGSI	83
IYPGNVHT	84
IDPETGGT	85

Table 6: Exemplary SIRP Antibody CDR-H3 Sequences

CDR-H3	SEQ ID NO:
AREDCTSISCSFDY	87
VRESVGYSSGWSFDY	90
ARLRFFDWFDY	91
ARRDYGSSFYAMDY	100
VRHGYHEYFDV	101
SRGGTNSWFAY	102
TGITRFAY	103

Table 7: Exemplary SIRP Antibody Light Chain CDR Triplets

CDR-L1	SEQ ID NO:	CDR-L2	SEQ ID NO:	CDR-L3	SEQ ID NO:
QSLLHSNGYNY	6	LGS	23	MQALQTPRT	37
QSISSW	9	KAS	25	QQYNSYSWT	40
TGAVTTSNY	10	GTN	26	ALWYSNHWV	41
QSLLYSTNQKNY	19	WAS	32	QQYYSYPWT	50
QSIVHSNGNTY	20	KVS	34	FQGSHFPYT	51
QSLVHSNGNTY	21	KVS	34	SQSTHVPFT	52
QSVSND	22	YAS	35	QQDYSSPWT	53

Table 8: Exemplary SIRP Antibody Heavy Chain CDR Triplets

CDR-H1	SEQ ID NO:	CDR-H2	SEQ ID NO:	CDR-H3	SEQ ID NO:
GYTFTGYY	55	INPNSGGT	71	AREDCTSISCSFDY	87
GFTFSNYG	57	IWYDGSYK	73	VRESVGYSSGWSFDY	90
GFTLSSYA	58	SSGSGANT	74	ARLRFFDWFDY	91
GYTFTSYW	66	IDPSTGYT	82	ARRDYGSSFYAMDY	100
GFAFSSYD	67	ISSGGGSI	83	VRHGYHEYFDV	101
GYTFTSYY	68	IYPGNVHT	84	SRGGTNSWFAY	102
GYTFTDYE	69	IDPETGGT	85	TGITRFAY	103

Table 9: Exemplary SIRP Antibody CDR Combinations, Antibodies 2, 5, 6 and 16-19

Antibody No.	CDR-L1	CDR-L2	CDR-L3	CDR-H1	CDR-H2	CDR-H3
Antibody 2	QSLLHSNGYNY (SEQ ID NO: 6)	LGS (SEQ ID NO: 23)	MQALQTPRT (SEQ ID NO: 37)	GYTFTGYY (SEQ ID NO: 55)	INPNSGGT (SEQ ID NO: 71)	AREDCTSISCSFDY (SEQ ID NO: 87)
Antibody 5	QSISSW (SEQ ID NO: 9)	KAS (SEQ ID NO: 25)	QQYNSYSWT (SEQ ID NO: 40)	GFTFSNYG (SEQ ID NO: 57)	IWYDGSYK (SEQ ID NO: 73)	VRESVGYSSGWSFDY (SEQ ID NO: 90)
Antibody 6	TGAVTTSNY (SEQ ID NO: 10)	GTN (SEQ ID NO: 26)	ALWYSNHWV (SEQ ID NO: 41)	GFTLSSYA (SEQ ID NO: 58)	SSGSGANT (SEQ ID NO: 74)	ARLRFFDWFDY (SEQ ID NO: 91)
Antibody 16	QSLLYSTNQKNY (SEQ ID NO: 19)	WAS (SEQ ID NO: 32)	QQYYSYPWT (SEQ ID NO: 50)	GYTFTSYW (SEQ ID NO: 66)	IDPSTGYT (SEQ ID NO: 82)	ARRDYGSSFYAMDY (SEQ ID NO: 100)
Antibody 17	QSIVHSNGNTY (SEQ ID NO: 20)	KVS (SEQ ID NO: 34)	FQGSHFPYT (SEQ ID NO: 51)	GFAFSSYD (SEQ ID NO: 67)	ISSGGGSI (SEQ ID NO: 83)	VRHGYHEYFDV (SEQ ID NO: 101
Antibody 18	QSLVHSNGNTY (SEQ ID NO: 21)	KVS (SEQ ID NO: 34)	SQSTHVPFT (SEQ ID NO: 52)	GYTFTSYY (SEQ ID NO: 68)	IYPGNVHT (SEQ ID NO: 84)	SRGGTNSWFAY (SEQ ID NO: 102)
Antibody 19	QSVSND (SEQ ID NO: 22)	YAS (SEQ ID NO: 35)	QQDYSSPWT (SEQ ID NO: 53)	GYTFTDYE (SEQ ID NO: 69)	IDPETGGT (SEQ ID NO: 85)	TGITRFAY (SEQ ID NO: 103)

[00115] In some embodiments, the SIRP antibodies provided herein include any one or more of the amino acid sequences of the CDR sequences provided in Tables 1-6.

[00116] In some embodiments, provided herein is a SIRP antibody, wherein the antibody comprises:

(a) any one of the CDR-L1 amino acid sequences of SEQ ID NOS: 6, 9-10, and 19-22 as set forth in Table 1;

(b) any one of the CDR-L2 amino acid sequences of SEQ ID NOS: 23, 25-26, 32 or 34-35 as set forth in Table 2;

(c) any one of the CDR-L3 amino acid sequences of SEQ ID NOS: 37, 40-41 or 50-53 as set forth in Table 3;

(d) any one of the CDR-H1 amino acid sequences of SEQ ID NOS: 55, 57-58 or 66-69 as set forth in Table 4;

(e) any one of the CDR-H2 amino acid sequences of SEQ ID NOS: 71, 73-74 or 82-85 as set forth in Table 5; and/or

(f) any one of the CDR-H3 amino acid sequences of SEQ ID NOS: 87, 90-91 and 100-103 as set forth in Table 6.

[00117] In some embodiments, provided herein is a SIRP antibody, wherein the light chain variable domain of the antibody comprises:

(g) a CDR-L1 comprising any one of the amino acid sequences of SEQ ID NOs: 6, 9-10, or 19-22;

(h) a CDR-L2 comprising any one of the amino acid sequences of SEQ ID NOs: 23, 25-26, 32 or 34-35; and

(i) a CDR-L3 comprising any one of the amino acid sequences of SEQ ID NOs: 37, 40-41 or 50-53.

[00118] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain variable domain of the antibody comprises:

(j) a CDR-H1 comprising any one of the amino acid sequences of SEQ ID NOs: 55, 57-58 or 66-69;

(k) a CDR-H2 comprising any one of the amino acid sequences of SEQ ID NOs: 71, 73-74 or 82-85; and

(l) a CDR-H3 comprising any one of the amino acid sequences of SEQ ID NOs: 87, 90-91 or 100-103.

[00119] In some embodiments, provided herein is a SIRP antibody, wherein the light chain variable domain of the antibody comprises any one of the sequences provided in Tables 1-3, and wherein the heavy chain variable domain of the antibody comprises:

(m) a CDR-H1 comprising any one of the amino acid sequences of SEQ ID NOs: 55, 57-58 or 66-69;

(n) a CDR-H2 comprising any one of the amino acid sequences of SEQ ID NOs: 71, 73-74 or 82-85; and

(o) a CDR-H3 comprising any one of the amino acid sequences of SEQ ID NOs: 87, 90-91 or 100-103.

[00120] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain variable domain of the antibody comprises any one of the sequences provided in Tables 4-6, and wherein the light chain variable domain of the antibody comprises:

(p) a CDR-L1 comprising any one of the amino acid sequences of SEQ ID NOs: 6, 9-10, or 19-22;

(q) a CDR-L2 comprising any one of the amino acid sequences of SEQ ID NOs: 23, 25-26, 32 or 34-35; and

(r) a CDR-L3 comprising any one of the amino acid sequences of SEQ ID NOs: 37, 40-41 or 50-53.

[00121] In some embodiments, provided herein is a SIRP antibody, wherein the light chain of the antibody comprises the amino acid sequences of:

a. SEQ ID NO: 6, SEQ ID NO: 23, and SEQ ID NO: 37;
b. SEQ ID NO: 9, SEQ ID NO: 25, and SEQ ID NO: 40;
c. SEQ ID NO: 10, SEQ ID NO: 26, and SEQ ID NO: 41;
d. SEQ ID NO: 19, SEQ ID NO: 32, and SEQ ID NO: 50;
e. SEQ ID NO: 20, SEQ ID NO: 34, and SEQ ID NO: 51;
f. SEQ ID NO: 21, SEQ ID NO: 34, and SEQ ID NO: 52; or
g. SEQ ID NO: 22, SEQ ID NO: 35, and SEQ ID NO: 53.

[00122] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain of the antibody comprises the amino acid sequences of:

a. SEQ ID NO: 55, SEQ ID NO: 71, and SEQ ID NO: 87;
b. SEQ ID NO: 57, SEQ ID NO: 73, and SEQ ID NO: 90.
c. SEQ ID NO: 58, SEQ ID NO: 74, and SEQ ID NO: 91;

d. SEQ ID NO: 66, SEQ ID NO: 82, and SEQ ID NO: 100;
e. SEQ ID NO: 67, SEQ ID NO: 83, and SEQ ID NO: 101;
f. SEQ ID NO: 68, SEQ ID NO: 84, and SEQ ID NO: 102; or
g. SEQ ID NO: 69, SEQ ID NO: 85, and SEQ ID NO: 103.

[00123] In some embodiments, provided herein is a SIRP antibody, wherein the antibody comprises the amino acid sequences of:

a. SEQ ID NO: 6, SEQ ID NO: 23, SEQ ID NO: 37, SEQ ID NO: 55, SEQ ID NO: 71, and SEQ ID NO: 87;
b. SEQ ID NO: 9, SEQ ID NO: 25, SEQ ID NO: 40, SEQ ID NO: 57, SEQ ID NO: 73, and SEQ ID NO: 90;
c. SEQ ID NO: 10, SEQ ID NO: 26, SEQ ID NO: 41, SEQ ID NO: 58, SEQ ID NO: 74, and SEQ ID NO: 91;
d. SEQ ID NO: 19, SEQ ID NO: 32, SEQ ID NO: 50, SEQ ID NO: 66, SEQ ID NO: 82, and SEQ ID NO: 100;
e. SEQ ID NO: 20, SEQ ID NO: 34, SEQ ID NO: 51, SEQ ID NO: 67, SEQ ID NO: 83, and SEQ ID NO: 101;
f. SEQ ID NO: 21, SEQ ID NO: 34, SEQ ID NO: 52, SEQ ID NO: 68, SEQ ID NO: 84, and SEQ ID NO: 102; or
g. SEQ ID NO: 22, SEQ ID NO: 35, SEQ ID NO: 53, SEQ ID NO: 69, SEQ ID NO: 85, and SEQ ID NO: 103.

iv. Exemplary SIRP Antibodies - Variable Region Sequences

[00124] The term variable region and variable domain are used interchangeably and refer to the portions of the light and heavy chains of an antibody that include the complementarity determining regions and framework regions (FRs).

[00125] Table 10 provides amino acid sequences for the variable domains of exemplary SIRP antibodies of the disclosure. Accordingly, in some embodiments a SIRP antibody of the disclosure comprises a variable heavy chain comprising an amino acid sequence selected from SEQ ID NOS: 105, 108-109, and 119-122, or at least 80% sequence identity thereto. In some embodiments a SIRP antibody of the disclosure comprises a variable light chain comprising an

amino acid sequence selected from SEQ ID NOS: 124, 127-128, 138-141, or at least 80% sequence identity thereto. In some embodiments a SIRP antibody of the disclosure comprises a variable heavy chain comprising an amino acid sequence selected from SEQ ID NOS: 105, 108-109, and 119-122, or at least 80% sequence identity thereto and comprises a variable light chain comprising an amino acid sequence selected from SEQ ID NOS: 124, 127-128, 138-141, or at least 80% sequence identity thereto.

[00126] In some embodiments, a SIRP antibody of the disclosure comprises the combination of VH/VL variable chain sequences of any one Antibodies 2, 5, 6 and 16-19 presented in Table 10.

Table 10: Exemplary Variable Heavy Chain and Variable Light Chain Amino Acid Sequences VH/VL pairs of SIRP antibodies

Antibody No.	Variable Heavy Chain Amino Acid Sequence	Variable Light Chain Amino Acid Sequence
2	QVQLVQSGAEVKKPGASVKVSCKASG YTFTGYYIFWMRQAPGQGLEWMGW INPNSGGTDYAQKFQGRVTMTMDTSI STAYMELSRLRSDDTAVYYCAREDCTSI SCSFDYWGQGTLVTVSS (SEQ ID NO: 105)	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHS NGYNYLDWYLQKPGQSPQLLIYLGSNRASG VPDRFSGSGSGTDFTLKISRVEAEDVGVYCC MQALQTPRTFGQGTKVEIK (SEQ ID NO: 124)
5	QVQLVESGGGVVQPGRSLRLSCAASG FTFSNYGMHWVRQAPGKGPEWVAVI WYDGSYKYYGDSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCVRESVGYS SGWSFDYWGQGILVTVSS (SEQ ID NO: 108)	DIQMTQSPSTLSASVGDRVTITCRASQSISS WLAWYQQKPGKVPKLLIYKASSLKTGVPSR FSGNGSGTEFTLTISSLQPDDFATYYCQQYN SYSWTFGQGTKVEIK (SEQ ID NO: 127)
6	EVQLLESGGGLVQPGGSLRLSCAASGF TLSSYAMSWVRQAPGKGLEWVSISSG SGANTYNADSLKGRFTISRDNSKNTLF LQMNSLRAEDTAVYYCARLRFFDWFD YWGQGALVTVSS (SEQ ID NO: 109)	QAVVTQESALTTSPGETVTLTCRSSTGAVTT SNYANWVQEKPDHLFTGLIGGTNNRTPGV PARFSGSLIGDKAALTITGAQTEDEAIYFCAL WYSNHWVFGGGTKLTVL (SEQ ID NO: 128)
16	QVQLQQSGAELAKPGASVKMSCKAS GYTFTSYWMHWVKQRPGQGLEWIG YIDPSTGYTFHNQKFKDKATLTADKSST TAYMQLRSLTSEDSAVYYCARRDYGSS FYAMDYWGHGTSITVSS (SEQ ID NO: 119)	DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLY STNQKNYLAWYQQKPGQSPKLLIYWASTRE SGVPDRFTGSGSGTDFTLTISSVKAEDLAVYY CQQYYSYPWTFGGGTKLEIK (SEQ ID NO: 138)
17	EVQVVESGGGLVKPGGSLKISCAASGF AFSSYDMSWVRQTPEKRLEWVAYISS GGGSIYYAETVKGRFTISRDNAKNTLYL QMSSLKSEDTAMYYCVRHGYHEYFDV WGAGTTVTVSS (SEQ ID NO: 120)	DVLMTQTPLSLPVSLGDQASISCRSSQSIVHS NGNTYLEWYLQKPGQSPKLLIYKVSNRFSGV PDRFSGSGSGTDFTLKISRVEAEDLGVYFCF QGSHFPYTFGGGTKLEIK (SEQ ID NO: 139)
18	QVQLQQSGPELVKPGASVRISCKASGY TFTSYYIHWVKQRPGQGLEWIGWIYP GNVHTQYNEKFKGKATLTADKSSTTAY	DVVMTQTPLSLPVSLGDQASISCRSSQSLVH SNGNTYLHWYLQKPGQSPKLLIYKVSNRFSG

	MQLSSLTSEDSAVYFCSRGGTNSWFA YWGQGTLVTVSA (SEQ ID NO: 121)	VPDRFSGSGSGTDFTLKISRVEAEDLGVYFCS QSTHVPFTFGSGTKLEIK (SEQ ID NO: 140)
19	QVQLQQSGAELVRPGASVTLSCKASG YTFTDYEMHWVKQTPVHGLEWIGAI DPETGGTAYNQKFKGKATLTADKSSST AYMELRSLTSEDSAVYYCTGITRFAYW GQGTLVTVSA (SEQ ID NO: 122)	SIVMTQTPKFLLVSAGDRVTITCKASQSVSN DVAWYQQKPGQSPKLLIYYASNRYTGVPDR FTGSGYGTDFTFTISTVQAEDLAVYFCQQDY SSPWTFGGGTKLEIK (SEQ ID NO: 141)

[00127] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 105 or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 124, or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 105, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 124. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 6, 23 and 37, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 55, 71 and 87.

[00128] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 108 or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 127, or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 108, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 127. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 9, 25 and 40, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 57, 73 and 90.

[00129] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 109 or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 128, or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 109, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 128. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 10, 26 and 41, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 58, 74 and 91.

[00130] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 119 or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 119, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 138. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 19, 32 and 50, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 66, 82 and 100.

[00131] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 120 or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 139, or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence

identity thereto. In some embodiments, the heavy variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 120, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 139. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 20, 34 and 51, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 67, 83 and 101.

[00132] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 121 or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 140, or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 121, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 140. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 21, 34 and 52, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 68, 84 and 102.

[00133] In some embodiments, provided herein is a SIRP antibody, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 122 or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 141, or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 122, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 141. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 22, 35 and 53, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 69, 85 and 103.

[00134] Table 11 provides full-length exemplary SIRP antibodies of the disclosure.

Table 11: Exemplary Combinations of Amino Acid with Fc Regions of SIRP Antibodies

Antibody No.	VH/VL Pair Amino Acid	Fc
Antibody 2	SEQ ID NO: 105/SEQ ID NO: 124	Rat IgG2b Fc
Antibody 5	SEQ ID NO: 108/SEQ ID NO: 127	Rat IgG2b Fc
Antibody 6	SEQ ID NO: 109/SEQ ID NO: 128	Rat IgG2b Fc
Antibody 16	SEQ ID NO: 119/SEQ ID NO: 138	Mouse IgG2a Fc
Antibody 17	SEQ ID NO: 120/SEQ ID NO: 139	Mouse IgG2a Fc
Antibody 18	SEQ ID NO: 121/SEQ ID NO: 140	Mouse IgG2a Fc
Antibody 19	SEQ ID NO: 122/SEQ ID NO: 141	Mouse IgG1 Fc
Antibody 20	SEQ ID NO: 109/SEQ ID NO: 128	Human IgG4 Fc with reduced effector function and reduced Fab arm exchange
Antibody 22	SEQ ID NO: 109/SEQ ID NO: 128	Human IgG1 Fc
Antibody 27	SEQ ID NO: 109/SEQ ID NO: 128	Human IgG1 Fc with increased affinity for FcγR

B. Generation of SIRP Antibodies

[00135] Production of the antibodies provided herein may be by use of any method known to those of ordinary skill in the art. In some embodiments, the antibodies are produced by hybridomas. In some embodiments, the antibodies are encoded by a nucleic acid and are expressed, purified, and isolated.

[00136] The terms polynucleotide and nucleic acid are used interchangeably herein, and refer to a polymeric form of nucleotides of any length, which may be ribonucleotides or deoxyribonucleotides. The terms include, but are not limited to, single-, double-, or multi-stranded DNA or RNA, genomic DNA, cDNA, DNA-RNA hybrids, or a polymer comprising purine and pyrimidine bases or other natural, chemically or biochemically modified, non-natural, or derivative nucleotide bases. The terms encompass nucleic acids containing known analogues of natural nucleotides and having similar binding properties, and are metabolized in a manner similar to naturally-occurring nucleotides, unless specifically limited or stated otherwise.

[00137] Accordingly, provided herein are nucleic acids encoding any of the antibodies disclosed herein, vectors comprising any of the nucleic acids encoding such antibodies, and host cells comprising any such vectors. Also provided herein are exemplary nucleic acid sequences encoding for the variable heavy chains and variable light chains of the SIRP antibodies disclosed herein.

[00138] Table 12 provides exemplary nucleic acid sequences for the SIRP antibodies of the disclosure. Accordingly, in some embodiments a nucleic acid sequence encoding for a SIRP antibody of the disclosure comprises a variable heavy chain nucleic acid sequence selected from SEQ ID NOS: 143, 146-147, and 157-160, or at least 80% sequence identity thereto. In some embodiments a nucleic acid sequence encoding for a SIRP antibody of the disclosure comprises a variable light chain nucleic acid sequence selected from SEQ ID NOS: 162, 165-166, and 176-179, or at least 80% sequence identity thereto. In some embodiments a nucleic acid sequence encoding for a SIRP antibody of the disclosure comprises a variable heavy chain nucleic acid sequence selected from SEQ ID NOS: 143, 146-147, and 157-160, or at least 80% sequence identity thereto, and a variable light chain nucleic acid sequence selected from SEQ ID NOS: 162, 165-166, and 176-179, or at least 80% sequence identity thereto. The person of ordinary skill in the art will appreciate that, because of redundancy in the triplet code, multiple nucleic acids may encode the same amino acid sequence. Thus, nucleic acid sequences that are not identical to those set forth in Table 12 may still encode the amino acid sequences set forth in Table 10.

Table 12: Variable Heavy Chain and Variable Light Chain Nucleic Acid Sequences of Exemplary SIRP antibodies

Antibody No.	Variable Heavy Chain Nucleic Acid Sequence	Variable Light Chain Nucleic Acid Sequence
2	CAGGTGCAGCTGGTGCAGTCTGGGGC TGAGGTGAAGAAGCCTGGGGCCTCAG TGAAGGTCTCCTGCAAGGCTTCTGGAT ACACCTTCACCGGCTACTATATATTCTG GATGCGACAGGCCCCTGGACAAGGGC TTGAGTGGATGGGATGGATCAACCCTA ACAGTGGTGGCACAGACTATGCACAG AAGTTTCAGGGCAGGGTCACCATGACC ATGGACACGTCCATCAGCACAGCCTAC ATGGAACTGAGCAGACTGAGATCTGAC GACACGGCCGTGTATTACTGTGCGAGA	GATATTGTGATGACTCAGTCTCCACTC TCCCTGCCCGTCACCCCTGGAGAGCC GGCCTCCATCTCCTGTAGGTCTAGTCA GAGCCTCCTGCATAGTAATGGATACA ACTATTTGGATTGGTACCTGCAGAAG CCAGGGCAGTCTCCACAGCTCCTGAT CTATTTGGGTTCTAATCGGGCCTCCGG GGTCCCTGACAGGTTCAGTGGCAGTG GATCAGGCACAGATTTTACACTGAAA ATCAGCAGAGTGGAGGCTGAGGATG TTGGGGTTTATTGCTGCATGCAAGCTC

Antibody No.	Variable Heavy Chain Nucleic Acid Sequence	Variable Light Chain Nucleic Acid Sequence
	GAGGATTGTACTAGTATCAGTTGCTCTT TTGACTATTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA (SEQ ID NO: 143)	TACAAACTCCTCGGACGTTCGGCCAA GGGACCAAGGTGGAAATCAAA (SEQ ID NO: 162)
5	CAGGTGCAGCTGGTGGAGTCTGGGGG AGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCGTCTGGATT CACCTTCAGTAACTATGGCATGCACTG GGTCCGCCAGGCTCCAGGCAAGGGGC CGGAGTGGGTGGCAGTTATATGGTAT GATGGAAGTTATAAATACTATGGAGAC TCCGTGAAGGGCCGATTCACCATTTCC AGAGACAATTCCAAGAACACGCTGTAT CTGCAAATGAACAGCCTGAGAGCCGA GGACACGGCTGTGTATTATTGTGTGAG AGAGAGCGTCGGGTATAGCAGTGGCT GGTCCTTTGACTACTGGGGCCAGGGAA TCCTGGTCACCGTCTCCTCA (SEQ ID NO: 146)	GACATCCAGATGACCCAGTCTCCTTCC ACCCTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGCCGGGCCAGTC AGAGTATTAGTAGCTGGTTGGCCTGG TATCAGCAGAAACCAGGGAAAGTCCC TAAGCTCCTGATCTATAAGGCGTCTAG TTTAAAAACTGGGGTCCCATCAAGGT TCAGCGGCAATGGTTCTGGGACAGAA TTCACTCTCACCATCAGCAGCCTGCAG CCTGATGATTTTGCAACTTATTACTGC CAACAGTATAATAGTTATTCGTGGAC GTTCGGCCAAGGGACCAAAGTGGAA ATCAAA (SEQ ID NO: 165)
6	GAGGTGCAGCTGTTGGAGTCTGGGGG AGGCTTGGTACAGCCGGGGGGGTCCC TGAGACTTTCCTGTGCAGCCTCTGGATT CACCTTAAGTAGCTATGCCATGAGCTG GGTCCGCCAGGCTCCAGGGAAGGGGC TGGAGTGGGTCTCAATTAGTAGTGGTA GTGGTGCTAACACATATAACGCAGACT CCCTGAAGGGCCGGTTCACCATCTCCA GGGACAATTCCAAGAACACGCTGTTTC TCCAAATGAACAGCCTGAGAGCCGAG GACACGGCCGTATATTACTGTGCGAGA TTACGATTTTTTGACTGGTTTGACTACT GGGGCCAGGGGGCCCTGGTCACCGTC TCCTCA (SEQ ID NO: 147)	CAGGCTGTTGTGACTCAGGAATCTGC ACTCACCACATCACCTGGTGAAACAG TCACACTCACTTGTCGCTCAAGTACTG GGGCTGTTACAACTAGTAACTATGCC AACTGGGTCCAAGAAAAACCAGATCA TTTATTCACTGGTCTAATAGGTGGTAC CAACAACCGAACTCCAGGTGTTCCTG CCAGATTCTCAGGCTCCCTGATTGGA GACAAGGCTGCCCTCACCATCACAGG GGCACAGACTGAGGATGAGGCAATA TATTTCTGTGCTCTATGGTACAGCAAC CATTGGGTGTTCGGTGGAGGAACCAA ACTGACTGTCCTA (SEQ ID NO: 166)
16	CAGGTCCAGCTTCAGCAGTCTGGGGCT GAACTGGCAAAGCCTGGGGCCTCAGT GAAGATGTCCTGCAAGGCTTCTGGCTA CACCTTTACTAGCTACTGGATGCACTG GGTAAAACAGAGGCCTGGACAGGGTC TGGAATGGATTGGATACATTGATCCTA GCACTGGTTATACTTTCCACAATCAGAA GTTCAAGGACAAGGCCACATTGACTGC AGACAAATCCTCCACCACAGCCTACAT GCAACTGAGAAGCCTGACATCTGAGG ACTCTGCAGTCTATTACTGTGCAAGAA GGGACTACGGTAGTAGCTTCTATGCTA TGGACTACTGGGGTCACGGAACCTCAA TCACCGTCTCCTCA (SEQ ID NO: 157)	GACATTGTGATGTCACAGTCTCCATCC TCCCTAGCTGTGTCAGTTGGAGAGAA GGTTACTATGAGCTGCAAGTCCAGTC AGAGCCTTTTATATAGTACCAATCAAA AGAACTACTTGGCCTGGTACCAGCAG AAACCGGGGCAGTCTCCTAAACTGCT GATTTACTGGGCATCCACTAGGGAAT CTGGGGTCCCTGATCGCTTCACAGGC AGTGGATCTGGGACAGATTTCACTCT CACCATCAGCAGTGTGAAGGCTGAAG ACCTGGCAGTTTATTACTGTCAGCAAT ATTATAGCTATCCGTGGACGTTCGGT GGAGGCACCAAGCTGGAAATCAAA (SEQ ID NO: 176)

Antibody No.	Variable Heavy Chain Nucleic Acid Sequence	Variable Light Chain Nucleic Acid Sequence
17	GAAGTGCAGGTGGTGGAGTCTGGGGG AGGCTTAGTGAAGCCTGGAGGGTCCCT GAAAATCTCATGTGCAGCCTCTGGATT CGCTTTCAGTAGCTATGACATGTCTTGG GTTCGCCAGACTCCGGAGAAGAGGCT GGAGTGGGTCGCATACATTAGTAGTG GCGGTGGTAGTATCTACTATGCAGAGA CTGTGAAGGGCCGATTCACCATCTCCA GAGACAATGCCAAGAACACCCTGTACC TGCAAATGAGCAGTCTGAAGTCTGAGG ACACAGCCATGTATTACTGCGTAAGAC ATGGTTACCACGAGTACTTCGATGTCT GGGGCGCAGGGACCACGGTCACCGTC TCCTCA (SEQ ID NO: 158)	GATGTTTTGATGACCCAAACTCCACTC TCCCTGCCTGTCAGTCTTGGAGATCAA GCCTCCATCTCTTGCAGATCTAGTCAG AGCATTGTACATAGTAATGGAAACAC CTATTTAGAATGGTACCTGCAGAAAC CAGGCCAGTCTCCAAAGCTCCTGATCT ACAAAGTTTCCAACCGATTTTCTGGGG TCCCAGACAGGTTCAGTGGCAGTGGA TCAGGGACAGATTTCACACTCAAGAT CAGCAGAGTGGAGGCTGAGGATCTG GGAGTTTATTTCTGCTTTCAAGGTTCA CATTTTCCGTACACGTTCGGAGGGGG GACCAAGCTGGAAATAAAA (SEQ ID NO: 177)
18	CAGGTCCAGCTGCAGCAGTCTGGACCT GAGCTGGTGAAGCCTGGGGCTTCAGT GAGGATATCCTGCAAGGCTTCTGGCTA CACCTTCACAAGCTACTATATACACTGG GTGAAGCAGAGGCCTGGACAGGGACT TGAGTGGATTGGATGGATTTATCCTGG AAATGTTCATACTCAGTACAATGAGAA GTTCAAGGGCAAGGCCACACTGACTGC AGACAAGTCCTCCACCACAGCCTACAT GCAGCTCAGCAGCCTGACCTCTGAAGA CTCTGCGGTCTATTTCTGTTCAAGAGGC GGGACTAACTCTTGGTTTGCTTACTGG GGCCAAGGGACTCTGGTCACTGTCTCT GCA (SEQ ID NO: 159)	GATGTTGTGATGACCCAAACTCCACTC TCCCTGCCTGTCAGTCTTGGAGATCAA GCCTCCATCTCTTGCAGATCTAGTCAG AGCCTTGTACACAGTAATGGAAACAC CTATTTACATTGGTACCTGCAGAAGCC AGGCCAGTCTCCAAAGCTCCTGATCTA CAAAGTTTCCAACCGATTTTCTGGGGT CCCAGACAGGTTCAGTGGCAGTGGAT CAGGGACAGATTTCACACTCAAGATC AGCAGAGTGGAGGCTGAGGATCTGG GAGTTTATTTCTGCTCTCAAAGTACAC ATGTTCCATTCACGTTCGGCTCGGGG ACAAAGTTGGAAATAAAA (SEQ ID NO: 178)
19	CAGGTTCAACTGCAGCAGTCTGGGGCT GAGCTGGTGAGGCCTGGGGCTTCAGT GACGCTGTCCTGCAAGGCTTCGGGCTA CACATTTACTGACTATGAAATGCACTG GGTGAAGCAGACACCTGTGCATGGCCT GGAATGGATTGGAGCTATTGATCCTGA AACTGGTGGTACTGCCTACAATCAGAA GTTCAAGGGCAAGGCCACACTGACTGC AGACAAATCCTCCAGCACAGCCTACAT GGAGCTCCGCAGCCTGACATCTGAGGA CTCTGCCGTCTATTACTGTACAGGGATT ACGAGGTTTGCTTACTGGGGCCAAGG GACTCTGGTCACTGTCTCTGCA (SEQ ID NO: 160)	AGTATTGTGATGACCCAGACTCCCAA ATTCCTGCTTGTATCAGCAGGAGACA GGGTTACCATAACCTGCAAGGCCAGT CAGAGTGTGAGTAATGATGTAGCTTG GTACCAACAGAAGCCAGGGCAGTCTC CTAAACTGCTGATATACTATGCATCCA ATCGCTACACTGGAGTCCCTGATCGCT TCACTGGCAGTGGATATGGGACGGAT TTCACTTTCACCATCAGCACTGTGCAG GCTGAAGACCTGGCAGTTTATTTCTGT CAGCAGGATTATAGCTCTCCGTGGAC GTTCGGTGGAGGCACCAAGCTGGAA ATCAAA (SEQ ID NO: 179)

[00139] In some embodiments, provided herein is a nucleic acid encoding any of the SIRP antibodies disclosed herein. In some embodiments, provided herein is a nucleic acid comprising

any one or more of the nucleic acid sequences of Table 12. In some embodiments, the heavy and light chain variable domains of the SIRP antibodies disclosed herein are encoded by a nucleic acid comprising any one or more of the nucleic acid sequences of Table 12.

[00140] In some embodiments, the heavy chain variable domain of the SIRP antibodies of the disclosure is encoded by the nucleic acid sequence of SEQ ID NO: 143, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 162, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 143, or a nucleic acid sequence with at least 97%, sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 162, or a nucleic acid sequence with at least 97% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 143, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 162.

[00141] In some embodiments, the heavy chain variable domain of the SIRP antibodies of the disclosure is encoded by the nucleic acid sequence of SEQ ID NO: 146, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 165, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 146, or a nucleic acid sequence with at least 97%, sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 165, or a nucleic acid sequence with at least 97% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 146, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 165.

[00142] In some embodiments, the variable domain of the SIRP antibodies of the disclosure is encoded by the nucleic acid sequence of SEQ ID NO: 147, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 166, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 147, or a nucleic acid sequence with at least 97%, sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 166, or a nucleic acid sequence with at least 97% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 147, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 166.

[00143] In some embodiments, the heavy chain variable domain of the SIRP antibodies of the disclosure is encoded by the nucleic acid sequence of SEQ ID NO: 157, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 176, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 157, or a nucleic acid sequence with at least 97%, sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 176, or a nucleic acid sequence with at least 97% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 157, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 176.

[00144] In some embodiments, the heavy chain variable domain of the SIRP antibodies of the disclosure is encoded by the nucleic acid sequence of SEQ ID NO: 158, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 177, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 158, or a nucleic acid sequence with at least 97%, sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 177, or a nucleic acid sequence with at least 97% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 158, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 177.

[00145] In some embodiments, the heavy chain variable domain of the SIRP antibodies of the disclosure is encoded by the nucleic acid sequence of SEQ ID NO: 159, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 178, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 159, or a nucleic acid sequence with at least 97%, sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 178, or a nucleic acid sequence with at least 97% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 159, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 178.

[00146] In some embodiments, the heavy chain variable domain of the SIRP antibodies of the disclosure is encoded by the nucleic acid sequence of SEQ ID NO: 160, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 179, or a nucleic acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%,

88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 160, or a nucleic acid sequence with at least 97%, sequence identity thereto; and/or wherein the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 179, or a nucleic acid sequence with at least 97% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 160, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 179. The disclosure also provides vectors comprising any nucleic acid of the disclosure. In some embodiments, the nucleic acid of the vector comprises any one or more of the nucleic acid sequences selected from Table 12. In some embodiments, the vector is an expression vector or an expression construct. In some embodiments, the vector is a mammalian vector. In some embodiments, the vector is a viral vector.

[0147] In some embodiments, the SIRP antibodies provided herein are produced by culturing a cell under suitable conditions for leading to the expression of the SIRP antibody, wherein the cell comprises a vector.

II. Uses of SIRP Antibodies

A. SIRP Antibody-Mediated Cell Depletion

[0148] Provided herein are methods of inducing cell depletion, the method comprising contacting the cell with any of the SIRP antibodies of the disclosure, wherein the SIRP antibody contains an Fc domain. The method may be carried out *in vitro* or *in vivo*. In some embodiments, the cell depletion involves ADCC. In some embodiments, the cell depletion involves ADCP. In some embodiments, the cell depletion involves both ADCC and ADCP.

[0149] In some embodiments, the cells are SIRPα-expressing cells. In some embodiments, the cells are SIRPβ1-expressing cells. In some embodiments, the cells are SIRPα and SIRPβ1 expressing cells. For example, a single cell expresses both SIRPα and SIRPβ1. In some embodiments, the cells comprise a first population of SIRPα-expressing cells, and a second population of SIRPβ1-expressing cells. In some embodiments, the cells do not express SIRPγ.

[0150] In some embodiments, the SIRPα-expressing cell is a myeloid cell. Myeloid, or myelogenous, cells are blood cells that arise from progenitor cells for granulocytes, monocytes, erythrocytes, or platelets. In some embodiments, the SIRPα-expressing cell is a monocyte, macrophage, dendritic cell, mast cell, eosinophil, basophil, neutrophil, or lymphocyte under certain physiological conditions (e.g. activated). In some embodiments, the SIRPα-expressing cell is a myeloid progenitor cell.

[0151] In some embodiments, the SIRPβ1-expressing cell is a myeloid cell. In some embodiments, the SIRPβ1-expressing cell is a granulocyte, for example an eosinophil or neutrophil. In some embodiments, the SIRPβ1-expressing cell is monocytes. In some embodiments, the monocytes are classical, intermediate, non-classical, or a combination thereof. In some embodiments, the SIRPβ1-expressing cell is a macrophage. In some embodiments, the SIRPβ1-expressing cell is a Kupffer cell or a Hofbauer cell. In some embodiments, the SIRPβ1-expressing cell is a dendritic cell. In some embodiments, the SIRPβ1-expressing cell is an alveolar cell. In some embodiments, the cell is not a SIRPγ expressing cell. Exemplary SIRPγ expressing cells include lymphocytes such as T cells, natural killer (NK) cells, and B cells. In some embodiments, the cell depletion is antibody dose-dependent.

[0152] Also provided herein are methods of depleting a population of cells in a subject, comprising administering to a subject any of the SIRP antibodies of the disclosure. In some embodiments, the cell depletion involves ADCC. In some embodiments, the cell depletion involves ADCP. In some embodiments, the cell depletion involves ADCP and ADCC. In some embodiments, the cells comprise SIRPα-expressing cells, SIRPβ1-expressing cells, or a combination thereof. In some embodiments, the cells comprise SIRPα-expressing cells. In some embodiments, the SIRPα-expressing cells are myeloid cells. In some embodiments, the SIRPα-expressing myeloid cell is a monocyte, macrophage, dendritic cell, mast cell, eosinophil, basophil, or neutrophil. In some embodiments, the SIRPα-expressing cell is a myeloid progenitor cell. In some embodiments, the cells are not SIRPα-expressing cells, e.g. lymphocytes, and are depleted. In some embodiments, the cells comprise SIRPβ1-expressing cells. In some embodiments, the SIRPβ1-expressing cells comprise myeloid cells. In some embodiments, the SIRPβ1-expressing cells comprise granulocytes, monocytes, macrophages or dendritic cells. In some embodiments, the granulocytes are eosinophils or neutrophils. In some embodiments, the SIRPβ1-expressing cells comprise macrophages. In some embodiments, the

SIRPβ1-expressing cells comprise Kupffer cells or Hofbauer cells. In some embodiments, the cells are tissue-resident cells. In some embodiments, the population of cells that are depleted in a subject comprises a first population of cells that express SIRPα and a second population of cells that express SIRPβ1. In some embodiments, the cells are circulating cells. In some embodiments, the cell depletion is antibody dose-dependent.

[0153] In some embodiments, methods lead to ADCC *in vitro*, and the SIRP antibody increases ADCC by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0154] In some embodiments, methods lead to ADCP *in vitro*, and the SIRP antibody increases ADCP by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0155] In some embodiments, the methods lead to ADCC and/or ADCP *in vitro*, and the SIRP antibody increases ADCC and/or ADCP by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing myeloid cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPβ1-expressing myeloid cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing myeloid cells and SIRPβ1-expressing myeloid cells *in vitro*. In some embodiments, the ADCC is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0156] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing myeloid cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPβ1-expressing myeloid cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing myeloid cells and SIRPβ1-expressing myeloid cells *in vitro*. In some embodiments, the ADCP is increased by at least 20%,

at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0157] In some embodiments, SIRP antibodies of the disclosure induce ADCP and ADCC of SIRPα-expressing myeloid cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP and ADCC of SIRPβ1-expressing myeloid cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP and ADCC of SIRPα-expressing myeloid cells and SIRPβ1-expressing myeloid cells *in vitro*. In some embodiments, the ADCC and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0158] In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing monocyte cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPβ1-expressing monocyte cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing monocyte cells and SIRPβ1-expressing monocyte cells *in vitro*. In some embodiments, the ADCC is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0159] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing monocyte cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPβ1-expressing monocyte cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing monocyte cells and SIRPβ1-expressing monocyte cells *in vitro*. In some embodiments, the ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0160] In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing monocyte cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPβ1-expressing monocyte cells *in vitro*. In some

embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing monocyte cells and SIRPβ1-expressing monocyte cells *in vitro*. In some embodiments, the ADCC and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0161] In some embodiments, SIRP antibodies of the disclosure a induce ADCC of SIRPα-expressing myeloid progenitor cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPβ1-expressing myeloid progenitor cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing myeloid progenitor cells and SIRPβ1-expressing myeloid progenitor cells *in vitro*. In some embodiments, the ADCC is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0162] In some embodiments, SIRP antibodies of the disclosure are induce ADCP of SIRPα-expressing myeloid progenitor cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPβ1-expressing myeloid progenitor cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing myeloid progenitor cells and SIRPβ1-expressing myeloid progenitor cells *in vitro*. In some embodiments, the ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0163] In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing myeloid progenitor cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPβ1-expressing myeloid progenitor cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing myeloid progenitor cells and SIRPβ1-expressing myeloid progenitor cells *in vitro*. In some embodiments, the ADCC and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0164] In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing macrophages *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPβ1-expressing macrophages *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing macrophages and SIRPβ1-expressing macrophages *in vitro*. In some embodiments, the ADCC is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0165] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing macrophages *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPβ1-expressing macrophages *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing macrophages and SIRPβ1-expressing macrophages *in vitro*. In some embodiments, the ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0166] In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing macrophages *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPβ1-expressing macrophages *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing macrophages and SIRPβ1-expressing macrophages *in vitro*. In some embodiments, the ADCC and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0167] In some embodiments, SIRP antibodies of the disclosure a induce ADCC of SIRPα-expressing dendritic cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPβ1-expressing dendritic cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing dendritic cells and SIRPβ1-expressing dendritic cells *in vitro*. In some embodiments, the ADCC is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least

55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0168] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing dendritic cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPβ1-expressing dendritic cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing dendritic cells and SIRPβ1-expressing dendritic cells *in vitro*. In some embodiments, the ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0169] In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing dendritic cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPβ1-expressing dendritic cells *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing dendritic cells and SIRPβ1-expressing dendritic cells *in vitro*. In some embodiments, the ADCC and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0170] In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing basophils *in vitro*. In some embodiments, the ADCC is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0171] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing basophils *in vitro*. In some embodiments, the ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0172] In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing basophils *in vitro*. In some embodiments, the ADCC and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0173] In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing neutrophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPβ1-expressing neutrophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing neutrophils and SIRPβ1-expressing neutrophils *in vitro*. In some embodiments, the ADCC is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0174] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing neutrophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPβ1-expressing neutrophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing neutrophils and SIRPβ1-expressing neutrophils *in vitro*. In some embodiments, the ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0175] In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing neutrophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPβ1-expressing neutrophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing neutrophils and SIRPβ1-expressing neutrophils *in vitro*. In some embodiments, the ADCC and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0176] In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing eosinophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPβ1-expressing eosinophils *in vitro*. In some embodiments, SIRP antibodies of the

disclosure induce ADCC of SIRPα-expressing eosinophils and SIRPβ1-expressing eosinophils *in vitro*. In some embodiments, the ADCC is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0177] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing eosinophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPβ1-expressing eosinophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing eosinophils and SIRPβ1-expressing eosinophils *in vitro*. In some embodiments, the ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0178] In some embodiments, SIRP antibodies of the disclosure induce ADCP and ADCC of SIRPα-expressing eosinophils *in vitro*. In some embodiments, SIRPα and/or SIRPβ1 antibodies of the disclosure induce ADCC and ADCP of SIRPβ1-expressing eosinophils *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing eosinophils and SIRPβ1-expressing eosinophils *in vitro*. In some embodiments, the ADCC and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0179] In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPα-expressing mast cells *in vitro*. In some embodiments, the ADCC is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0180] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-expressing mast cells *in vitro*. In some embodiments, the ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0181] In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPα-expressing mast cells *in vitro*. In some embodiments, the ADCC and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%. In some embodiments, SIRP antibodies of the disclosure induce antibody-mediated depletion of cells where the cells do not express SIRPα, or express SIRPα only under certain physiological conditions such as when activated (e.g. activated lymphocytes). In some embodiments, SIRP antibodies of the disclosure induce antibody-mediated depletion of cells where the cells do not express SIRPβ1, or express SIRPβ1 only under certain physiological conditions. In some embodiments, the ADCC, and/or ADCP is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0182] In some embodiments, the methods lead to ADCC *in vivo*, and the SIRP antibody increases ADCC by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0183] In some embodiments, the methods lead to ADCP *in vivo*, and the SIRP antibody increases ADCP by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0184] In some embodiments, the methods lead to ADCC and/or ADCP *in vivo*, and the SIRP antibody increases ADCC and/or ADCP by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0185] In some embodiments, the methods lead to cell depletion *in vivo*, and the SIRP antibody increases ADCC and ADCP by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0186] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing myeloid cells *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPβ1-expressing myeloid cells *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPα-expressing myeloid cells and SIRPβ1-expressing myeloid cells *in vivo*. In some embodiments, the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0187] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing monocytes *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPβ1-expressing monocytes *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPα-expressing monocytes and SIRPβ1-expressing monocytes *in vivo*. In some embodiments, the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0188] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing neutrophils *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPβ1-expressing neutrophils *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPα-expressing neutrophils and SIRPβ1-expressing neutrophils *in vivo*. In some embodiments, the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0189] In some embodiments, SIRP antibodies of the disclosure a induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing eosinophils *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPβ1-expressing eosinophils *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPα-expressing eosinophils and SIRPβ1-expressing eosinophils *in vivo*. In some embodiments, the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%,

at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0190] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing basophils *in vivo*. In some embodiments, the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0191] In some embodiments, SIRP antibodies of the disclosure induce antibody-mediated depletion of cells where the cells do not express SIRPα, or express SIRPα only under certain physiological conditions, for example such as when activated (e.g. activated lymphocytes). In some embodiments, SIRP antibodies of the disclosure induce antibody-mediated depletion of cells where the cells do not express SIRPβ1, or express SIRPβ1 only under certain physiological conditions. In some embodiments, the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0192] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing myeloid progenitor cells *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPβ1-expressing myeloid progenitor cells *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPα-expressing myeloid progenitor cells and SIRPβ1-expressing myeloid progenitor cells *in vivo*. In some embodiments, the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0193] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing macrophages *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPβ1-expressing macrophages *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPα-expressing macrophages and SIRPβ1-expressing macrophages *in vivo*. In some embodiments,

the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0194] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing dendritic cells *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPβ1-expressing dendritic cells *in vivo*. In some embodiments, SIRP antibodies of the disclosure induce cell depletion of SIRPα-expressing dendritic cells and SIRPβ1-expressing dendritic cells *in vivo*. In some embodiments, the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

[0195] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing mast cells *in vivo*. In some embodiments, the cell depletion is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%.

B. Therapeutic SIRP Antibodies

[0196] As discussed in Section IA above, provided herein are antibodies that recognize and bind to SIRPα and/or SIRPβ1, including SIRPα variants. The antibodies disclosed herein may be used for therapeutics in a subject.

[0197] Accordingly, provided herein are methods of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an SIRP antibody of the disclosure, or pharmaceutical compositions thereof. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human subject. In some embodiments, the mammalian subject is a non-human primate, e.g. a cynomolgus monkey.

i. Treatment of Diseases/Conditions

[0198] In some embodiments, the SIRP antibodies provided herein are useful for depleting a population of cells in the subject, for the treatment of a disease or condition in the subject. In some embodiments, the therapeutic SIRP antibodies provided herein are useful for treating a disease or condition involving the overactivation or hyperproliferation of certain cells, e.g. SIRPα and/or SIRPβ1-expressing cells (e.g. myeloid cells) as a part of the pathology.

[0199] In some embodiments, a therapeutically effective amount of the antibody or the pharmaceutical composition is sufficient to deplete a population of cells in the subject, e.g. by ADCC and/or ADCP. In some embodiments, the cells are overactivated or hyperproliferative. In some embodiments, the cells are SIRPα and/or SIRPβ1-expressing cells. In some embodiments, the cells do not express SIRPγ. In some embodiments, the SIRPα and/or SIRPβ1-expressing cells are myeloid cells or myeloid progenitor cells. In some embodiments, the SIRPα and/or SIRPβ1-expressing myeloid cells are selected from the group consisting of monocytes, macrophages, dendritic cells, mast cells, eosinophils, basophils, and neutrophils. In some embodiments, the cells are tissue resident cells. In other embodiments, the cells are circulating cells. In some embodiments, the cell depletion is antibody dose-dependent. In some embodiments, a therapeutically effective amount of the antibody or the pharmaceutical composition is sufficient to deplete a population of SIRPα and/or SIRPβ1-expressing cells in a subject. In some embodiments, the SIRPα and/or SIRPβ1-expressing cells comprise myeloid cells. In some embodiments, the SIRPα and/or SIRPβ1-expressing cells comprise monocytes, macrophages, dendritic cells, mast cells, eosinophils, basophils, neutrophils or any combination thereof.

[0200] In some embodiments, the disease or condition is characterized by overactivation and/or hyperproliferation of myeloid cells (including myeloid progenitor cells), or other SIRPα-expressing or SIRPβ1-expressing cells. In some embodiments, the disease or condition is characterized by the overactivation and/or hyperproliferation of additional cell types, such as lymphocytes.

[0201] In some embodiments, the disease or condition comprises cytokine release syndrome (CRS). In some embodiments, the CRS is associated with iatrogenic immune activation, e.g. associated with checkpoint inhibitors for the treatment of malignancies, associated with T cell therapy, associated with T cell therapy such as chimeric antigen receptor (CAR) T cell therapy or TCR T cell therapy, associated with T cell activating bispecific monoclonal antibody therapy,

or associated with NK cell activating bispecific monoclonal antibody therapy. In other embodiments, the CRS is associated with an infection, such as a viral infection, for example COVID-19.

[0202] In some embodiments, the disease or condition comprises a disease or condition characterized by the aberrant activity and/or proliferation of granulocytes. In some embodiments, the granulocytes comprise neutrophils, eosinophils, or mast cells.

[0203] In some embodiments, the therapeutic SIRP antibodies provided herein are useful for treating a disease or condition that is characterized by the aberrant activity and/or proliferation of neutrophils. In some embodiments, the disease or condition comprises neutrophilic dermatoses, psoriatic arthritis, generalized pustular psoriasis, pyoderma gangrenosum, Sweet's syndrome, subcorneal pustular dermatosis, neutrophilic eccrine hidradenitis, bowel-associated dermatosis-arthritis syndrome (BADAS), rheumatoid neutrophilic dermatitis, or Behçet's disease.

[0204] In some embodiments, he therapeutic SIRP antibodies provided herein are useful for treating a disease or condition that is characterized by the aberrant activity and/or proliferation of eosinophils. In some embodiments, the disease or condition comprises acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, eosinophilic cardiomyopathy/Loeffler endocarditis, Löffler syndrome or episodic angioedema with eosinophilia/Gleich syndrome.

[0205] In some embodiments, the therapeutic SIRP antibodies provided herein are useful for treating a disease or condition characterized by the aberrant activity and/or proliferation of mast cells. In some embodiments, the disease or condition comprises cutaneous mastocytosis, mastocytic enterocolitis, systemic mastocytosis, mast cell activation syndrome, hereditary alpha tryptasemia syndrome, or chronic urticaria.

[0206] In some embodiments, the disease or condition comprises an autoimmune disorder. In some embodiments, the autoimmune disorder involves the presentation of self antigens by antigen presenting cells (e.g. – dendritic cells) occurring in germinal centers of secondary lymphoid tissue that results in the activation of autoreactive T and B cells, the latter of which produce autoantibodies that mediate cytokine release and sometimes IgG-induced phagocytosis.

By targeting and depleting these antigen presenting dendritic cells and autoreactive lymphocytes, the antibodies described here can treat these diseases by halting this process of self-antigen presentation.

[0207] In other embodiments, the therapeutic SIRP antibodies provided herein are useful for treating disease or condition associated with autoantibodies such as autoimmune hemolytic anemia, immune/idiopathic thrombocytopenia purpura, epidermolysis bullosa acquisita, pemphigus foliaceus, pemphigus vulgaris, anti-glomerular basement membrane disease (Goodpasture Syndrome), antiphospholipid syndrome, catastrophic antiphospholipid syndrome, and antibody-mediated rejection (AMR).

[0208] In some embodiments, the therapeutic SIRP antibodies of the disclosure are useful in treating hematological malignancies. In some embodiments, the hematological malignancy comprises acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic eosinophilic leukemia, or chronic neutrophilic leukemia.

[0209] In some embodiments, the therapeutic SIRP antibodies of the disclosure are useful in treating a disease or condition selected from the group consisting of cytokine release syndrome (CRS), systemic mastocytosis, hypereosinophilic syndrome (including primary, secondary, and idiopathic), hyper IgE syndrome, systemic inflammatory response syndrome, acute respiratory distress syndrome, autoimmune neutropenia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic eosinophilic leukemia, secondary hemophagocytic lymphohistiocytosis (sHLH) or cytokine release syndrome (CRS) associated with associated with T cell therapy, sHLH or CRS associated with chimeric antigen receptor (CAR) T cell therapy, T cell receptor T cell therapy (TCR-T), sHLH or CRS associated with T cell activating bispecific monoclonal antibody therapy, autoimmune hemolytic anemia, immune/idiopathic thrombocytopenia purpura, epidermolysis bullosa acquisita, pemphigus foliaceus, pemphigus vulgaris, anti-glomerular basement membrane disease (Goodpasture Syndrome), antiphospholipid syndrome, catastrophic antiphospholipid syndrome, antibody-mediated rejection (AMR), acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, cutaneous mastocytosis, mastocytic enterocolitis, mast cell activation syndrome, eosinophilic cardiomyopathy/Loeffler endocarditis,

coronary artery disease (CAD)/ peripheral artery disease (PAD), myelofibrosis, Löffler syndrome, chronic neutrophilic leukemia, episodic angioedema with eosinophilia / Gleich syndrome, hereditary alpha tryptasemia syndrome, and chronic urticaria.

C. Pharmaceutical Compositions

[0210] The disclosure also provides pharmaceutical compositions comprising any one of the SIRP antibodies disclosed herein, and optionally a pharmaceutical acceptable excipient or carrier. In some embodiments, the pharmaceutical composition is sterile. The pharmaceutical compositions may be formulated to be compatible with their intended routes of administration. In some embodiments, the pharmaceutical compositions of the disclosure are suitable for administration to a human subject.

D. Combination Therapies

[0211] The administration of any one of the therapeutic SIRP antibodies provided herein may be in combination with any other known drugs or treatments for diseases or conditions as described in IIC. In some embodiments, the disease or condition is associated with overactivation and/or hyperproliferation of myeloid cells, other SIRPα and/or SIRPβ1-expressing cells, or lymphocytes. In some embodiments, the disease or condition is associated with IgG-mediated phagocytosis or the disease or condition is associated with IgG-mediated cytokine release. In some embodiments, the disease or condition is an autoimmune disease or condition. In some embodiments, the disease or condition comprises a neoplastic disorder or malignancy. In exemplary embodiments, the disease or condition being treated is a hyper inflammatory syndrome such as HLH or CRS in which a therapeutic SIRP antibody may be used in combination with corticosteroids (e.g. – dexamethasone).

[0212] In some embodiments, a therapeutic SIRP antibody is provided to treat a CRS that occurs due to infections, in combination with the appropriate antiviral for the treatment of a viral infection, or in combination with the appropriate antibiotic therapy for the treatment of a bacterial infection. By way of example only, a therapeutic antibody of the disclosure could be administered in combination with an antiviral therapy for example, an antiviral therapy for COVID-19, SARS (SARS-CoV), MERS, Ebola, or Epstein Barr virus, or in combination with an antibiotic therapy, for example an antibiotic therapy for the treatment of sepsis. In some

embodiments, the SIRP antibody is administered in combination with a standard therapy for the infection.

[0213] In some embodiments, a therapeutic SIRP antibody provided herein to treat a CRS or sHLH that occurs due to malignancies, is used in combination with the appropriate chemotherapeutic or malignancy-associated treatment of an oncological indication. In some embodiments, a therapeutic SIRP antibody provided herein to treat a CRS or sHLH that occurs due to an autoimmune disorder, such as a rheumatological disorder including systemic lupus erythematosus or rheumatoid arthritis, in combination with the appropriate treatment of such a disorder. Exemplary appropriate treatments include, but are not limited to, corticosteroids.

E. Administration of Therapeutic SIRP Antibodies

[0214] The *in vivo* administration of the therapeutic SIRP antibodies described herein may be carried out intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, intrathecally, intraventricularly, intranasally, transmucosally, through implantation, or through inhalation. Intravenous administration may be carried out via injection or infusion. Administration of the therapeutic SIRP antibodies may be performed with any suitable excipients, carriers, or other agents to provide suitable or improved tolerance, transfer, delivery, and the like. In exemplary embodiments, the route of administration is subcutaneous. In exemplary embodiments, the route of administration is intravenous.

F. Diagnostic Antibodies

[0215] The antibodies provided herein may also be used for diagnostic purposes. For example, diagnostic antibodies could be used for detecting the presence of a SIRPα and/or SIRPβ1 mediated disorder, or for detecting SIRPα and/or SIRPβ1 levels in a subject prior to dosing (e.g. as a companion diagnostic).

III. Kits and Articles of Manufacture

[0216] The disclosure also provides a kit or article of manufacture comprising any one of the antibodies disclosed herein, or any pharmaceutical composition disclosed herein. In some embodiments, the kits may further include instructional materials for carrying out any of the methods disclosed herein. In some embodiments, the kits may further include sterile containers

or vials for holding the antibodies and/or pharmaceutical compositions disclosed herein. In some embodiments, the kits may further include sterile delivery devices for administering the antibodies and/or pharmaceutical compositions disclosed herein. In some embodiments, an article of manufacture comprises any pharmaceutical composition of the disclosure.

EXAMPLES

Example 1: Hybridoma Library Screens for Identification of Anti-Human SIRPα and SIRPβ1 Antibodies

[0217] Anti-human SIRP monoclonal antibodies (referred to interchangeably in these examples as SIRP antibodies) were identified from various rodent models of immunization. Rodent strains were immunized with the extracellular domain of human SIRPα (hSIRPα). Using standard techniques, hybridoma libraries (six libraries) were generated from the splenocytes of immunized animals. Anti-hSIRPα antibody-producing clones were identified by flow cytometric analyses of hSIRPα-expressing cells incubated in the supernatant of individual clones. Seventeen individual clones were identified (Antibodies 2, 5, 6, and 16-19). Antibodies 2, 5 and 6 have a human variable region and a rat IgG2b Fc domain. Antibodies 16-18 have a human variable region and a mouse IgG2a Fc domain. Antibody 19 has a human variable region and a mouse IgG1 Fc domain.

Example 2: Binding of SIRP Antibodies to SIRPα, SIRPβ1, and SIRPγ Proteins

[0218] Selected hybridoma supernatants of Example 1 were further tested for binding to human SIRPα V1 and cynomolgus monkey SIRPα by enzyme-linked immunosorbent assay (ELISA). Briefly, 1 μg/mL of the extracellular domain of the SIRPα was coated onto high protein-binding plates and blocked. Supernatants were diluted 1:5 and added to coated plates. The antibodies were detected by anti-rat or anti-mouse IgG antibodies and a chemiluminescent substrate. FIG. 1A shows the results of binding of selected SIRP, the data depict the relative luminescence units read by a plate-reader capable of detecting chemiluminescence.

[0219] Selected hybridoma supernatants of Example 1 were further tested for binding to human SIRPα V1, SIRPβ1, and SIRPγ by enzyme-linked immunosorbent assay (ELISA). Briefly, 2 μg/mL of the extracellular domain of each of the SIRPs was coated onto high protein-binding plates and blocked. Supernatants were added undiluted to coated plates. The antibodies were

detected by anti-rat or anti-mouse IgG antibodies and a chemiluminescent substrate. FIG. 1B shows the results of binding of selected SIRP antibodies to the extracellular domain of the three human SIRP proteins. The data depict the relative luminescence units read by a plate-reader capable of detecting chemiluminescence.

[0220] FIG. 2A shows binding curves of Antibodies 5 and 6 to human SIRPα V1 and cynomolgus monkey the SIRPα by ELISA. Select SIRP antibodies were purified by Protein G from hybridoma supernatants and analyzed in a titration via ELISA. Briefly, 1 μg/mL of extracellular domain SIRPα was coated onto high protein-binding plates and blocked. Purified antibodies were added in a titration to the coated plates. The antibodies were detected by an anti-rat IgG antibody and a chemiluminescent substrate.

[0221] FIGS. 2B-2E shows binding curves of SIRP antibodies to human SIRPα V1, human SIRPβ1, human SIRPγ, cynomolgus monkey SIRPα, cynomolgus monkey SIRPβ1, and cynomolgus monkey SIRPγ by ELISA. Selected SIRP antibodies were purified by Protein G from hybridoma supernatants and analyzed in a titration via ELISA. Briefly, 2 μg/mL of extracellular domain of each of the SIRPs was coated onto high protein-binding plates and blocked. Purified antibodies were added in a titration to the coated plates. The antibodies were detected by an anti-rat IgG or an anti-mouse IgG antibody and a chemiluminescent substrate.

[0222] FIG. 3A shows binding curves of SIRP antibodies with human Fc to human SIRPα V1 and cynomolgus monkey SIRPα by ELISA. A SIRP antibody from Example 2 was fully made human. DNA was transiently transfected into CHO cells for 7 days. Antibodies were purified by Protein A from cell supernatants and analyzed in a titration via ELISA as previously described for FIGS. 2A using an anti-human IgG antibody as the detection antibody. The results are presented as compared to an isotype control, an unrelated human IgG1 antibody with an irrelevant CDR.

[0223] FIGS. 3B-3C show binding curves of a selected SIRP antibody with human Fc to human SIRPα V1, human SIRPβ1, human SIRPγ, cynomolgus monkey SIRPα, cynomolgus monkey SIRPβ1, and cynomolgus monkey SIRPγ by ELISA as previously described for FIG. 2B-2E.

[0224] Antibodies 2, 6, 22, and 27 were tested for their affinities to two hSIRPα variants (V1 and V2), and to cynomolgus monkey (herein referred to as "cyno") SIRPα. The composition of

Antibodies 2, 6, 22, and 27 is presented in Tables 10 and 11. The affinities of these SIRPα antibodies were determined using surface plasmon resonance. The SIRPα antibodies were flowed onto a chip and captured by an anti-human IgG covalently coupled to the surface of the chip. A three-point titration of the extracellular binding domain of hSIRPα was performed per the manufacturer's recommended protocols. The resulting kinetic data were analyzed and fitted globally using a 1:1 binding model and calculated affinities are presented in Table 13 and Table 14 below. The tables show the KD (affinity) of binding of selected antibodies to monomeric human SIRPα and monomeric cynomolgus monkey SIRPα, as assayed by BIACORE.

Table 13: Affinities of SIRP Antibodies with rat Fc to Human SIRPα V1 and Cyno SIRPα

Antibody No.	Human SIRPα V1 (M)	Cyno SIRPα (M)
2	8.95E-08	non-binding
6	4.10E-09	5.61E-08

Table 14 – Affinities of SIRP Antibodies with human Fc to Human SIRPα V1 and Cyno SIRPα

Antibody No.	Human SIRPα V1 (M)	Human SIRPα V2 (M)	Cyno SIRPα (M)
22	2.59E-09	1.15E-08	3.55E-08
27	2.00E-09	Not tested	3.06E-08

[0225] SIRP antibodies were tested for their affinities to human SIRPα, SIRPβ1, and SIRPγ using a biolayer interferometry (BLI) Octet system (Pall ForteBio). The composition of these antibodies is presented in Tables 10 and 11. Each SIRP antibody with rat or mouse Fc was immobilized on a biosensor tip by an anti-mouse IgG capture (AMC). SIRP-His monomer protein at three concentrations (100 nM, 33.3 nM, 11.1 nM) were exposed to the biosensor to measure on-rate kinetics of SIRP antibodies binding to SIRP-His protein. The biosensors were then exposed to wash buffer to measure off-rate kinetics. The resulting kinetic data were analyzed and fitted using a 1:1 binding model with k_{on} and k_{dis} fitted separately at each SIRP-His

protein concentration. KD affinities were calculated as k_{dis} to k_{on} ratio at each concentration of SIRP-His and averaged. This average of the KD affinities for each antibody is presented in Table 15 below. The table shows the KD of binding of selected antibodies to monomeric human SIRPα, SIRPβ1, and SIRPγ, as assayed by ForteBio Octet.

Table 15: Affinities of SIRP Antibodies with rat or mouse Fcs to Human SIRPα V1, SIRPβ1, and SIRPγ

Antibody No.	Human SIRPα V1 (M)	Human SIRPβ1 (M)	Human SIRPγ (M)
2	1.10E-08	3.62E-06	N/A
5	1.73E-08	N/A	N/A
6	1.21E-09	4.56E-10	N/A
16	1.21E-09	8.39E-08	N/A
17	2.06E-07	N/A	N/A
19	3.79E-09	7.59E-08	N/A

N/A = Not applicable, fit $R^2 < 0.75$

Example 3: Binding of SIRP antibodies to cells *in vitro via* Flow Cytometry

[0226] Selected antibodies and isotype control were tested for binding to human monocytes, neutrophils, and lymphocytes, and platelets. Isotype control has the same irrelevant CDR as FIG. 3A but contains the same amino acid substitutions in the Fc region as some of the SIRP antibodies for increased FcγR binding (referring to Table 11). FIGS. 4A-4B show the results of binding studies performed with SIRP antibodies to monocytes, neutrophils, CD4+ T lymphocytes, CD8+ T lymphocytes, and B lymphocytes in human whole blood. FIG. 4C shows the results of binding studies performed with SIRP antibodies to human platelets in platelet-rich plasma. Titration of fluorescent dye-conjugated SIRP antibodies were incubated with whole blood or platelet-rich plasma. Positive signal was detected on monocytes, neutrophils, and platelets via flow cytometry; however, isotype control also displayed comparable positive signal for platelets suggesting that the observed binding of SIRP antibodies to human platelets is occurring via Fc/FcγR interactions. Monocytes were identified as the SSC^{low}/CD14+ population. Neutrophils were identified as SSC^{high}/CD16+ population. CD4+ T cells were identified as SSC^{low}/CD14-/CD4+ population. CD8+ T cells were identified as the SSC^{low} /CD3+/CD8+ population. B cells were identified as the SSC^{low}/CD3-/CD20+ population. Platelets were identified as the SSC^{low}/CD41+ population. Graphs depict the median fluorescence intensity (MFI) of each population. Selected antibodies and isotype control were tested for binding to

cynomolgus monkey monocytes, granulocytes, and lymphocytes, and platelets. Isotype control has the same irrelevant CDR as FIG. 3A but contains the same amino acid substitutions in the Fc region as some of the SIRP antibodies for increased FcγR binding (referring to Table 11). FIGS. 4D-4E show the results of binding studies performed with SIRP antibodies to monocytes, granulocytes, and B lymphocytes in cynomolgus monkey whole blood. FIG. 4F shows the results of binding studies performed with SIRP antibodies to cynomolgus monkey platelets in platelet-rich plasma. Titration of fluorescent dye-conjugated SIRP antibodies were incubated with whole blood or platelet-rich plasma. Positive signal was detected on monocytes, granulocytes, T cells, and platelets via flow cytometry; however, isotype control also displayed comparable positive signal for platelets suggesting that the observed binding of SIRP antibodies to cynomolgus monkey platelets is occurring via Fc/FcγR interactions. Cynomolgus monkey cell populations were identified the same way as for human cells except cynomolgus monkey granulocytes were identified as high side scatter (SSC) SSC^{high} only. Graph depicts the median fluorescence intensity (MFI) of each population.

[0227] Selected antibodies were tested for binding to stably transfected human SIRPα, SIRPβ1 (co-transfected with DAP12), or SIRPγ Chinese hamster ovary (CHO) cells via flow cytometry. A titration of SIRP antibodies was added to the cells and detected using a fluorescently labelled secondary antibody. Graph depicts the median fluorescence intensity (MFI) at each concentration. FIGS. 4G-4H show the binding curves of SIRP antibodies to human SIRPα, SIRPβ, or SIRPγ-expressing CHO cells detected using an anti-rat or anti-mouse IgG antibody. FIG. 4I shows the binding curves of a selected SIRP antibody to human SIRPα, SIRPβ, or SIRPγ-expressing CHO cells detected using an anti-human IgG antibody.

Example 4: Effect of SIRP Antibodies on ADCC

[0228] ADCC induced by a selected SIRP antibody and an isotype control on primary human and cynomolgus monkey monocytes and resting T lymphocytes (humans) were evaluated. SIRP expressing-human and cynomolgus monkey primary monocyte or human resting T lymphocytes (target) cells were stained with intracellular CellTracker™ Green, washed, and exposed to the SIRP antibody or isotype control antibody at various concentrations. The isotype control had the same irrelevant CDRs as the isotype control in FIG. 3A, but contained the same amino acid substitutions in the Fc region as the SIRP antibody for increased FcγR binding (referring to

Table 11). The target cells were incubated with human NK (effector) cells at an effector-cell to target-cell ratio of 2:1 for 4 hours at 37°C. Samples were stained with Zombie Violet dye and analyzed via flow cytometry. The graphs in FIGS. 5A-5C depict percent of cells positive for Zombie Violet dye with respect to total cells positive for CellTracker™ Green (% ADCC). FIG. 5A shows ADCC of human and cyno monocytes induced by selected antibody of the disclosure. FIG. 5B shows little to no ADCC of human CD4+ T cells induced by a selected SIRP antibody. FIG. 5C shows little to no ADCC of human CD8+ T cells induced by a selected SIRP antibody. The ADCC effect is antibody-dose dependent.

Example 5: Effect of SIRP Antibodies on ADCP

[0229] FIG.6 depicts the results of a surrogate ADCP bioassay that measures the binding and activation of FcγRIIa by a selected SIRP antibody bound to target cells. Briefly, SIRP expressing-human and cynomolgus monkey primary monocyte (target) cells were exposed to the SIRP antibody or isotype control at various concentrations. The isotype control had the same irrelevant CDRs as FIG. 3A, but contained the same amino acid substitutions in the Fc region as the SIRP antibody for increased FcγR binding (referring to Table 11). Opsonized cells were incubated with FcγRIIa-H Jurkat (effector) cells from Promega at an effector-cell to target-cell ratio of 2:1 for 6 hours at 37°C. Bio-Glo™ Luciferase Assay reagent was added, and relative luminescence was measured with a plate reader.

Example 6: Determination of SIRP antibody Competition with CD47 for Binding to SIRPα

[0230] ELISA analyses were performed to assess whether the SIRP antibodies of the disclosure compete with CD47-Fc for binding to hSIRPα, and whether any of the SIRPα antibodies could displace CD47-Fc from binding to hSIRPα. To carry out the competition experiments, the extracellular binding domain of SIRPα was coated onto a 384-well plate and allowed to incubate overnight. Next, blocking solution was added. Next, the SIRP antibody and controls at a concentration of 10 μg/mL was incubated on the plate for 1 hour. Biotinylated CD47-Fc at a concentration of 2.5 μg/mL was next added and allowed to equilibrate for 1 hour. Next, following a wash, streptavidin-HRP was added, and the plate was washed again, and next developed using substrate, following standard protocols. The plate was then read on a plate reader to assess the luminescence. A non-SIRPα-binding human IgG4 monoclonal antibody was used as a negative binding control. Non-biotinylated CD47-Fc was used as a positive control.

Antibody 6 was tested, and data shown in FIG. 7. Antibody 6 showed no attenuation of the CD47-Fc signal as compared to isotype control, suggesting that Antibody 6 does not compete with CD47 for binding to SIRPα.

[0231] SIRP antibodies were tested for their ability to interfere with SIRPα-CD47 binding using the biolayer interferometry (BLI) Octet system (Pall ForteBio). Streptavidin (SA) biosensors were coated with biotinylated recombinant CD47-His. Human SIRPα conjugated to an Fc region was tested to determine its ability to bind to CD47 immobilized on the biosensors and a response value during association is generated. To test for inhibition of SIRPα-CD47 binding, selected SIRP antibodies (200 nM) were each pre-incubated at a 10-fold molar excess with SIRPα protein (20 nM) and then tested for their ability to block binding of SIRPα to CD47-His-biotin immobilized on the biosensors. Table 16 shows total response values calculated during association for each antibody-SIRPα complex measured and compared, as percent of response, to the binding of SIRPα alone to CD47. A greater than or equal to 100% response indicates that the binding of the Antibody to SIRPα does not prevent SIRPα from binding to CD47. A less than 100% response indicates the antibody blocks or partially blocks SIRPα from binding to CD47.

Table 16: Assessment of SIRP Antibodies to Block SIRPα-CD47 Interaction

Antibody No.	**Response (%)**
2	53.32
5	70.88
6	101.58
16	66.45
17	126.50
19	93.12

CLAIMS

What is claimed is:

1. An Fc-containing antibody that is specific for one or more of SIRPα and SIRPβ1, wherein binding of the antibody to one or more of SIRPα and SIRPβ1 on a cell induces depletion of the cell.

2. An antibody that is specific for one or more of SIRPα and SIRPβ1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, and

   wherein the heavy chain variable region comprises:

   i. a complementarity determining region 1 (CDR-H1) sequence selected from the group consisting of SEQ ID NOS: 55, 57-58 and 66-69;

   ii. a CDR-H2 sequence selected from the group consisting of SEQ ID NOS: 71, 73-74 and 82-85; and

   iii. a CDR-H3 sequence selected from the group consisting of SEQ ID NOS: 87, 90-91 and 100-103; and/or

   wherein the light chain variable region comprises:

   i. a light chain CDR 1 (CDR-L1) sequence selected from the group consisting of SEQ ID NOS: 6, 9-10, and 19-22;

   ii. a CDR-L2 sequence selected from the group consisting of SEQ ID NOS: 23, 25-26, 32 and 34-35; and

   iii. a CDR-L3 sequence selected from the group consisting of SEQ ID NOS: 37, 40-41 and 50-53.

3. The antibody of claim 1 or 2, wherein the antibody comprises the heavy and light variable chain CDR sequence combination selected from the group consisting of:

   a. SEQ ID NO: 6, SEQ ID NO: 23, SEQ ID NO: 37, SEQ ID NO: 55, SEQ ID NO: 71, and SEQ ID NO: 87;
   b. SEQ ID NO: 9, SEQ ID NO: 25, SEQ ID NO: 40, SEQ ID NO: 57, SEQ ID NO: 73, and SEQ ID NO: 90;

c. SEQ ID NO: 10, SEQ ID NO: 26, SEQ ID NO: 41, SEQ ID NO: 58, SEQ ID NO: 74, and SEQ ID NO: 91;
d. SEQ ID NO: 19, SEQ ID NO: 32, SEQ ID NO: 50, SEQ ID NO: 66, SEQ ID NO: 82, and SEQ ID NO: 100;
e. SEQ ID NO: 20, SEQ ID NO: 34, SEQ ID NO: 51, SEQ ID NO: 67, SEQ ID NO: 83, and SEQ ID NO: 101;
f. SEQ ID NO: 21, SEQ ID NO: 34, SEQ ID NO: 52, SEQ ID NO: 68, SEQ ID NO: 84, and SEQ ID NO: 102; and
g. SEQ ID NO: 22, SEQ ID NO: 35, SEQ ID NO: 53, SEQ ID NO: 69, SEQ ID NO: 85, and SEQ ID NO: 103.

4. The antibody of any one of claims 1-3, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NOS: 105, 108-109, 119-122.

5. The antibody of any one of claims 1-4, wherein the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NOS: 124, 127-128, 138-141.

6. The antibody of any one of claims 1-5, wherein the heavy chain variable region sequence and the light chain variable region sequence are selected from the group consisting of:

a. SEQ ID NO: 105 and SEQ ID NO: 124;
b. SEQ ID NO: 108 and SEQ ID NO: 127;
c. SEQ ID NO: 109 and SEQ ID NO: 128;
d. SEQ ID NO: 119 and SEQ ID NO: 138;
e. SEQ ID NO: 120 and SEQ ID NO: 139;
f. SEQ ID NO: 121 and SEQ ID NO: 140; and
g. SEQ ID NO: 122 and SEQ ID NO: 141.

7. The antibody of any one of claims 1-5, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 105 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 124, or an amino acid sequence with at least 80% sequence identity thereto.

8. The antibody of any one of claims 1-5, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 108 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 127, or an amino acid sequence with at least 80% sequence identity thereto.

9. The antibody of any one of claims 1-5, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 109 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 128, or an amino acid sequence with at least 80%, sequence identity thereto.

10. The antibody of any one of claims 1-5, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 119 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 80% sequence identity thereto.

11. The antibody of any one of claims 1-5, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 120 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 139, or an amino acid sequence with at least 80% sequence identity thereto.

12. The antibody of any one of claims 1-5, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 121 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 140, or an amino acid sequence with at least 80% sequence identity thereto.

13. The antibody of any one of claims 1-5, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 122 or an amino acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain

variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 141, or an amino acid sequence with at least 80% sequence identity thereto.

14. The antibody of any one of claims 2-13, wherein the antibody comprises an Fc domain.

15. The antibody of any one of claims 1-14, wherein the antibody is an Fc-containing antibody, and the binding of the antibody to one or more of SIRPα and SIRPβ1, on a cell induces depletion of the cell.

16. The antibody of any one of claims 1-15, wherein the cell depletion involves antibody dependent cellular phagocytosis (ADCP).

17. The antibody of any one of claims 1-16, wherein the cell depletion involves antibody dependent cellular cytotoxicity (ADCC).

18. The antibody of any one of claims 1-17, wherein the cell depletion involves depletion of SIRPα positive cells.

19. The antibody of any one of claims 1-18, wherein the cell depletion involves depletion of SIRPβ1 positive cells.

20. The antibody of any one of claims 1-17, wherein the cell depletion involves depletion of SIRPα positive cells and depletion of SIRPβ1 positive cells.

21. The antibody of claim 18 or 20, wherein the SIRPα positive cells are myeloid cells or myeloid progenitor cells.

22. The antibody of claim 18 or 20, wherein the SIRPα positive cells are selected from the group consisting of monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, and mast cells.

23. The antibody of any one of claims 19-22, wherein the SIRPβ1 positive cells are myeloid cells.

24. he antibody of any one of claims 19-22, wherein the SIRPβ1 positive cells are selected from the group consisting of monocytes, macrophages, dendritic cells, eosinophils, basophils and neutrophils.

25. The antibody of any one of claims 1-24, wherein the antibody is a monoclonal antibody.

26. The antibody of any one of claims 1-24 wherein the antibody is an antibody fragment.

27. The antibody of any one of claims 1-24 wherein the antibody is a human antibody.

28. The antibody of any one of claims 1-24, wherein the antibody is a humanized antibody.

29. The antibody of any one of claims 1-24wherein the antibody is a chimeric antibody.

30. The antibody of any one of claims 1-24 wherein the antibody is a full-length antibody.

31. The antibody of any one of claims 1 or 14-30, wherein the Fc domain is selected from the group consisting of human IgG1, IgG2, IgG3, and IgG4.

32. The antibody of claim 31, wherein the Fc domain comprises SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 16.

33. The antibody of claim 31, wherein the Fc domain comprises one or more amino acid substitutions relative to SEQ ID NO: 3, SEQ ID NO: 4, or SEQ ID NO: 16.

34. The antibody of claim 31, wherein the Fc domain of the antibody is human IgG1 and comprises at least one amino acid substitution at a position selected from the group consisting of: 214, 215, 221, 222, 228, 234, 235, 236, 239, 240, 241, 243, 244, 245, 247, 250, 252, 254, 256, 262, 263, 264, 265, 266, 267, 268, 269, 270, 292, 296, 297, 298, 299, 300, 305, 313, 324, 325, 326, 327, 328, 329, 330, 332, 333, 334, 345, 356, 358, 396, 428, 430, 433, 434, and 440 wherein the position numbers of the amino acid residues are of the EU numbering scheme.

35. The antibody of claim 31, wherein the IgG1 Fc comprises a sequence selected from the group consisting of:

a. SEQ ID NO: 11;
b. SEQ ID NO: 12, wherein X_1 is V or A;
c. SEQ ID NO: 13, wherein X_1 is V or A; X_2 is G or A; X_3 is S or D; and X_4 is I or E;
d. SEQ ID NO: 14, wherein X_1 is V or A;
e. SEQ ID NO: 15, wherein X_1 is V or A; X_2 is M or L; and X_3 is N or S; and
f. SEQ ID NO: 16, wherein X_1 is K or R; X_2 is D or E; and X_3 is L or M.

36. The antibody of claim 31, wherein the IgG4 Fc comprises a sequence of SEQ ID NO: 17, 18 or 24, wherein X_1 in SEQ ID NO: 24 is S or P; and X_2 in SEQ ID NO: 24 is L or E.

37. The antibody of any one of claims 1-36, wherein the binding of the antibody does not disrupt the interaction between CD47 and SIRPα.

38. The antibody of any one of claims 1-36, wherein the binding of the antibody disrupts the interaction between CD47 and SIRPα.

39. The antibody of any one of claims 1-38, wherein the antibody binds SIRPα and exhibits little or no binding to SIRPβ1 and SIRPγ.

40. The antibody of any one of claims 1-38, wherein the antibody binds SIRPβ1 and exhibits little or no binding to SIRPα and SIRPγ.

41. The antibody of any one of claims 1-37, wherein antibody binds SIRPα and SIRPβ1, and exhibits little or no binding to SIRPγ.

42. The antibody of any one of claims 1-39 or 41, wherein the antibody comprises a binding affinity to SIRPα of about 100 pM, about 1 nM, about 5 nM, about 10 nM, about 50 nM, about 100 nM, about 500 nM, or about 1 μM.

43. The antibody of any one of claims 1-38, or 40-41, wherein the antibody comprises a binding affinity for SIRPβ1 of about 0.05 nM about 0.1 nM, about 5 nM, about 10 nM, about 50 nM, about 100 nM, about 500 nM, or about 1 μM, or about 5 μM .

44. A pharmaceutical composition comprising the antibody of any one of claims 1-43, and optionally a pharmaceutically acceptable carrier.

45. A nucleic acid encoding for the antibody of any one of claims 1-43.

46. The nucleic acid of claim 45, comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOS: 143, 146-147, 157-160, 162, 165-166, and 176-179.

47. The nucleic acid of claim 45 or 46, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 143, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 162, or a nucleic acid sequence with at least 80% sequence identity thereto.

48. The nucleic acid of claim 45 or 46, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 146, or a nucleic acid sequence with at least

80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 165, or a nucleic acid sequence with at least 80% sequence identity thereto.

49. The nucleic acid of claim 45 or 46, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 147, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 166, or a nucleic acid sequence with at least 80% sequence identity thereto.

50. The nucleic acid of claim 45 or 46, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 157, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 176, or a nucleic acid sequence with at least 80% sequence identity thereto.

51. The nucleic acid of claim 45 or 46, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 158, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 177, or a nucleic acid sequence with at least 80% sequence identity thereto.

52. The nucleic acid of claim 45 or 46, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 159, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 178, or a nucleic acid sequence with at least 80% sequence identity thereto.

53. The nucleic acid of claim 45 or 46, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 160, or a nucleic acid sequence with at least 80% sequence identity thereto; and/or wherein the light chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 179, or a nucleic acid sequence with at least 80% sequence identity thereto.

54. A vector comprising the nucleic acid of any one of claims 45-53.

55. A method of inducing the depletion of a population of cells, the method comprising contacting the population of cells with the antibody of any one of claims 1-43.

56. The method of claim 55, wherein at least a subset of the population of cells expresses SIRPα.

57. The method of claim 56, wherein the population of cells that express SIRPα comprise myeloid cells or myeloid progenitor cells.

58. The method of claim 55, wherein the population of cells that express SIRPα comprise monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, or mast cells.

59. The method of any one of claims 55-58, wherein at least a subset of the population of cells expresses SIRPβ1.

60. The method of claim 59, wherein the population of cells that express SIRPβ1 comprise myeloid cells or myeloid progenitor cells.

61. The method of claim 59, wherein the population of cells that express SIRPβ1 comprise monocytes, macrophages, dendritic cells, eosinophils, basophils, neutrophils or mast cells.

62. The method of any one of claims 55-61, wherein at least a subset of the population of cells expresses SIRPα and SIRPβ1.

63. The method of any one of claims 55-62, wherein the population of cells whose depletion is induced comprises a first population of cells expressing SIRPα and a second population of cells expressing SIRPβ1.

64. The method of any one of claims 55-63, wherein the method is *in vitro*.

65. The method of any one of claims 55-63, wherein the method is *in vivo*.

66. The method any one of claims 55-65, wherein the population of cells comprises tissue-resident cells.

67. The method any one of claims 55-66, wherein the population of cells comprises circulating cells.

68. The method of any one of claims 55-67, wherein the cell depletion involves ADCC.

69. The method of any one of claims 55-68, wherein the cell depletion involves ADCP.

70. The method of any one of claims 55-69, wherein the cell depletion involves ADCC and ADCP.

71. A method of treating a disease or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibody of any one of claims 1-43 or the pharmaceutical composition of claim 44.

72. The method of claim 71, wherein the disease or condition is characterized by overactivation and/or hyperproliferation of myeloid cells, and the antibody induces depletion of myeloid cells.

73. The method of claim 72, wherein the myeloid cells comprise monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, or mast cells.

74. The method of claim 73, wherein the myeloid cells comprise eosinophils, and wherein the disease or condition comprises acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, eosinophilic cardiomyopathy/Loeffler endocarditis, Löffler syndrome or episodic angioedema with eosinophilia/Gleich syndrome.

75. The method of claim 73, wherein the myeloid cells comprise mast cells, and wherein the disease or condition comprises cutaneous mastocytosis, mastocytic enterocolitis, systemic mastocytosis, mast cell activation syndrome, hereditary alpha tryptasemia syndrome, or chronic urticaria.

76. The method of claim 73, wherein the myeloid cells comprise neutrophils, and wherein the disease or condition comprises neutrophilic dermatoses, psoriatic arthritis, generalized pustular psoriasis, pyoderma gangrenosum, Sweet's syndrome, subcorneal pustular dermatosis, neutrophilic eccrine hidradenitis, bowel-associated dermatosis-arthritis syndrome (BADAS), rheumatoid neutrophilic dermatitis, or Behçet's disease.

77. The method of claim 73, wherein the disease or condition comprises an autoimmune disorder or an inflammatory disorder.

78. The method of claim 77, wherein the autoimmune disorder comprises presentation of self antigens by antigen presenting dendritic cells in germinal centers of secondary lymphoid tissue of the subject.

79. The method of claim 71, wherein the disease or condition comprises a hematological malignancy.

80. The method of claim 79, wherein the hematological malignancy comprises acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic eosinophilic leukemia, or chronic neutrophilic leukemia.

81. The method of any one of claims 71-80 the subject is human.

82. The method of any one of claims 71-81, wherein the route of administration is intravenous.

83. The method of any one of claims 71-81, wherein the route of administration is subcutaneous.

84. A cell expressing SIRPα, wherein the cell bound is to an antibody of any one of claims 1-43, wherein the antibody is bound to the SIRPα.

85. A cell expressing SIRPβ1, wherein the cell bound is to an antibody of any one of claims 1-43, wherein the antibody is bound to the SIRPβ1.

86. A cell expressing SIRPα and SIRPβ1, wherein the cell bound is to an antibody of any one of claims 1-43, wherein the antibody is bound to the SIRPα and SIRPβ1.

87. A kit or article of manufacture comprising an antibody of any one claims 1-43, or the pharmaceutical composition of claim 44.

88. Use of the antibody of any one claims 1-43, or the pharmaceutical composition of claim 44 for the treatment of a disease or disorder in a subject in need thereof.

89. Us of the antibody of any one claims 1-43, or the pharmaceutical composition of claim 44 for the manufacture of a medicament for the treatment of a disease or disorder in a subject in need thereof.

FIG. 1A

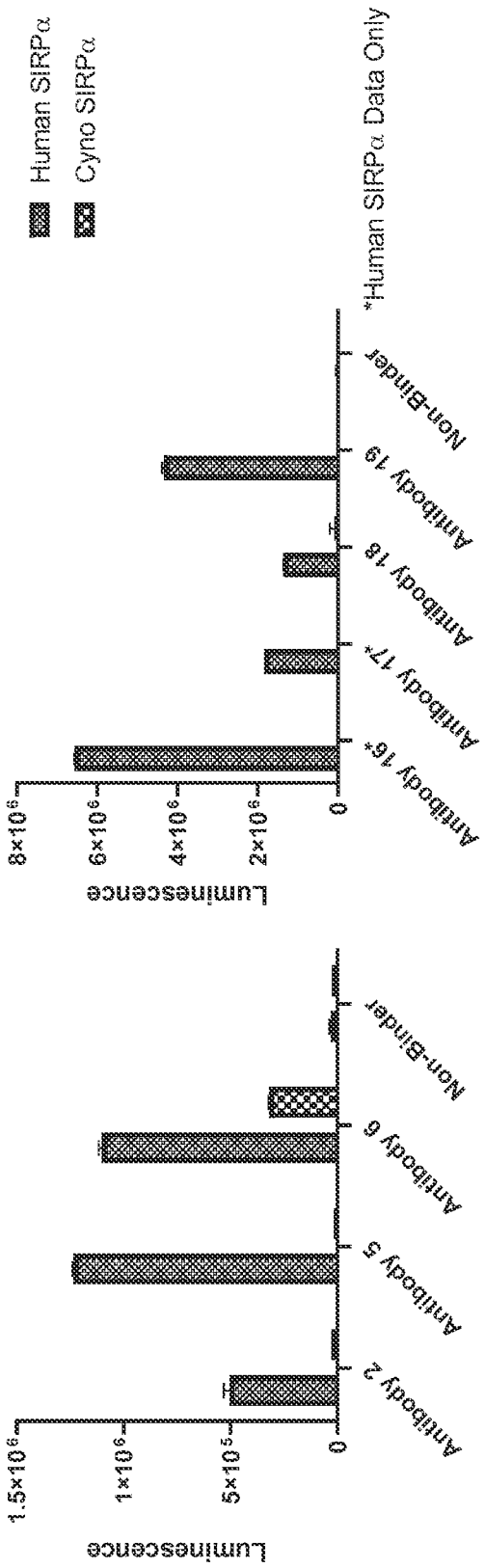

Human SIRPα
Cyno SIRPα
*Human SIRPα Data Only
Luminescence
8×10^6
6×10^6
4×10^6
2×10^6
0
Antibody 16*
Antibody 17*
Antibody 18
Antibody 19
Non-Binder
Luminescence
1.5×10^6
1×10^6
5×10^5
0
Antibody 2
Antibody 5
Antibody 6
Non-Binder

FIG. 1B

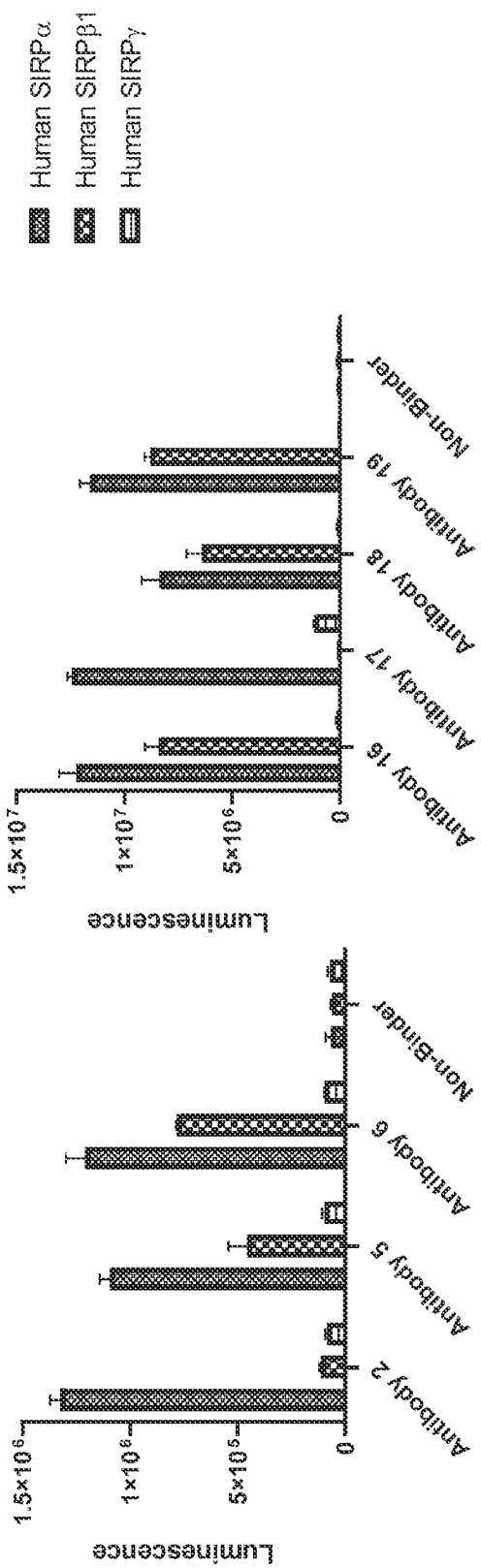

Human SIRPα
Human SIRPβ1
Human SIRPγ
Luminescence
1.5×10⁷
1×10⁷
5×10⁶
0
Antibody 16
Antibody 17
Antibody 18
Antibody 19
Non-Binder
Luminescence
1.5×10⁶
1×10⁶
5×10⁵
0
Antibody 2
Antibody 5
Antibody 6
Non-Binder

FIG. 2A

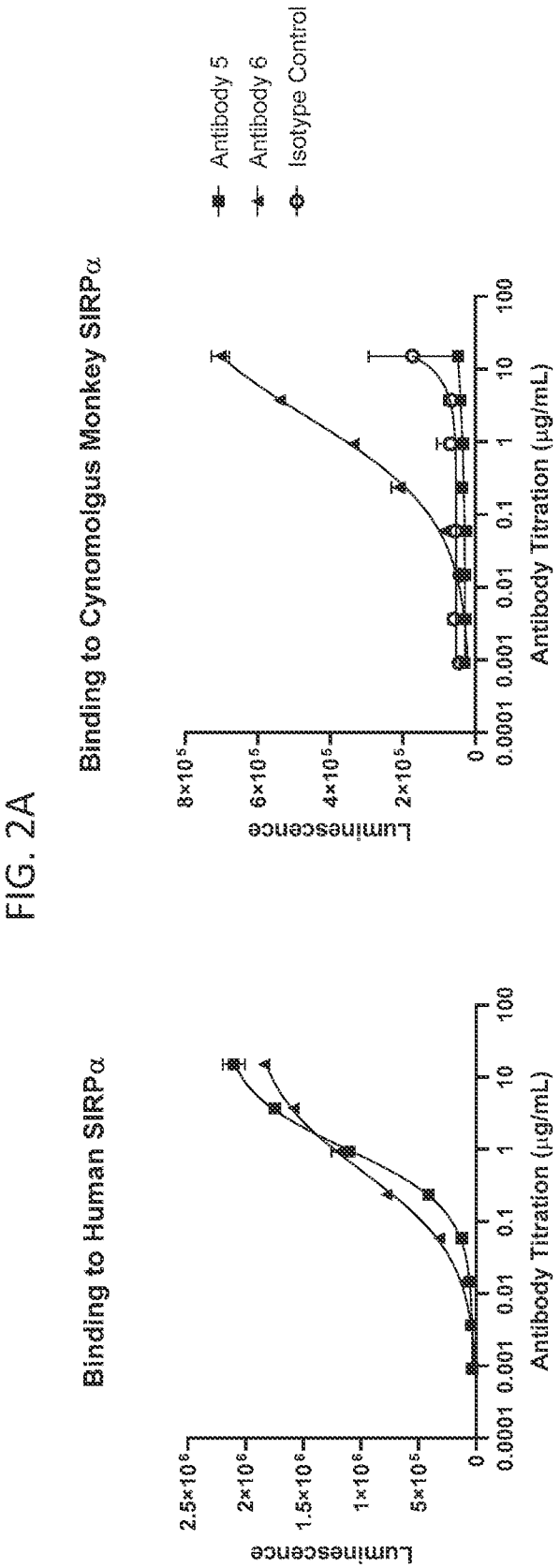

Binding to Human SIRPα
Luminescence
2.5×10^6
2×10^6
1.5×10^6
1×10^6
5×10^5
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Binding to Cynomolgus Monkey SIRPα
Luminescence
8×10^5
6×10^5
4×10^5
2×10^5
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Antibody 5
Antibody 6
Isotype Control

FIG. 2B

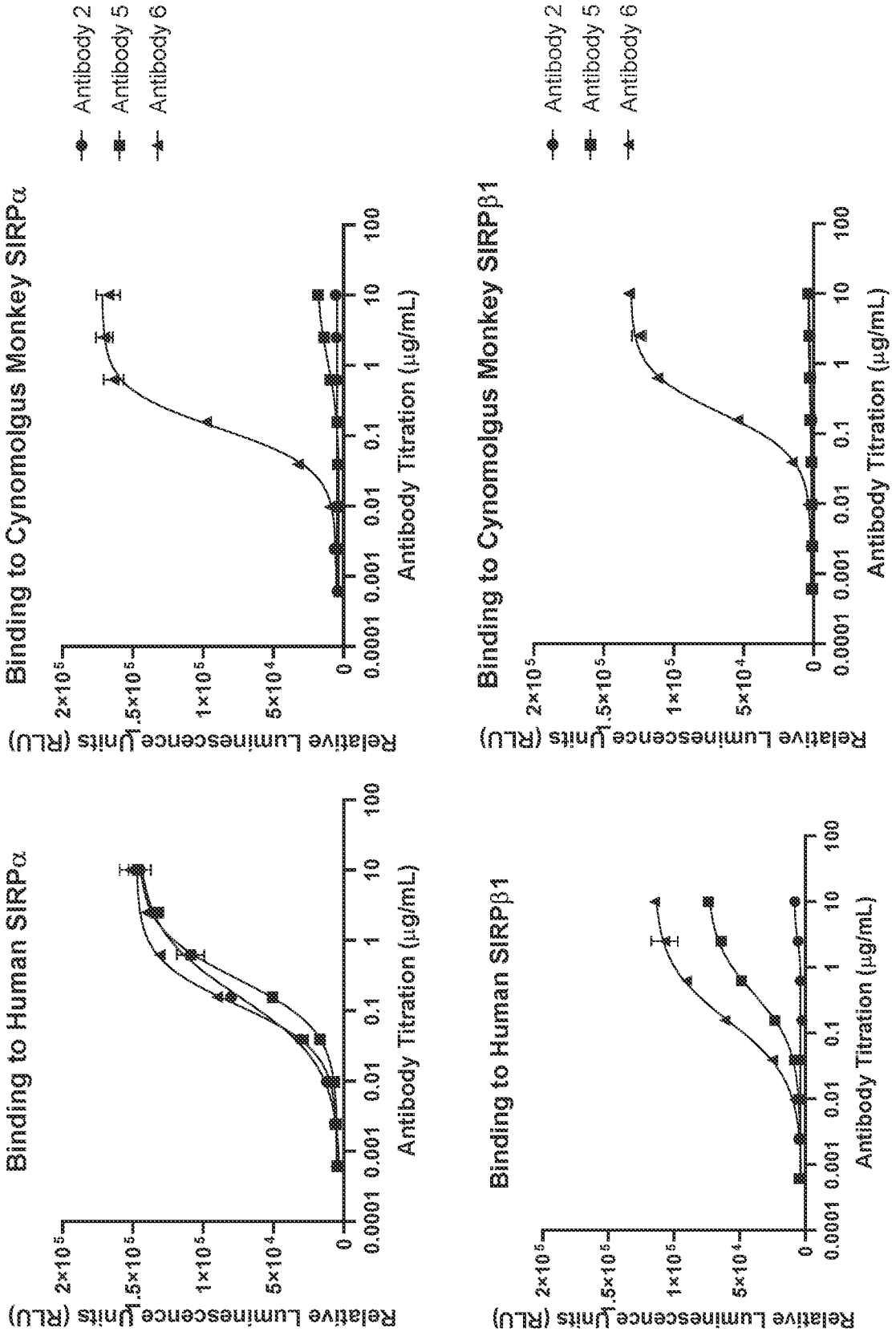

Binding to Human SIRPα
Binding to Cynomolgus Monkey SIRPα
Binding to Human SIRPβ1
Binding to Cynomolgus Monkey SIRPβ1
Antibody 2
Antibody 5
Antibody 6
Relative Luminescence Units (RLU)
Antibody Titration (μg/mL)
2×10^5
1.5×10^5
1×10^5
5×10^4
0
0.0001
0.001
0.01
0.1
1
10
100

FIG. 2C

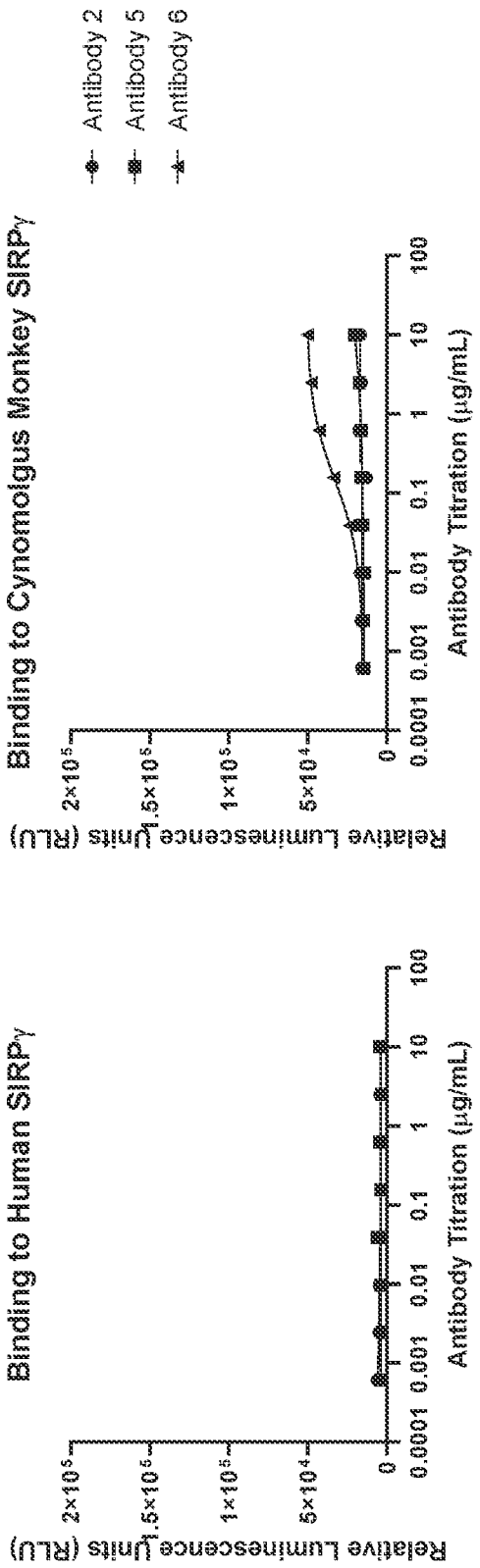

Binding to Human SIRPγ
Relative Luminescence Units (RLU)
2×10⁵
1.5×10⁵
1×10⁵
5×10⁴
0
0.0001
0.001
0.01
0.1
1
10
100
Antibody Titration (µg/mL)
Binding to Cynomolgus Monkey SIRPγ
Relative Luminescence Units (RLU)
2×10⁵
1.5×10⁵
1×10⁵
5×10⁴
0
0.0001
0.001
0.01
0.1
1
10
100
Antibody Titration (µg/mL)
Antibody 2
Antibody 5
Antibody 6

FIG. 2D

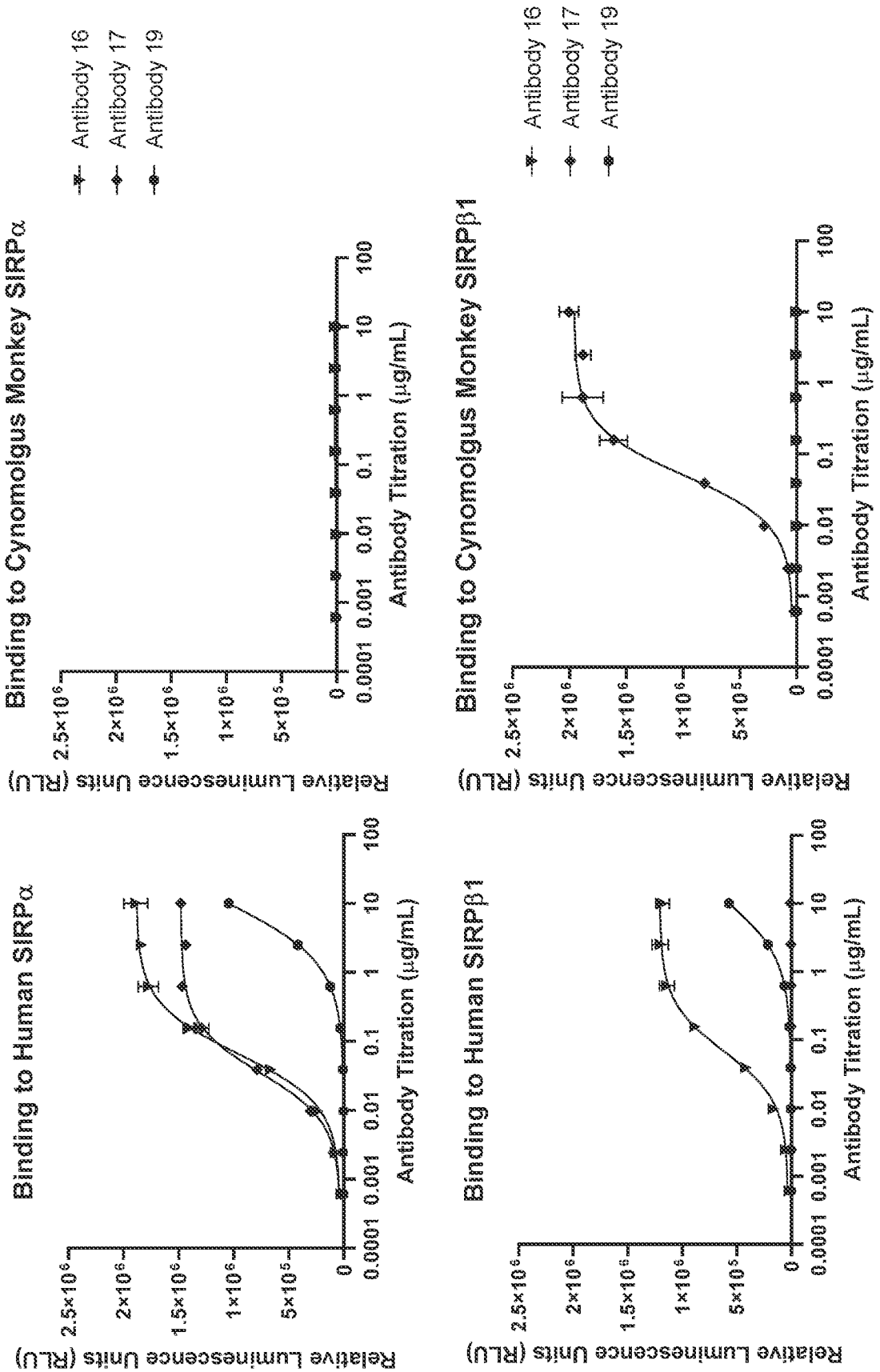

Binding to Human SIRPα
Binding to Cynomolgus Monkey SIRPα
Binding to Human SIRPβ1
Binding to Cynomolgus Monkey SIRPβ1
Relative Luminescence Units (RLU)
Antibody Titration (μg/mL)
Antibody 16
Antibody 17
Antibody 19

FIG. 2E

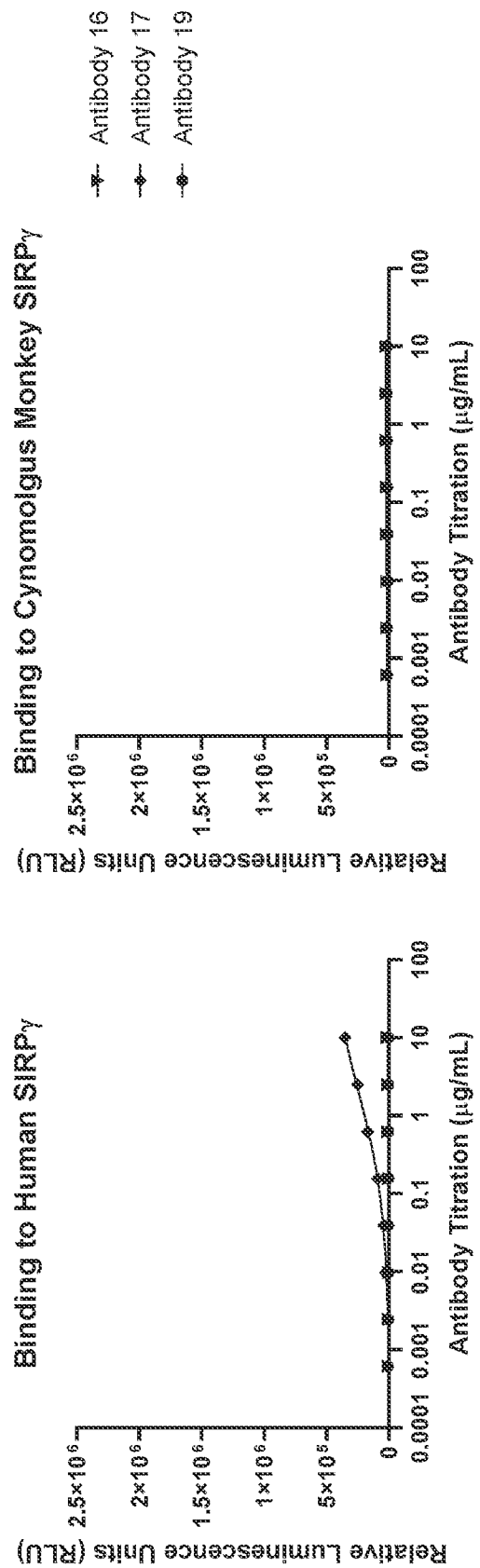

Binding to Human SIRPγ
Binding to Cynomolgus Monkey SIRPγ
Relative Luminescence Units (RLU)
2.5×10^6
2×10^6
1.5×10^6
1×10^6
5×10^5
0
0.0001
0.001
0.01
0.1
1
10
100
Antibody Titration (μg/mL)
Antibody 16
Antibody 17
Antibody 19

FIG. 3A

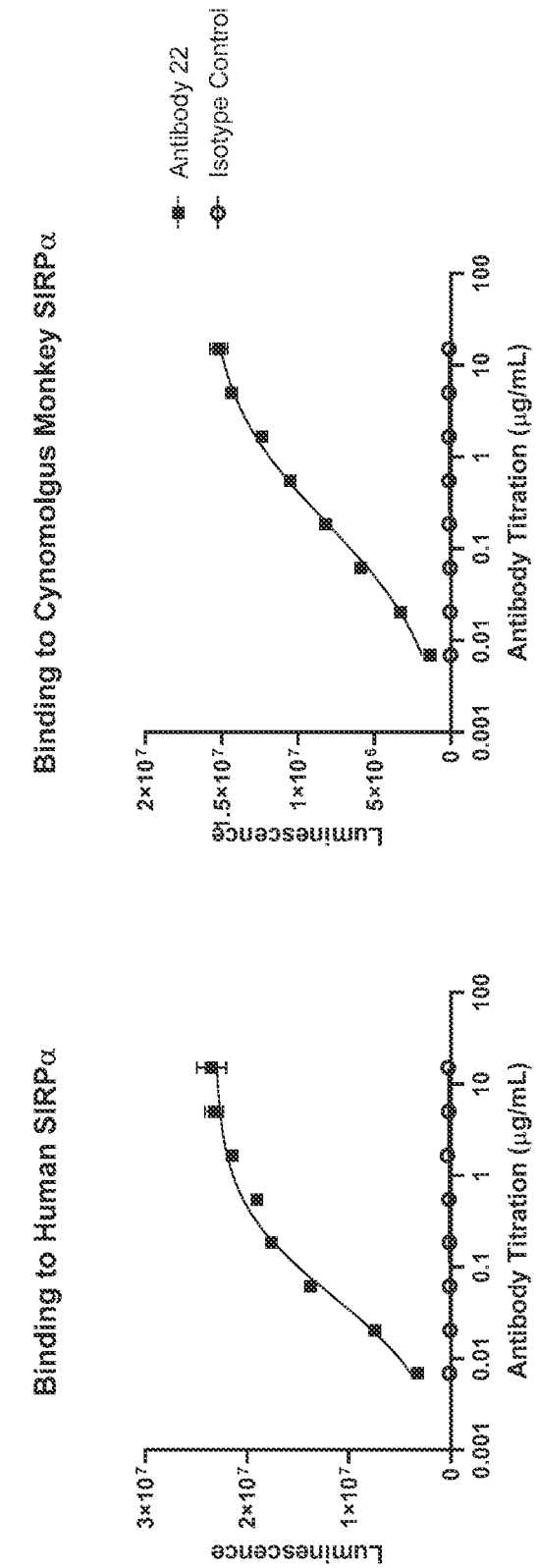

Binding to Human SIRPα
Luminescence
3×10^7
2×10^7
1×10^7
0
0.001
0.01
0.1
1
10
100
Antibody Titration (μg/mL)
Binding to Cynomolgus Monkey SIRPα
Luminescence
2×10^7
1.5×10^7
1×10^7
5×10^6
0
0.001
0.01
0.1
1
10
100
Antibody Titration (μg/mL)
Antibody 22
Isotype Control

FIG. 3B

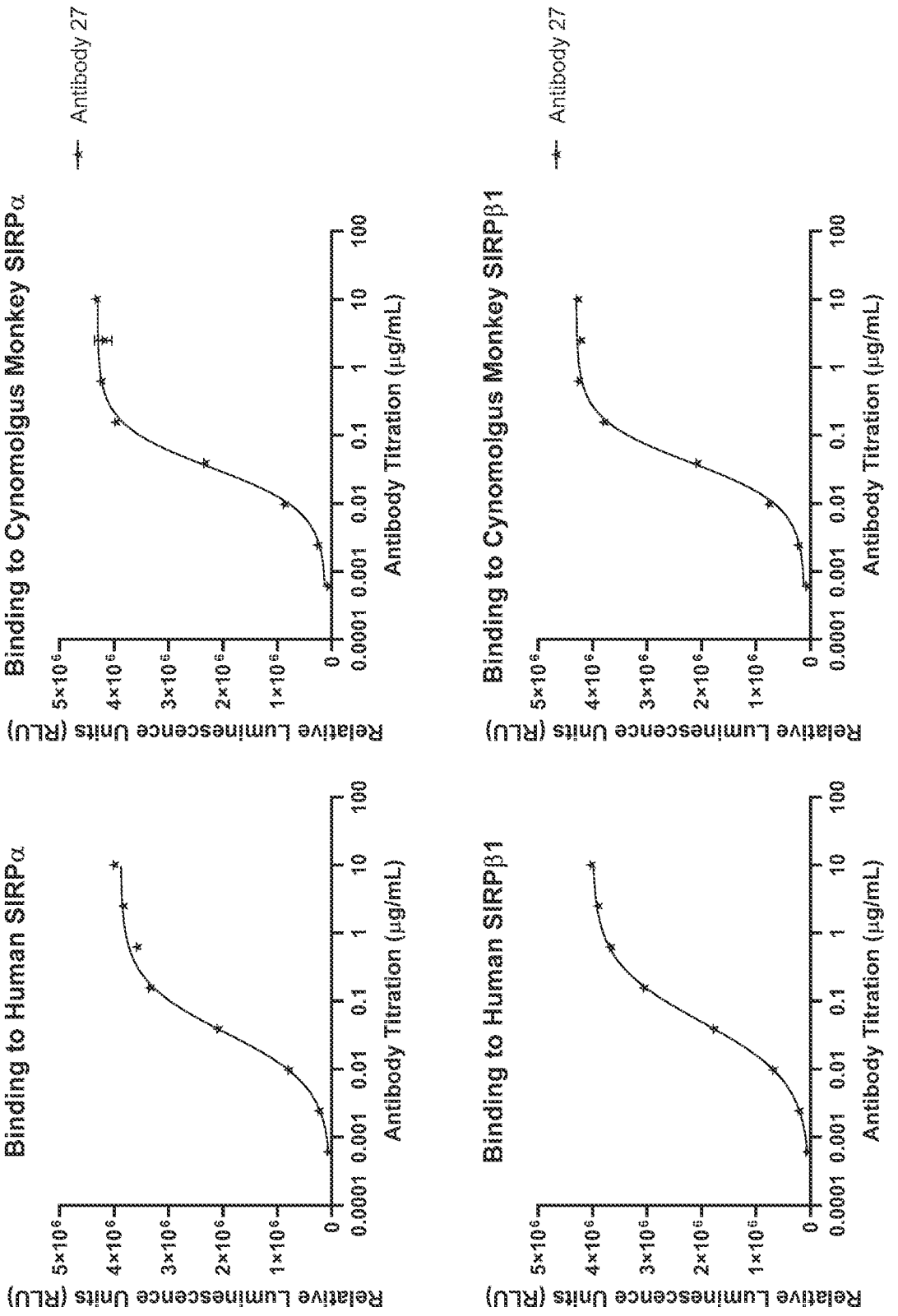

Binding to Human SIRPα
Binding to Cynomolgus Monkey SIRPα
Binding to Human SIRPβ1
Binding to Cynomolgus Monkey SIRPβ1
Antibody 27
Relative Luminescence Units (RLU)
Antibody Titration (μg/mL)
0
1×10^6
2×10^6
3×10^6
4×10^6
5×10^6
0.0001
0.001
0.01
0.1
1
10
100

FIG. 3C

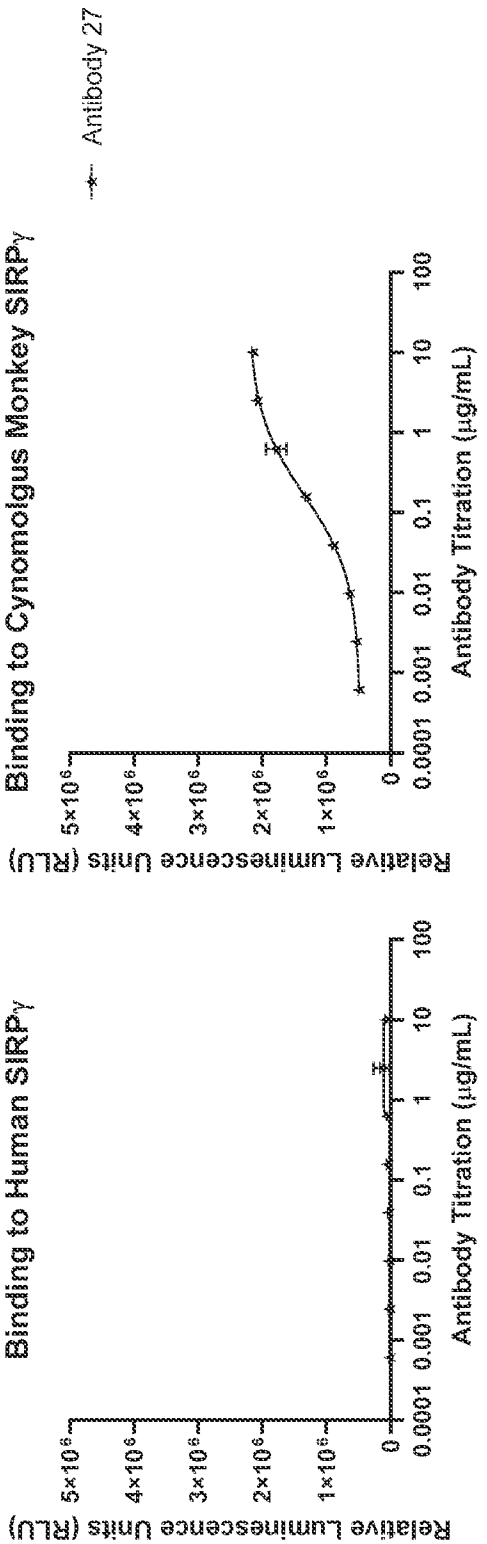

Binding to Human SIRPγ
Relative Luminescence Units (RLU)
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Binding to Cynomolgus Monkey SIRPγ
Antibody 27
Relative Luminescence Units (RLU)
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)

FIG. 4A

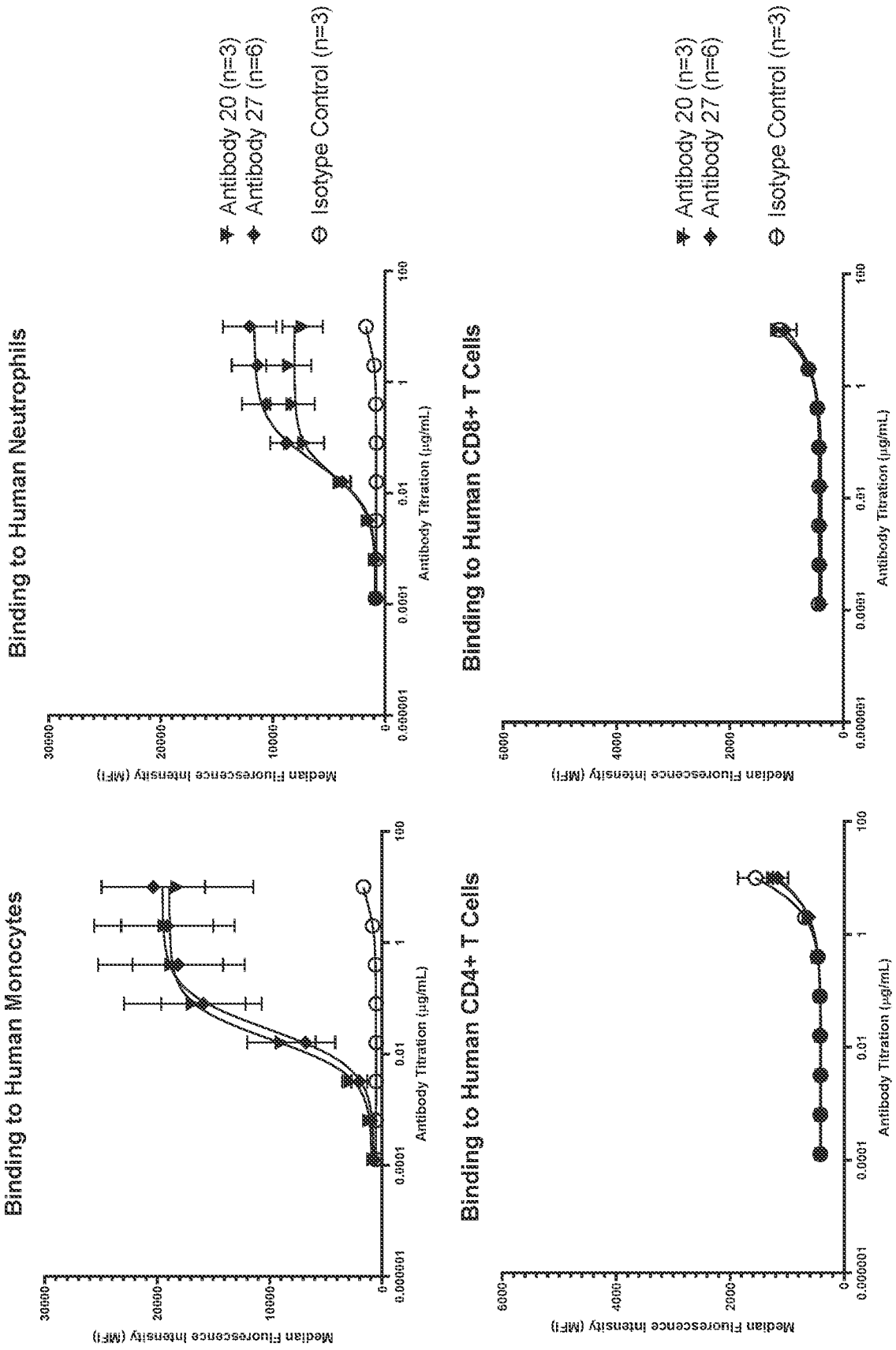

Binding to Human Monocytes
Binding to Human Neutrophils
Binding to Human CD4+ T Cells
Binding to Human CD8+ T Cells
Antibody 20 (n=3)
Antibody 27 (n=6)
Isotype Control (n=3)
Median Fluorescence Intensity (MFI)
Antibody Titration (µg/mL)
30000
20000
10000
0
6000
4000
2000
0.000001
0.0001
0.01
1
100

FIG. 4B

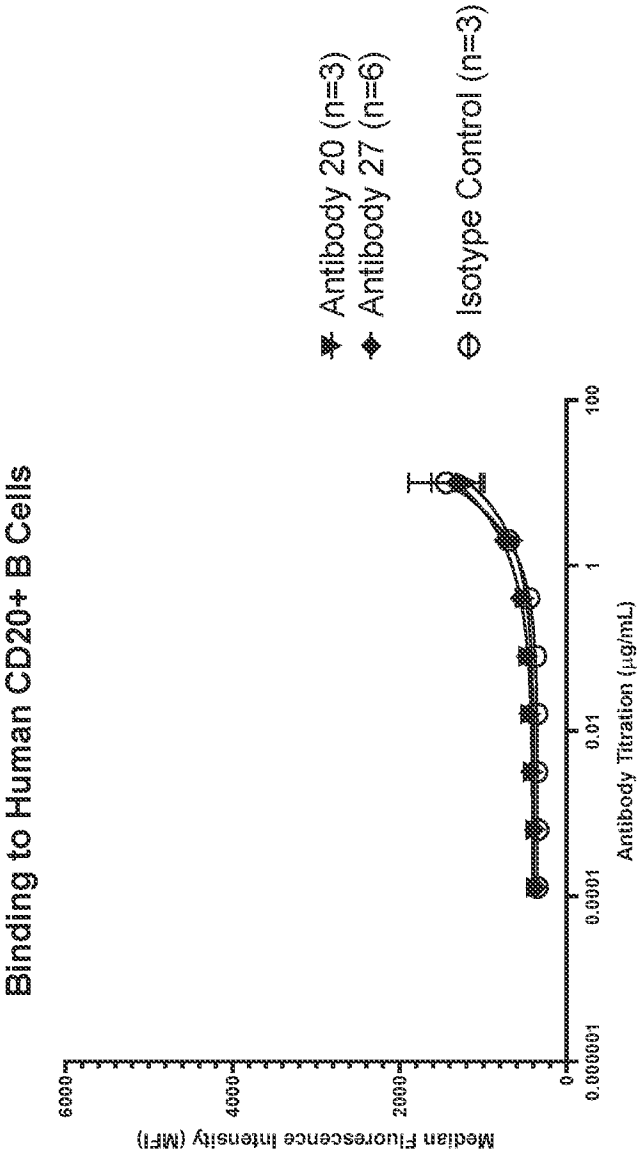

Binding to Human CD20+ B Cells
Antibody 20 (n=3)
Antibody 27 (n=6)
Isotype Control (n=3)
Median Fluorescence Intensity (MFI)
6000
4000
2000
0
0.000001
0.0001
0.01
1
100
Antibody Titration (µg/mL)

FIG. 4C

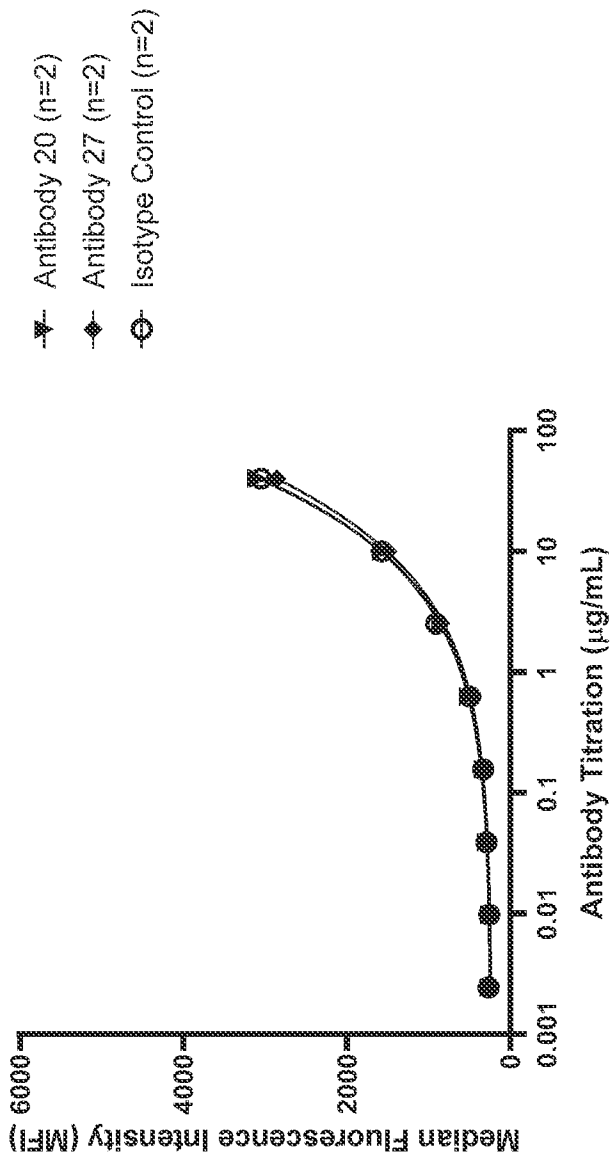

Binding to Human Platelets
Antibody 20 (n=2)
Antibody 27 (n=2)
Isotype Control (n=2)
Median Fluorescence Intensity (MFI)
6000
4000
2000
0
0.001
0.01
0.1
1
10
100
Antibody Titration (µg/mL)

FIG. 4D

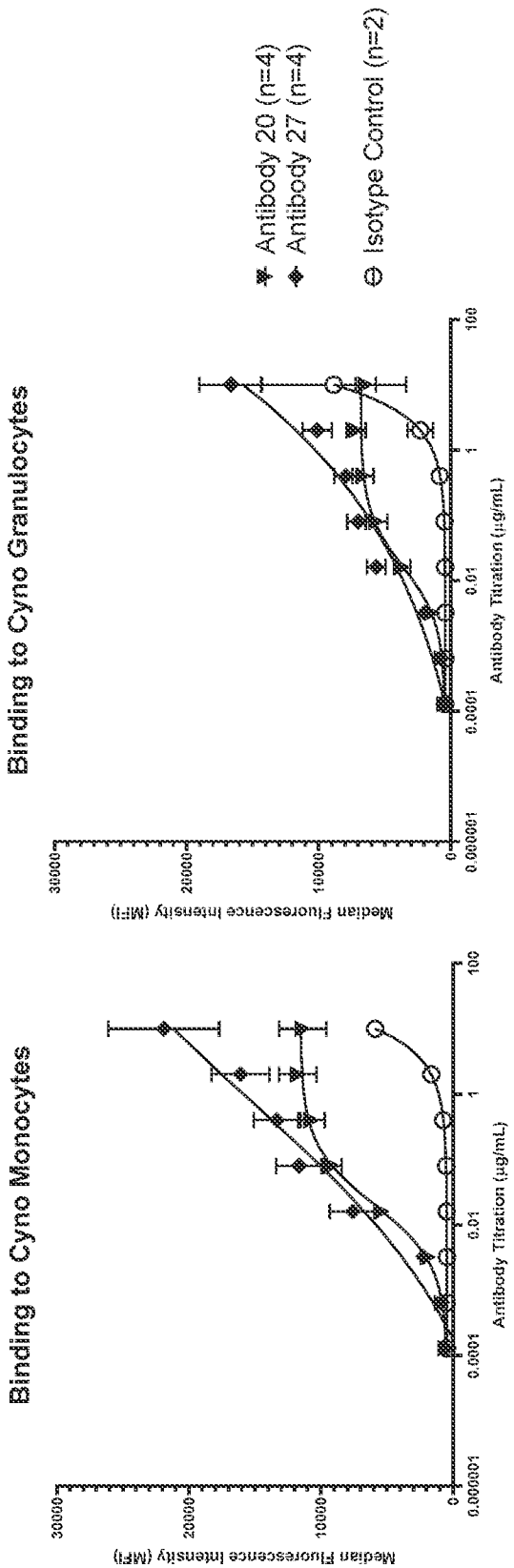

Binding to Cyno Granulocytes
Median Fluorescence Intensity (MFI)
30000
20000
10000
0
0.000001
0.0001
0.01
1
100
Antibody Titration (µg/mL)
Antibody 20 (n=4)
Antibody 27 (n=4)
Isotype Control (n=2)
Binding to Cyno Monocytes
Median Fluorescence Intensity (MFI)
30000
20000
10000
0
0.000001
0.0001
0.01
1
100
Antibody Titration (µg/mL)

FIG. 4E

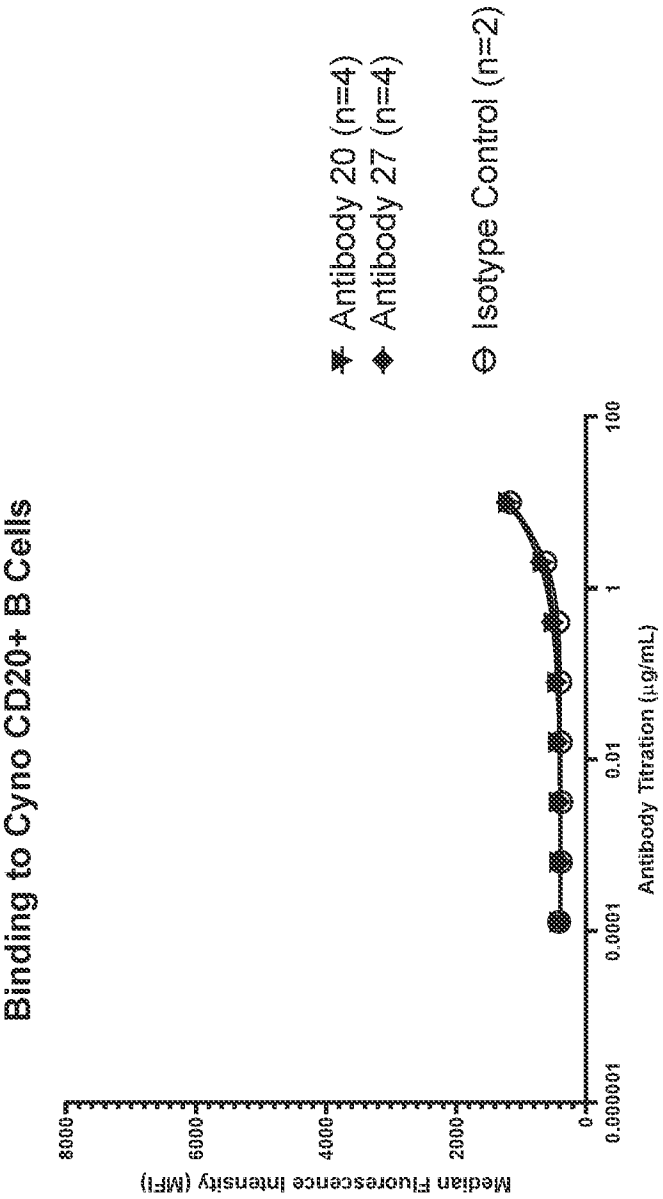

Binding to Cyno CD20+ B Cells
Antibody 20 (n=4)
Antibody 27 (n=4)
Isotype Control (n=2)
Median Fluorescence Intensity (MFI)
8000
6000
4000
2000
0
0.000001
0.0001
0.01
1
100
Antibody Titration (µg/mL)

FIG. 4F

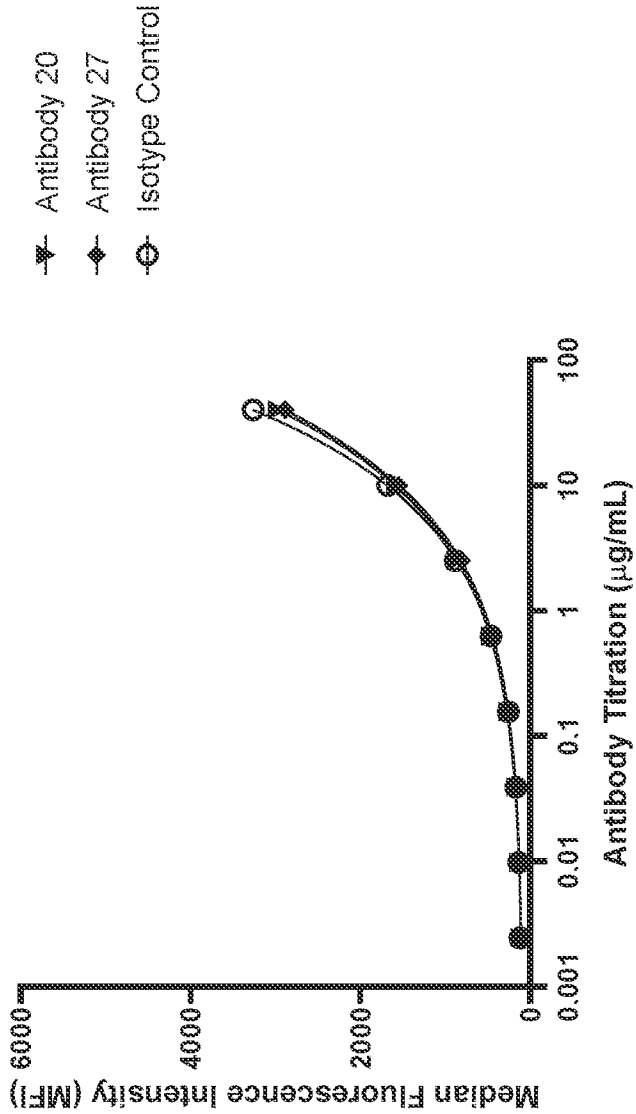

Binding to Cyno Platelets
Antibody 20
Antibody 27
Isotype Control
Median Fluorescence Intensity (MFI)
6000
4000
2000
0
0.001
0.01
0.1
1
10
100
Antibody Titration (µg/mL)

FIG. 4G

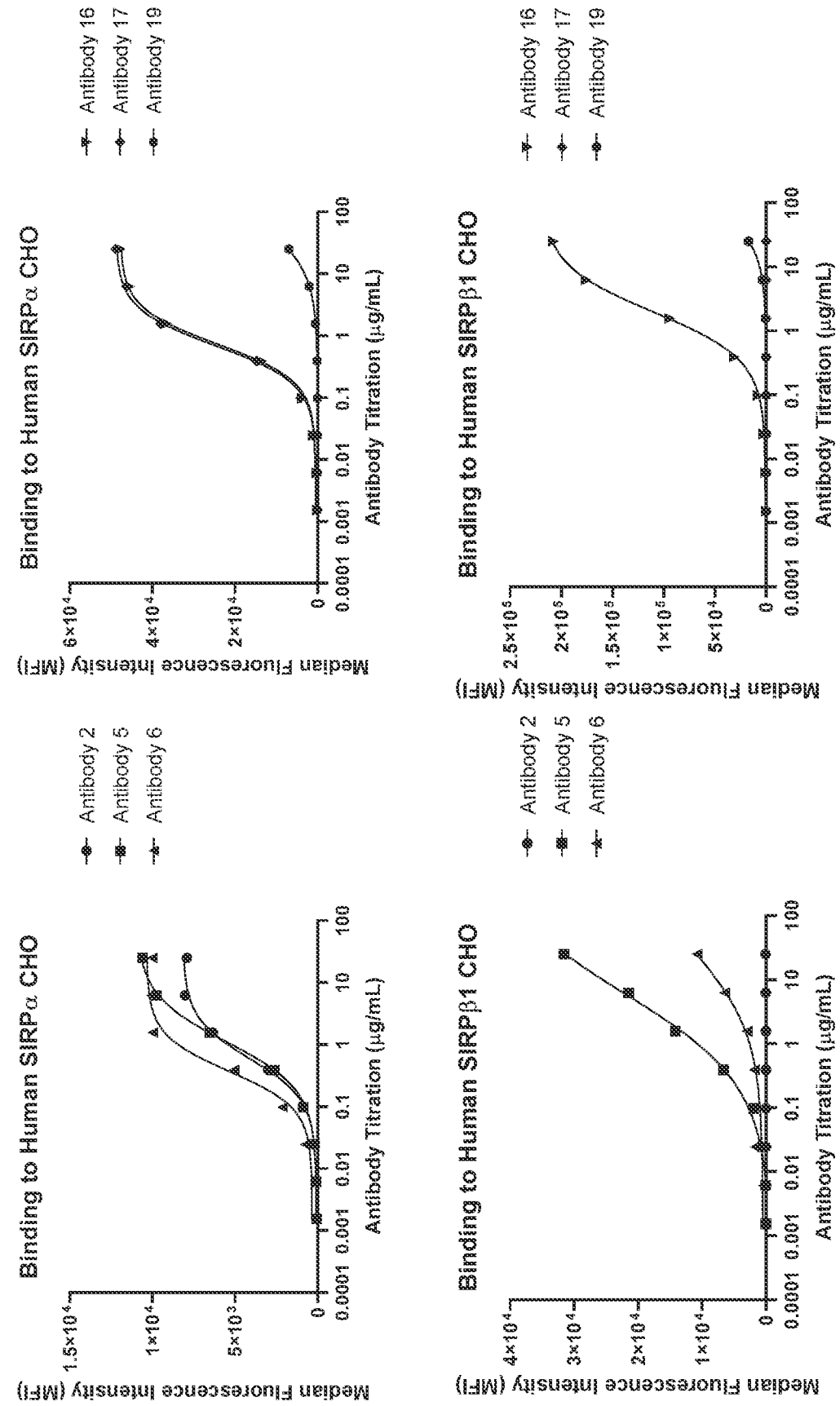

Binding to Human SIRPα CHO
Median Fluorescence Intensity (MFI)
Antibody Titration (μg/mL)
Antibody 2
Antibody 5
Antibody 6
Antibody 16
Antibody 17
Antibody 19
Binding to Human SIRPβ1 CHO

FIG. 4H

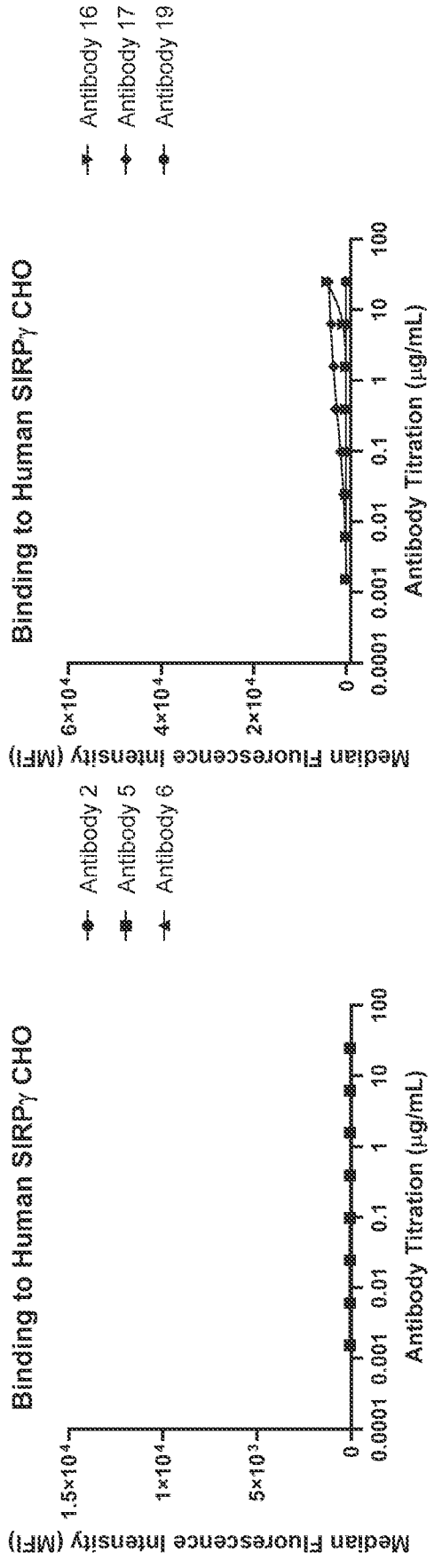

Binding to Human SIRPγ CHO
Median Fluorescence Intensity (MFI)
1.5×10^4
1×10^4
5×10^3
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (µg/mL)
Antibody 2
Antibody 5
Antibody 6
Binding to Human SIRPγ CHO
Median Fluorescence Intensity (MFI)
6×10^4
4×10^4
2×10^4
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (µg/mL)
Antibody 16
Antibody 17
Antibody 19

FIG. 4I

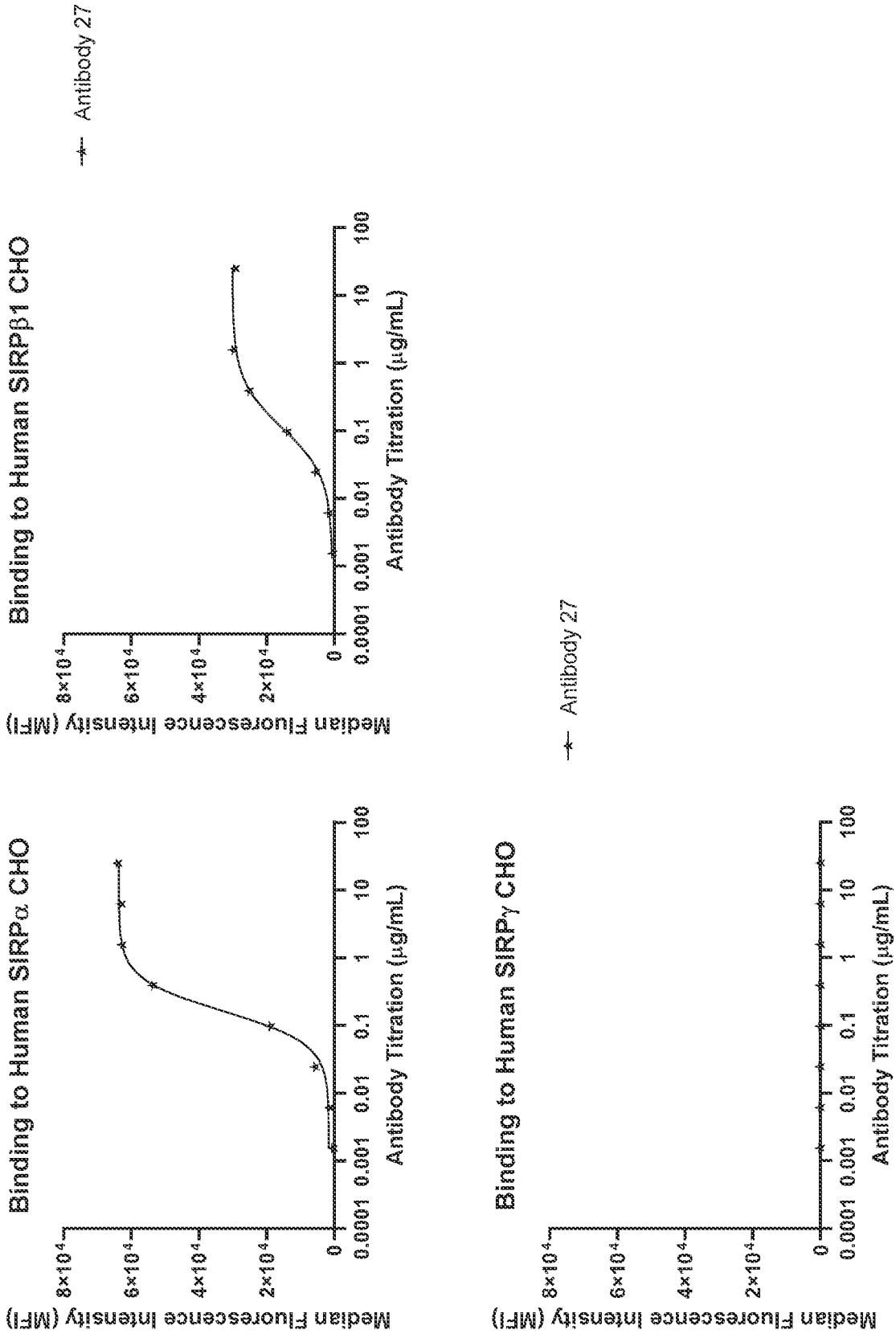

Binding to Human SIRPβ1 CHO
Antibody 27
Median Fluorescence Intensity (MFI)
8×10⁴
6×10⁴
4×10⁴
2×10⁴
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Binding to Human SIRPα CHO
Median Fluorescence Intensity (MFI)
Antibody Titration (μg/mL)
Binding to Human SIRPγ CHO
Antibody 27
Median Fluorescence Intensity (MFI)
Antibody Titration (μg/mL)

FIG. 5A

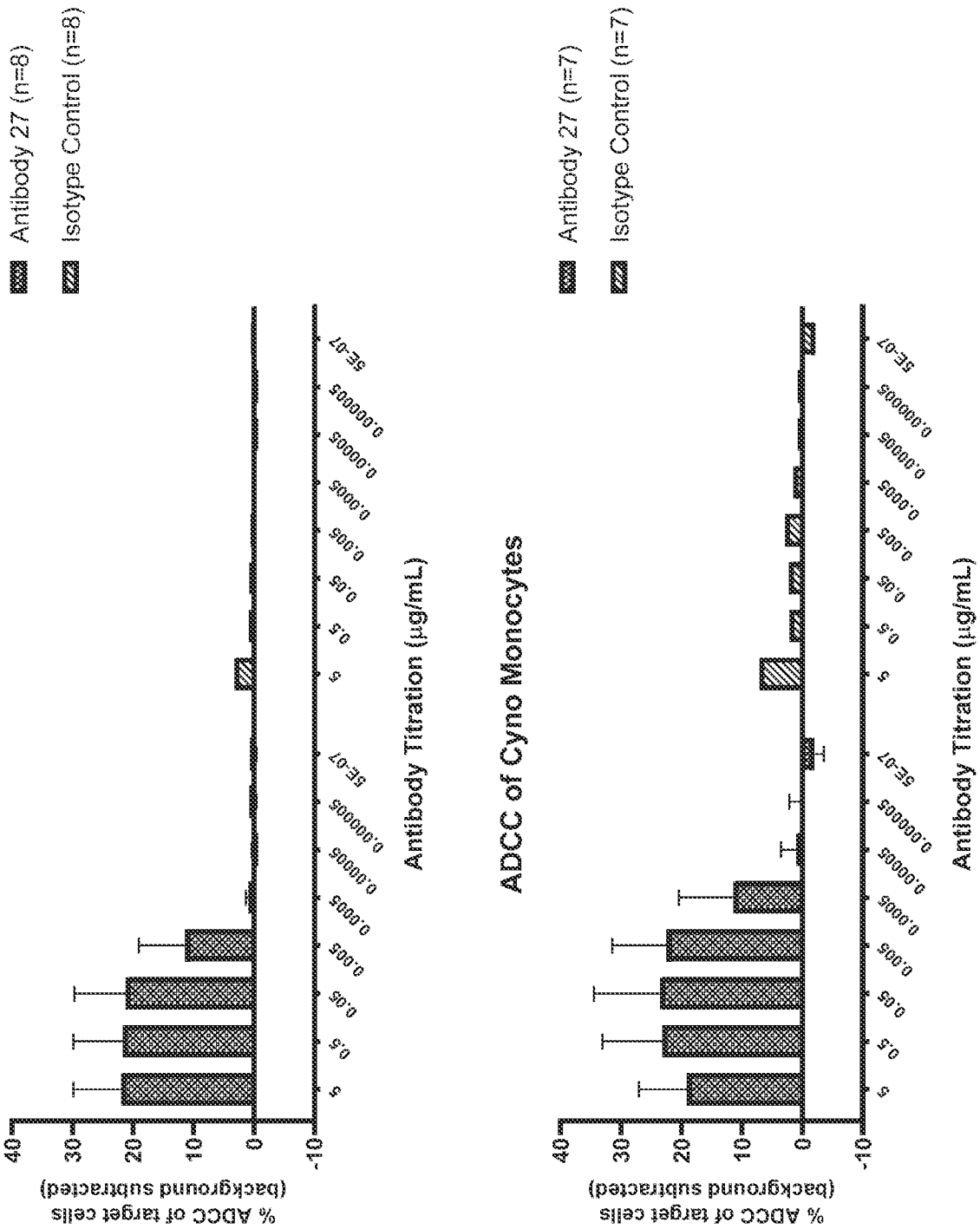

ADCC of Human Monocytes
Antibody 27 (n=8)
Isotype Control (n=8)
% ADCC of target cells (background subtracted)
40
30
20
10
0
-10
5
0.5
0.05
0.005
0.0005
0.00005
5E-07
Antibody Titration (µg/mL)
ADCC of Cyno Monocytes
Antibody 27 (n=7)
Isotype Control (n=7)
% ADCC of target cells (background subtracted)
40
30
20
10
0
-10
5
0.5
0.05
0.005
0.0005
0.00005
5E-07
Antibody Titration (µg/mL)

FIG. 5B

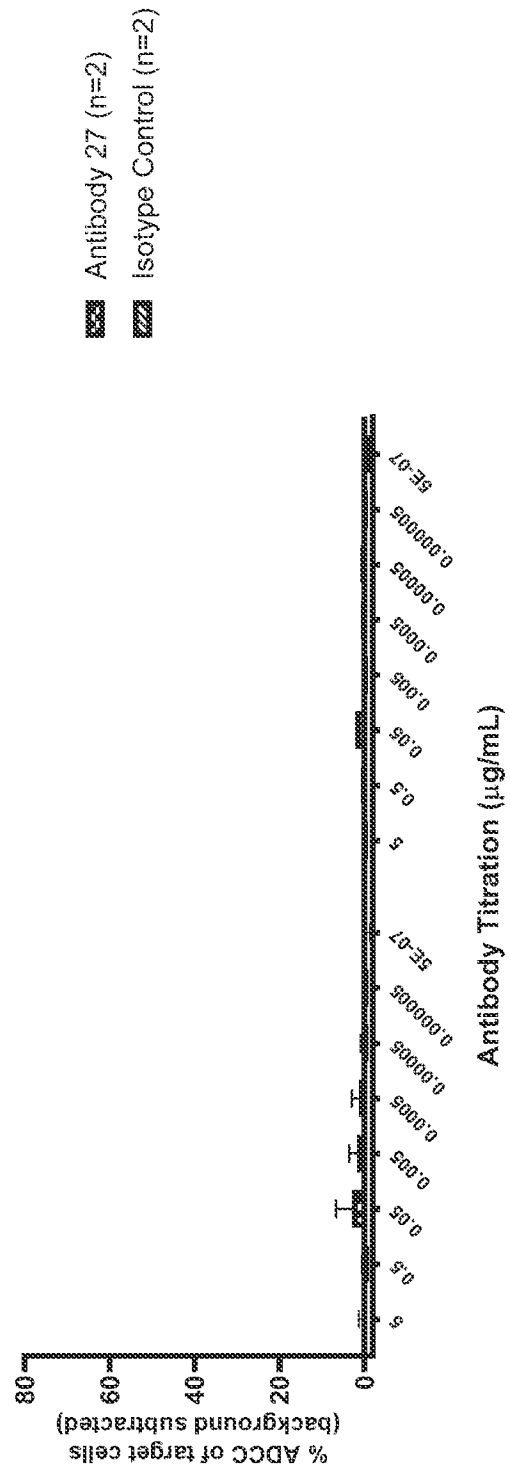
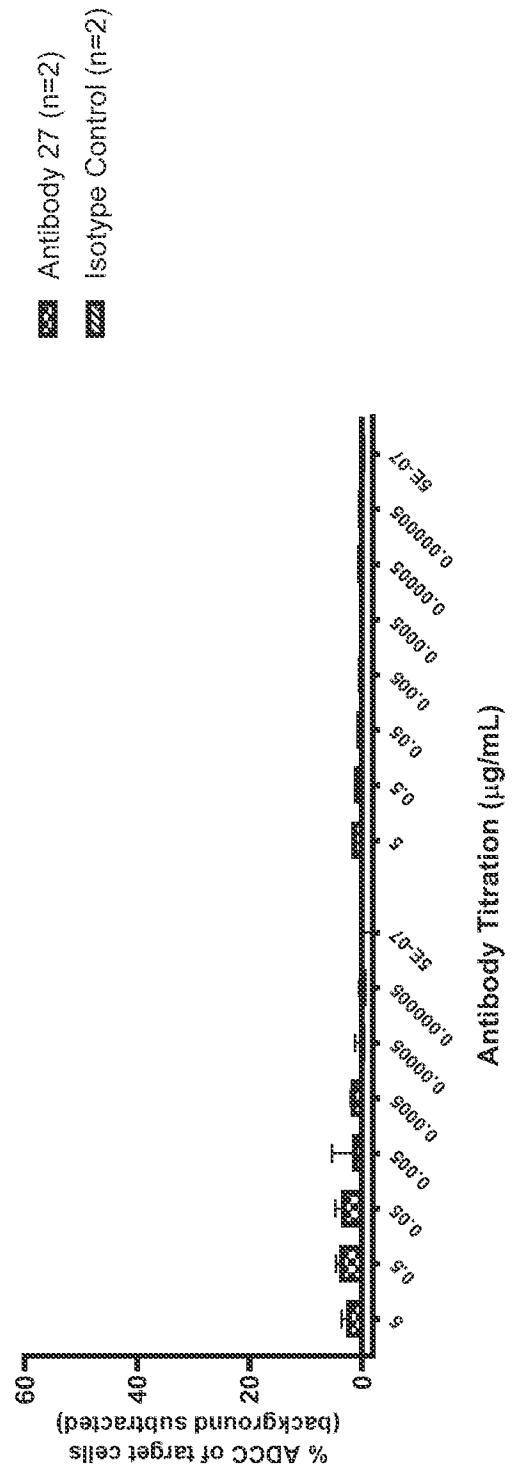

ADCC of Human CD4+ T Cells
Antibody 27 (n=2)
Isotype Control (n=2)
% ADCC of target cells
(background subtracted)
0
20
40
60
80
5
0.5
0.05
0.005
0.0005
0.00005
0.000005
5E-07
Antibody Titration (µg/mL)

FIG. 5C


ADCC of Human CD8+ T Cells
Antibody 27 (n=2)
Isotype Control (n=2)
% ADCC of target cells
(background subtracted)
60
40
20
0
Antibody Titration (µg/mL)
5
0.5
0.05
0.005
0.0005
0.00005
0.000005
5E-07
0.000005
0.00005
0.0005
0.005
0.05
0.5
5
0.5
0.05
0.005
0.0005
0.00005
0.000005
5E-07

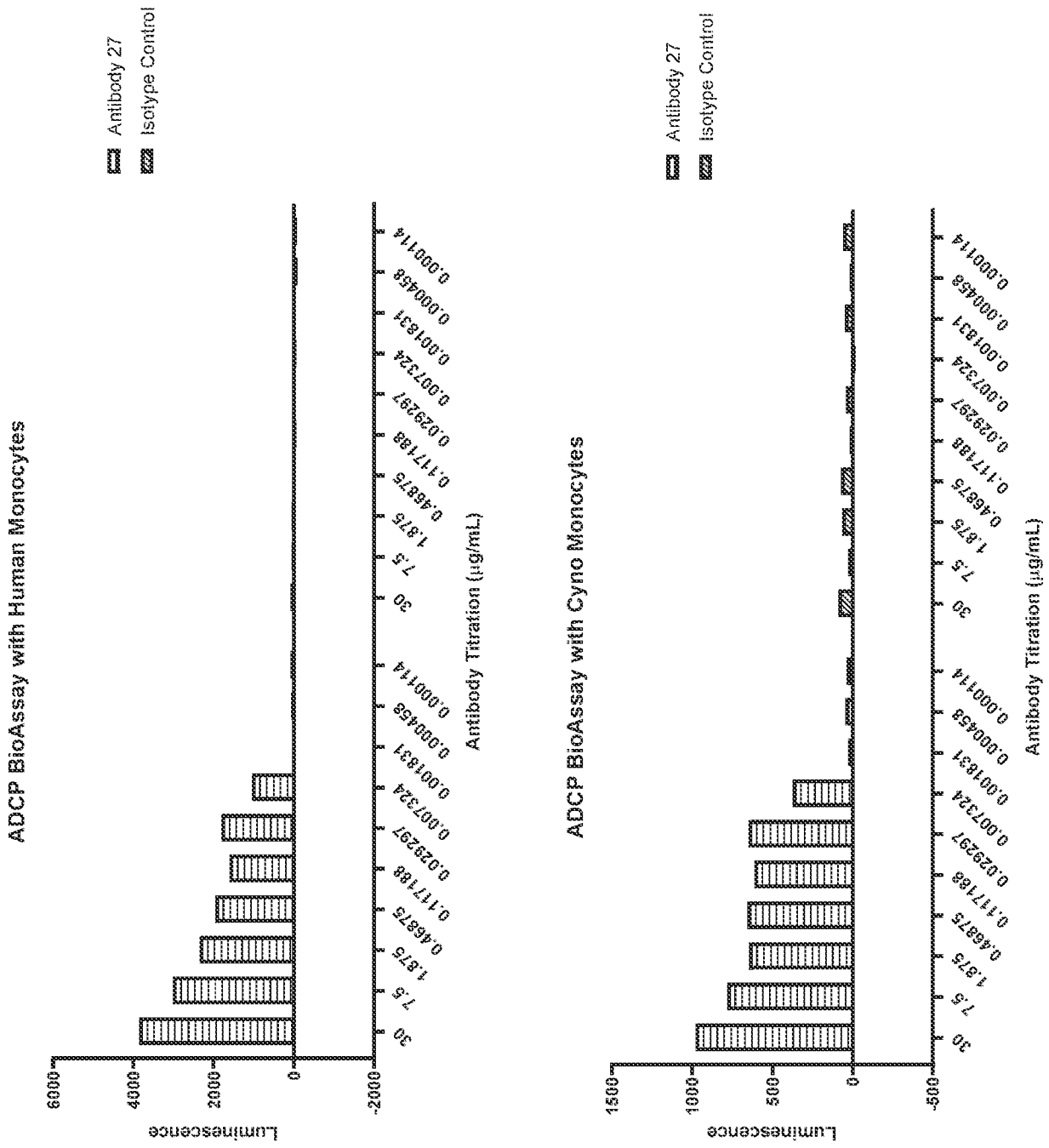
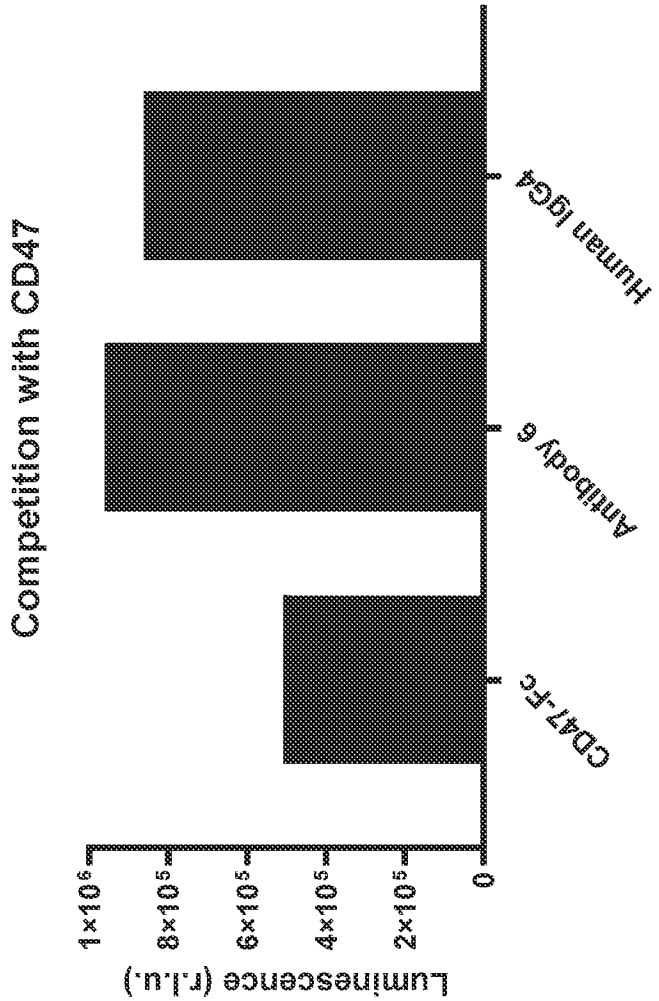

ADCP BioAssay with Human Monocytes
Antibody 27
Isotype Control
Luminescence
6000
4000
2000
0
-2000
30
7.5
1.875
0.4688
0.1172
0.02929
0.007324
0.001831
0.0004578
0.0001144
Antibody Titration (µg/mL)
ADCP BioAssay with Cyno Monocytes
Antibody 27
Isotype Control
Luminescence
1500
1000
500
0
-500
30
7.5
1.875
0.4688
0.1172
0.02929
0.007324
0.001831
0.0004578
0.0001144
Antibody Titration (µg/mL)

FIG. 6

FIG. 7


Competition with CD47
Luminescence (r.l.u.)
1×10^6
8×10^5
6×10^5
4×10^5
2×10^5
0
CD47-Fc
Antibody 6
Human IgG4