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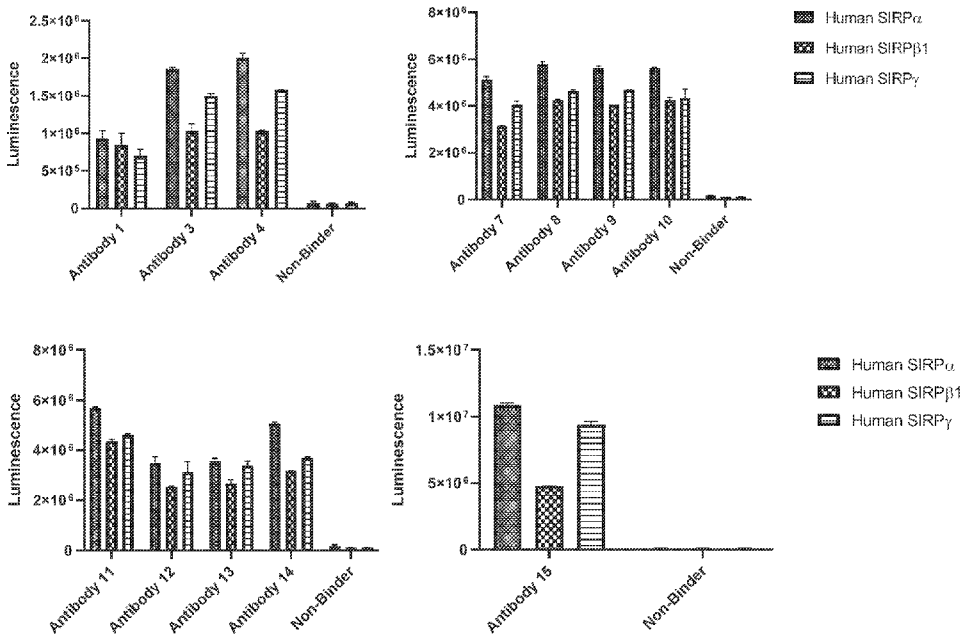
(54) Title: SIRP ALPHA, SIRP BETA 1, AND SIRP GAMMA ANTIBODIES AND USES THEREOF

FIG. 1B



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

[Continued on next page]

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SIRP ALPHA, SIRP BETA 1, AND SIRP GAMMA 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 cell-surface 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. SIRP family members 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. SIRPγ (also called CD172-antigen-like family member B, CD172g, and SIRP-beta-2) is expressed by lymphocytes such as T cells, and also binds to CD47. There is a need for agents that bind to SIRPα, SIRPβ1, as well as SIRPγ 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, and is also specific for SIRPγ, wherein binding of the antibody to one or more of SIRPα, SIRPβ1, and SIRPγ on a cell induces depletion of the cell.

[0004] The disclosure provides antibodies that are specific for one or more of SIRPα and SIRPβ1, and antibodies specific for SIRPγ, 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: 54, 56, and 59-65; (ii) a CDR-H2 sequence selected from the group consisting of SEQ ID NOS: 70, 72, and 75-81; and (iii) a CDR-H3 sequence selected from the group consisting of SEQ ID NOS: 86, 88-89, and 92-99; 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: 5, 7-8, and 11-18; (ii) a CDR-L2 sequence selected from the group consisting of SEQ ID NOS: 23-24, and 27-33; and (iii) a CDR-H3 sequence selected from the group consisting of SEQ ID NOS: 36, 38-39, and 42-49.

[0005] In some embodiments of the antibodies of disclosure, the antibody comprises the heavy and light variable chain CDR sequence combination selected from the group consisting of: (a) SEQ ID NO: 5, SEQ ID NO: 23, SEQ ID NO: 36, SEQ ID NO: 54, SEQ ID NO: 70, and SEQ ID NO: 86; (b) SEQ ID NO: 7, SEQ ID NO: 24, SEQ ID NO: 38, SEQ ID NO: 54, SEQ ID NO: 72, and SEQ ID NO: 88; (c) SEQ ID NO: 8, SEQ ID NO: 24, SEQ ID NO: 39, SEQ ID NO: 56, SEQ ID NO: 72, and SEQ ID NO: 89; (d) SEQ ID NO: 11, SEQ ID NO: 27, SEQ ID NO: 42, SEQ ID NO: 59, SEQ ID NO: 75, and SEQ ID NO: 92; (e) SEQ ID NO: 12, SEQ ID NO: 28, SEQ ID NO: 43, SEQ ID NO: 60, SEQ ID NO: 76, and SEQ ID NO: 93; (f) SEQ ID NO: 13, SEQ ID NO: 29, SEQ ID NO: 44, SEQ ID NO: 61, SEQ ID NO: 76, and SEQ ID NO: 94; (g) SEQ ID NO: 13, SEQ ID NO: 30, SEQ ID NO: 45, SEQ ID NO: 62, SEQ ID NO: 77, and SEQ ID NO: 95; (h) SEQ ID NO: 14, SEQ ID NO: 31, SEQ ID NO: 46, SEQ ID NO: 63, SEQ ID NO: 78, and SEQ ID NO: 96; (i) SEQ ID NO: 15, SEQ ID NO: 31, SEQ ID NO: 47, SEQ ID NO: 62, SEQ ID NO: 79, and SEQ ID NO: 97; (j) SEQ ID NO: 16, SEQ ID NO: 31, SEQ ID NO: 47, SEQ ID NO: 62, SEQ ID NO: 79, and SEQ ID NO: 97; (k) SEQ ID NO: 17, SEQ ID NO: 32, SEQ ID NO: 48, SEQ ID NO: 64, SEQ ID NO: 80, and SEQ ID NO: 98; and (l) SEQ ID NO: 18, SEQ ID NO: 33, SEQ ID NO: 49, SEQ ID NO: 65, SEQ ID NO: 81, and SEQ ID

NO: 99. In some embodiments, the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NOS: 104, 106-107, and 110-118. In some embodiments, the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NOS: 123, 125-126, and 129-137.

[0006] In some embodiments of the antibodies of the disclosure, the heavy chain variable region sequence and the light chain variable region sequence are selected from the group consisting of: (a) SEQ ID NO: 104 and SEQ ID NO: 123; (b) SEQ ID NO: 106 and SEQ ID NO: 125; (c) SEQ ID NO: 107 and SEQ ID NO: 126; (d) SEQ ID NO: 110 and SEQ ID NO: 129; (e) SEQ ID NO: 111 and SEQ ID NO: 130; (f) SEQ ID NO: 112 and SEQ ID NO: 131; (g) SEQ ID NO: 113 and SEQ ID NO: 132;(h) SEQ ID NO: 114 and SEQ ID NO: 133; (i) SEQ ID NO: 115 and SEQ ID NO: 134; (j) SEQ ID NO: 116 and SEQ ID NO: 135; (k) SEQ ID NO: 117 and SEQ ID NO: 136; and (l) SEQ ID NO: 118 and SEQ ID NO: 137.

[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: 104 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: 123, 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: 106 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: 125, 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: 107 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: 126, 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: 110 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: 129, 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: 111 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: 130, 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: 112 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: 131, 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: 113 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: 132, 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: 114 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: 133, 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: 115 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: 134, 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: 116 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: 135, 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: 117 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: 136, 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: 118 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: 137, or an amino acid sequence with at least 80% sequence identity thereto. In some embodiments, the antibody comprises an Fc domain.

[0008] In some embodiments of the antibodies of the disclosure, the antibody is an Fc-containing antibody, and the binding of the antibody to one or more of SIRPα, SIRPβ1, and SIRPγ 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 SIRPγ positive cells. In some embodiments, the SIRPγ cells are lymphocytes. In some embodiments, the lymphocytes are T cells or NK cells. In some embodiments, the T cells are cytotoxic T cells, helper T cells, memory T cells, regulatory T cells, natural killer T cells, mucosal associated invariant T cells, gamma delta T cells, or a combination thereof. In some embodiments, the cell depletion involves depletion of SIRPγ positive cells and SIRPα and/or SIRPβ1 positive cells. In some embodiments, the SIRPα and/or SIRPβ1 cells are myeloid cells or myeloid progenitor cells. In some embodiments, the SIRPα and/or SIRPβ1 cells are selected from the group consisting of monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, and mast cells.

[0009] 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.

[0010] 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: 26. 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: 26. 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: 19; (b) SEQ ID NO: 20, wherein X1 is V or A; (c) SEQ ID NO:

21, 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: 22, wherein X1 is V or A; (e) SEQ ID NO: 25, wherein X1 is V or A; X2 is M or L; and X3 is N or S; and (f) SEQ ID NO: 26, 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: 34, 35 or 37, wherein X1 in SEQ ID NO: 37 is S or P; and X2 in SEQ ID NO: 37 is L or E.

[0011] In some embodiments of the antibodies of the disclosure, the binding of the antibody does not disrupt the interaction between CD47 and SIRPα, and/or the interaction between CD47 and SIRPγ. In some embodiments, binding of the antibody disrupts the interaction between CD47 and SIRPα, and/or the interaction between CD47 and SIRPγ. In some embodiments, the antibody binds SIRPα, SIRPβ1 and SIRPγ. In some embodiments, the antibody binds SIRPα and SIRPγ and exhibits little or no binding to SIRPβ1. In some embodiments, the antibody binds SIRPβ1 and SIRPγ and exhibits little or no binding to SIRPα.

[0012] In some embodiments of the antibodies of the disclosure, the antibody comprises a binding affinity for 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 0.5 nM, about 0.1 nM, about 5 nM, about 10 nM, about 50 nM, about 100 nM, about 500 nM, about 1 μM, about 5 μM, or about 10 μM. In some embodiments, the antibody comprises a binding affinity for SIRPγ of about 0.0001 nM, about 0.0005 nM, about 0.001 nM, about 0.005 nM, about 0.1 nM, 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, about 1 μM, about 2 μM, or about 3 μM.

[0013] The disclosure provides a pharmaceutical composition comprising an antibody of the disclosure, and optionally a pharmaceutically acceptable carrier.

[0014] The disclosure provides a nucleic acid encoding for the antibody of the disclosure. In some embodiments, the nucleic acid comprises nucleic acid sequence selected from the group consisting of SEQ ID NOS: 142, 144-145, 148-156, 161, 163-164, and 167-175. In some embodiments, the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 142, 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: 161, 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: 144, 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: 163, 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: 145, 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: 164, 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: 148, 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: 167, 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: 149, 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: 168, 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: 150, 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: 169, 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: 151, 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: 170, 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: 152, 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: 171, 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: 153, 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: 172, 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: 154, 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: 173, 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: 155, 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: 174, 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: 156, 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: 175, or a nucleic acid sequence with at least 80% sequence identity thereto.

[0015] The disclosure provides vectors comprising the nucleic acid of the disclosure.

[0016] 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.

[0017] In some embodiments of the methods of the disclosure, at least a subset of the population of cells expresses SIRPγ. In some embodiments, the population of cells that express SIRPγ comprise lymphocytes. In some embodiments, the lymphocytes comprise T cells or NK cells. In some embodiments, at least a subset of the population of cells expresses SIRPα and/or SIRPβ1. In some embodiments, the population of cells that express SIRPα and/or SIRPβ1 comprise myeloid cells or myeloid progenitor cells. In some embodiments, the population of cells that express SIRPα and/or SIRPβ1 comprise monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, or mast cells. In some embodiments, 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.

[0018] 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.

[0019] 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 pharmaceutical composition of the disclosure.

[0020] 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 lymphocytes, and the antibody induces depletion of lymphocytes. In some embodiments, the lymphocytes are T cells. In some embodiments, the disease or condition comprises aplastic anemia, cell mediated rejection of solid organ transplant, graft failure post-HSCT (hematopoietic stem cell transplant), lymphocyte-variant hypereosinophilia, atopic dermatitis, lymphocytic myocarditis, axial spondyloarthritis, celiac disease, or Rasmussen's encephalitis.

[0021] 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. In some embodiments, the myeloid cells comprise eosinophils, and the disease or condition comprises acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, lymphocyte-variant hypereosinophilia, eosinophilic cardiomyopathy/Loeffler endocarditis, Löffler syndrome or episodic angioedema with eosinophilia/Gleich syndrome. In some embodiments, the myeloid cells comprise mast cells, and the disease or condition comprises cutaneous mastocytosis, mastocytic enterocolitis, systemic mastocytosis, mast cell activation syndrome, hereditary alpha tryptasemia syndrome, chronic urticaria or severe allergic conjunctivitis. In some embodiments, the myeloid cells comprise neutrophils, and 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.

[0022] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or condition comprises a disease or disorder associated with both lymphocytes and myeloid cells. In some embodiments, the disease or disorder comprises histiocytosis. In some embodiments, the histiocytosis comprises hemophagocytic lymphohistiocytosis (HLH)

(including primary and secondary HLH), macrophage activation syndrome, Langerhans cell histiocytosis (LCH), indeterminate cell histiocytosis, Erdheim-Chester disease (ECD), mixed LCH/ECD, Rosai Dorfman disease, malignant histiocytosis, cutaneous non-LCH histiocytoses, juvenile xanthogranuloma, infection-associated HLH, or malignancy-triggered HLH. In some embodiments, the malignancy-triggered HLH includes an HLH triggered by a hematological malignancy or solid tumor. In some embodiments, the disease or disorder comprises a non-mendelian secondary HLH (secondary HLH, or sHLH). In some embodiments, the secondary HLH comprises an infection-associated HLH. In some embodiments, the infection-associated HLH comprises virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, or fungal-associated (fungal induced) HLH. In some embodiments, the sHLH is associated with a rheumatologic condition. In some embodiments, the sHLH is associated with a kidney transplant or hematologic stem cell transplant.

[0023] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or condition comprises sHLH or cytokine release syndrome (CRS). In some embodiments, the sHLH or CRS is associated with iatrogenic immune activation, infection, T cell therapy, chimeric antigen receptor – T cell therapy (CAR-T), T cell receptor T cell therapy (TCR-T), T cell activating bispecific antibody therapy, or iatrogenic immune suppression.

[0024] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or condition comprises a granulomatous disease or condition, or a disease characterized by the presence of multinucleated giant cells. In some embodiments, the disease or condition comprises sarcoidosis, Crohn's disease, Takayasu arteritis, giant cell arteritis, psoriatic arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis), giant cell myocarditis, chronic granulomatous disease, eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome), or chronic beryllium disease (berylliosis).

[0025] 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 myeloid cells (e.g. dendritic cells) in germinal centers of secondary lymphoid tissue of the subject.

[0026] In some embodiments, the disease or condition comprises Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), Lambert-Eaton myasthenic syndrome (LEMS), myasthenia gravis (MG), neuromyelitis optica (NMO), bullous pemphigoid, epidermolysis bullosa acquisita, pemphigus foliaceus, pemphigus vulgaris, anti-glomerular basement membrane disease (Goodpasture Syndrome), membranous nephropathy, ankylosing spondylitis, rheumatoid arthritis, rheumatoid vasculitis, lupus nephritis, lupus vasculitis, systemic lupus erythematosus (SLE), scleroderma (systemic sclerosis), Behcet's disease, granulomatosis with polyangiitis (Wegener's Granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome), microscopic polyangiitis (MPA), Kawasaki disease, anti-glomerular basement membrane disease (Goodpasture Syndrome), antiphospholipid syndrome and catastrophic antiphospholipid syndrome, Graves ophthalmopathy, Castleman disease, and antibody-mediated rejection (AMR), Sjögren's syndrome, multiple sclerosis, Hashimoto's thyroiditis, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune neutropenia, systemic juvenile idiopathic arthritis, axial spondyloarthritis, celiac disease, autoimmune hepatitis, or psoriatic arthritis.

[0027] In some embodiments, the disease or condition comprises disseminated encephalomyelitis, acute respiratory distress syndrome, Addison's disease, Adult-Onset Still's disease, ankylosing spondylitis, antibody-mediated rejection (AMR), anti-glomerular basement membrane disease (Goodpasture Syndrome), antiphospholipid syndrome, aplastic anemia, atopic dermatitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune lymphoproliferative syndrome, axial spondyloarthritis, Behcet's disease, bullous pemphigoid, Castleman disease, catastrophic antiphospholipid syndrome, celiac disease, cell mediated rejection of solid organ transplant, Chediak-Higashi syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic neutrophilic leukemia, chronic urticaria, coronary artery disease (CAD)/ peripheral artery disease (PAD), COVID-19, cutaneous mastocytosis, eosinophilic cardiomyopathy/Loeffler endocarditis, epidermolysis bullosa acquisita, Evans syndrome, Felty's syndrome, general pustular psoriasis, giant cell myocarditis, graft failure post-HSCT (hematopoietic stem cell transplant), graft vs. host disease, Graves' disease, Graves ophthalmopathy, Guillain-Barre syndrome, Hashimoto's thyroiditis, hereditary alpha tryptasemia syndrome, hyper IgE syndrome, Idiopathic interstitial pneumonia, idiopathic pulmonary fibrosis, IgA nephropathy, immune/idiopathic thrombocytopenia purpura, inclusion body myositis, inflammatory bowel disease, Kawasaki disease, Lambert-Eaton myasthenic

syndrome (LEMS), linear IgA disease, Löffler syndrome, lupus nephritis, lupus vasculitis, mast cell activation syndrome, mastocytic enterocolitis, membranous nephropathy, microscopic polyangiitis (MPA), multiple sclerosis, myasthenia gravis, myelodysplastic syndromes, myelofibrosis, myocarditis, neuromyelitis optica (NMO), neutrophilic dermatoses, paraneoplastic syndrome, pemphigus foliaceus, pemphigus vulgaris, primary biliary cholangitis, primary sclerosing cholangitis, pyoderma gangrenosum, Rasmussen's encephalitis, rheumatoid arthritis, rheumatoid vasculitis, Schmidt syndrome, scleroderma (systemic sclerosis), severe allergic conjunctivitis, Sjogren syndrome, Susac syndrome, systemic inflammatory response syndrome, systemic juvenile idiopathic arthritis, systemic lupus erythematosus, systemic mastocytosis, type 1 diabetes, ulcerative colitis, uveitis, vitiligo or X-linked lymphoproliferative disease.

[0028] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or disorder comprises a hematological malignancy. In some embodiments, the hematological malignancy comprises acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, chronic neutrophilic leukemia, juvenile myelomonocytic leukemia, chronic eosinophilic leukemia, large granular lymphocyte leukemia, T-cell prolymphocytic leukemia, hepatosplenic lymphoma, Hodgkin's lymphomas, T-cell lymphoblastic lymphoma or leukemia, T-cell non-lymphoblastic lymphoma, NK-cell lymphoma/leukemia, myeloid neoplasia, or chronic neutrophilic leukemia.

[0029] In some embodiments of the methods of treating a disease or condition of the disclosure, the disease or disorder comprises hemophagocytic lymphohistiocytosis (HLH) (including primary and secondary HLH), macrophage activation syndrome, Langerhans cell histiocytosis (LCH), indeterminate cell histiocytosis, Erdheim-Chester disease (ECD), mixed LCH/ECD, Rosai Dorfman disease, malignant histiocytosis, cutaneous non-LCH histiocytosis, juvenile xanthogranuloma, virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, fungal-associated/fungal-induced HLH, malignancy-triggered HLH, HLH occurring during chemotherapy, HLH associated with systemic-onset juvenile idiopathic arthritis (SoJIA), HLH associated with adult-onset Still's disease, HLH associated with systemic lupus erythematosus (SLE), HLH associated with vasculitis, HLH associated with auto-immune conditions, HLH associated with a kidney transplant, HLH associated with hematologic stem cell transplants, sHLH or CRS associated with checkpoint inhibitors for the treatment of malignancies, sHLH or

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, cytokine release syndrome (CRS), systemic mastocytosis, hypereosinophilic syndrome (including primary, secondary, and idiopathic), hyper IgE syndrome, X-linked lymphoproliferative disease, graft vs. host disease, type 1 diabetes, systemic lupus erythematosus, lupus nephritis, systemic inflammatory response syndrome, acute respiratory distress syndrome, autoimmune lymphoproliferative syndrome, X-linked hyper IgM syndrome, paraneoplastic syndrome, Susac syndrome, linear IgA disease, autoimmune neutropenia, idiopathic pulmonary fibrosis, inclusion body myositis, vitiligo, Addison's disease, Graves' disease, Hashimoto's thyroiditis, Schmidt syndrome, acute disseminated encephalomyelitis, sarcoidosis, ankylosing spondylitis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, eosinophilic granulomatosis with polyangiitis, pyoderma gangrenosum, giant cell arteritis, rheumatoid arthritis, systemic juvenile idiopathic arthritis, Sjogren's syndrome, primary sclerosing cholangitis, primary biliary cholangitis, myasthenia gravis, multiple sclerosis, Guillain-Barre syndrome, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic eosinophilic leukemia, large granular lymphocyte leukemia, T-cell prolymphocytic leukemia, hepatosplenic lymphoma, Hodgkin's lymphoma, T-cell lymphoblastic lymphoma/leukemia, T-cell non-lymphoblastic lymphoma, B-cell leukemia, B-cell lymphoma (non-Hodgkin's), NK-cell lymphoma or leukemia, myeloid neoplasia, autoimmune hemolytic anemia, immune/idiopathic thrombocytopenia purpura, Evans syndrome, Felty's syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), Lambert-Eaton myasthenic syndrome (LEMS), neuromyelitis optica (NMO), bullous pemphigoid, epidermolysis bullosa acquisita, pemphigus foliaceus, pemphigus vulgaris, membranous nephropathy, rheumatoid vasculitis, lupus vasculitis, scleroderma (systemic sclerosis), Behcet's disease, granulomatosis with polyangiitis (Wegener's Granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome), microscopic polyangiitis (MPA), Kawasaki disease, anti-glomerular basement membrane disease (Goodpasture Syndrome), antiphospholipid syndrome, catastrophic antiphospholipid syndrome, Graves ophthalmopathy, Castleman disease, antibody-mediated rejection (AMR), acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, uveitis, giant cell myocarditis, cutaneous

mastocytosis, mastocytic enterocolitis, mast cell activation syndrome, IgA nephropathy, Chediak-Higashi 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, myocarditis, episodic angioedema with eosinophilia / Gleich syndrome, idiopathic interstitial pneumonia, hereditary alpha tryptasemia syndrome, chronic urticaria, severe allergic conjunctivitis, Adult-onset Still's, aplastic Anemia, cell mediated rejection of solid organ transplant, graft failure Post-hematopoietic stem cell transplant (HSCT), lymphocyte-variant hypereosinophilia, myelodysplastic syndromes, atopic dermatitis, axial spondyloarthritis, celiac disease, hyperthyroidism, Rasmussen's encephalitis, chronic beryllium disease (Berylliosis), Takayasu arteritis, autoimmune hepatitis, neutrophilic dermatoses, psoriatic arthritis, Corona Virus Disease 2019 (COVID-19), or general pustular psoriasis.

[0030] In some embodiments of the methods of treating a disease or condition of the disclosure, the subject is human.

[0031] In some embodiments of the methods of treating a disease or condition of the disclosure, the antibody or pharmaceutical composition is administered intravenously. In some embodiments, the antibody or pharmaceutical composition is administered subcutaneously.

[0032] The disclosure provides cells expressing SIRPγ, wherein the cells are bound to an antibody of the disclosure, wherein the antibody is bound to the SIRPγ.

[0033] The disclosure provides kits or articles of manufacture comprising the antibodies or pharmaceutical compositions of the disclosure.

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

[0035] The disclosure provides use of the antibodies or the pharmaceutical compositions of the disclosure for the manufacture of a medicament for the treatment of a disease or disorder in a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] FIG. 1A shows binding of selected antibodies of the disclosure to human SIRPα and cynomolgus monkey (cyno) SIRPα by enzyme-linked immunosorbent assay (ELISA).

[0037] FIG. 1B shows binding of selected antibodies of the disclosure to human SIRPα, SIRPβ1 and SIRPγ by ELISA.

[0038] FIGS. 2A-2B show binding curves of selected antibodies to human and cynomolgus monkey SIRPα by ELISA.

[0039] FIG. 2C shows binding curves of selected antibodies to human and cynomolgus monkey SIRPα (top row) and SIRPβ1 (bottom row) by ELISA.

[0040] FIG. 2D shows binding curves of selected antibodies to human and cynomolgus monkey SIRPγ by ELISA.

[0041] FIG. 2E shows binding curves of selected antibodies to human and cynomolgus monkey SIRPα (top row) and SIRPβ1 (bottom row) by ELISA.

[0042] FIG. 2F shows binding curves of selected antibodies to human and cynomolgus monkey SIRPγ by ELISA.

[0043] FIG. 2G shows binding curves of Antibody 15 to human and cynomolgus monkey SIRPα (top row) and SIRPβ1 (bottom row) by ELISA.

[0044] FIG. 2H shows binding curves of Antibody 15 to human and cynomolgus monkey SIRPγ by ELISA.

[0045] FIG. 3A shows binding curves of selected antibodies of the disclosure to human SIRPα and cynomolgus monkey SIRPα by ELISA.

[0046] FIG. 3B shows binding curves of selected antibodies of the disclosure to human SIRPβ1 and human SIRPγ by ELISA.

[0047] FIG. 3C shows binding curves of Antibody 29 to human SIRPα, SIRPβ1 and SIRPγ by ELISA.

[0048] FIG. 3D shows binding curves of selected antibodies of the disclosure to human and cynomolgus monkey SIRPα (top row) and SIRPβ1 (bottom row) by ELISA.

[0049] FIG. 3E shows binding curves of selected antibodies of the disclosure to human and cynomolgus monkey SIRPγ by ELISA.

[0050] FIG. 4A shows the binding curves of selected antibodies of the disclosure to monocytes, neutrophils, T lymphocytes and B lymphocytes in human whole blood by flow cytometry.

[0051] FIG. 4B shows the binding curves of selected antibodies of the disclosure to monocytes, granulocytes and T lymphocytes in cynomolgus monkey (cyno) whole blood by flow cytometry.

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

[0053] FIG. 4D shows binding curves of selected antibodies of the disclosure to human SIRPβ1/DAP12-expressing CHO cells by flow cytometry.

[0054] FIG. 4E shows binding curves of selected antibodies of the disclosure to human SIRPγ-expressing CHO cells by flow cytometry.

[0055] FIG. 4F shows binding curves of selected antibodies of the disclosure to human SIRPα, SIRPβ1/DAP12 or SIRPγ-expressing CHO cells by flow cytometry.

[0056] FIG. 5 shows the effect of selected antibodies of the disclosure on antibody dependent cellular cytotoxicity (ADCC) of THP-1 cells *in vitro*.

[0057] FIG. 6A shows the effect of selected antibodies of the disclosure on ADCC of human monocytes *in vitro*.

[0058] FIG. 6B shows the effect of selected antibodies of the disclosure on ADCC of human and cynomolgus monkey (cyno) monocytes *in vitro*.

[0059] FIG. 6C shows the effect of selected antibodies of the disclosure on ADCC of human and cynomolgus monkey (cyno) CD4+ T cells *in vitro*.

[0060] FIG. 6D shows the effect of selected antibodies of the disclosure on ADCC of human and cynomolgus monkey (cyno) CD8+ T cells *in vitro*.

[0061] FIG. 7 shows the effect of selected antibodies of the disclosure on antibody dependent cellular phagocytosis (ADCP) of MOLM-13 cells by THP-1 cells *in vitro*.

[0062] FIG. 8 shows the effect of selected antibodies of the disclosure on ADCP of human monocytes by human monocytes *in vitro*.

[0063] FIGS. 9A-9B show the effect of selected antibodies of the disclosure on monocyte depletion *in vivo*.

[0064] FIGS. 10A-10B show the effect of selected antibodies of the disclosure on neutrophil depletion *in vivo*.

[0065] FIGS. 11A-11B show the effect of selected antibodies of the disclosure on lymphocyte depletion *in vivo*.

[0066] FIGS. 12A-12B show the effect of selected antibodies of the disclosure on eosinophil depletion *in vivo*.

[0067] FIGS. 13A-13B show the effect of selected antibodies of the disclosure on basophil depletion *in vivo*.

[0068] FIG. 14 is a graph depicting the results of an ELISA experiment assessing the ability of various antibodies to compete with CD47 for binding to human SIRPα.

DETAILED DESCRIPTION

[0069] Provided herein are antibodies that bind to both (a) SIRPγ and (b) 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 SIRPγ, 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, SIRPβ1 (e.g., myeloid cells), or SIRPγ expressing cells (e.g. lymphocytes) as a part of the pathology.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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).

[0074] 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

[0075] Provided herein are antibodies that bind to SIRPγ, and also bind to SIRPα, SIRPβ1 or a combination of SIRPα and SIRPβ1. Thus, antibodies that bind to (a) SIRPγ and SIRPα, (b) SIRPγ and SIRPβ1, or (c) SIRPγ, SIRPα and SIRPβ1 are envisaged as within the scope of the instant disclosure, and are referred to herein collectively as "SIRP antibody," "SIRP antibodies" or "anti-SIRP antibodies" and the like. It is referred to throughout that the binding specificity of the SIRP antibodies of the disclosure is such that the SIRP antibodies show binding to SIRPγ, and one or more of SIRPα and/or SIRPβ1 (that is, the antibodies show binding to SIRPγ as well as SIRPα and/or SIRPβ1).

[0076] The skilled artisan will appreciate that, depending on context, a SIRP antibody of the disclosure that has the ability to bind to SIRPγ as well as SIRPα and/or SIRPβ1 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 SIRPγ as well as SIRPα can bind to a cell expressing only SIRPγ, or a cell expressing only SIRPα. Alternatively, a binding surface, such as a cell, may express more than one, or all, of the targets to which the antibody can bind. In such a situation, the antibody is also expected to bind that surface. For example, an antibody that can bind to SIRPβ1 and SIRPγ can bind to a cell that expresses both SIRPβ1 and SIRPγ. Thus, although the SIRP antibodies of the disclosure bind SIRPγ as well as SIRPα and/or SIRPβ1, the binding of all of the targets simultaneously is not required for activity.

[0077] 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.

[0078] 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.

[0079] In some embodiments, the SIRP antibodies provided herein are antibody fragments, retaining SIRPγ as well as SIRPβ1 and/or SIRPα 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.

[0080] Also provided herein are SIRP antibody-drug conjugates, bispecific antibodies comprising at least one arm specific for SIRPγ as well as SIRPα and/or SIRPβ1, and multispecific antibodies that exhibit binding for SIRPγ as well as SIRPα and/or SIRPβ1.

[0081] 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.

[0082] 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)
```

[0083] 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)
```

[0084] The amino acid sequence of hSIRPα isoform 2 is provided herein as SEQ ID NO: 6.

```
  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: 6)
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[0085] The amino acid sequence of human SIRPα isoform 4 is provided in SEQ ID NO: 40.

```
  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: 40)
```

[0086] In some embodiments, the SIRP antibodies also bind to one or more variants or isoforms of a SIRPα of a single species. In some embodiments, the SIRP antibodies also bind to one or more variants or isoforms of a SIRPα of more than one species. In some embodiments, the SIRP antibodies also bind to one or more variants or isoforms of human SIRPα. In some

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

[0087] In some embodiments, the SIRP antibodies also 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 also bind to hSIRPα V1. In some embodiments, the SIRP antibodies also bind to hSIRPα V2. In some embodiments, the SIRP antibodies also bind to hSIRPα V1 and V2. In some embodiments, the SIRP antibodies also 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).

[0088] 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.

[0089] In some embodiments, the SIRP antibodies also bind specifically to hSIRPα V1. In some embodiments, the SIRP antibodies also bind specifically to hSIRPα V2. In some embodiments, the SIRP antibodies also bind specifically to hSIRPα V1 and hSIRPα V2. In some embodiments, the SIRP antibodies also bind specifically to one or more variants of SIRPα, but show little or no binding to SIRPβ1.

[0090] Human SIRPβ1 (hSIRPβ1) has at least 3 isoforms. The amino acid sequence of hSIRPβ1 isoform 1 is provided in SEQ ID NO: 8.

```
  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: 8)
```

[0091] In some embodiments, the SIRP antibodies also bind to one or more variants or isoforms of a SIRPβ1 of a single species. In some embodiments, the SIRP antibodies also bind to one or more variants or isoforms of a SIRPβ1 of more than one species. In some embodiments, the

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

[0092] In some embodiments, the SIRP antibodies also 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 also bind the extracellular domain of SIRPβ1 (e.g. amino acids 1-371 of SEQ ID NO: 8). In some embodiments, the SIRP antibodies also bind specifically to one or more variants or isoforms of SIRPα, in addition to binding to SIRPγ and SIRPβ1.

[0093] Human SIRPγ has at least 4 isoforms. The amino acid of hSIRPγ isoform 1 is provided as SEQ ID NO: 9.

```
  1 MPVPASWPHP PGPFLLLTLL LGLTEVAGEE ELQMIQPEKL LLVTVGKTAT LHCTVTSLLP
 61 VGPVLWFRGV GPGRELIYNQ KEGHFPRVTT VSDLTKRNNM DFSIRISSIT PADVGTYYCV
121 KFRKGSPENV EFKSGPGTEM ALGAKPSAPV VLGPAARTTP EHTVSFTCES HGFSPRDITL
181 KWFKNGNELS DFQTNVDPTG QSVAYSIRST ARVVLDPWDV RSQVICEVAH VTLQGDPLRG
241 TANLSEAIRV PPTLEVTQQP MRVGNQVNVT CQVRKFYPQS LQLTWSENGN VCQRETASTL
301 TENKDGTYNW TSWFLVNISD QRDDVVLTCQ VKHDGQLAVS KRLALEVTVH QKDQSSDATP
361 GPASSLTALL LIAVLLGPIY VPWKQKT (SEQ ID NO: 9)
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[0094] In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of a SIRPγ of a single species. In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of a SIRPγ of more than one species. In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of human SIRPγ. In some embodiments, the SIRP antibodies bind to one or more variants or isoforms of a non-human primate SIRPγ, e.g. a cynomolgus monkey SIRPγ.

[0095] In some embodiments, the SIRP antibodies bind to a plurality of SIRPγ variants or isoforms found in a particular species, e.g. the SIRP antibodies bind to more than one of SIRPγ human isoforms 1-3. In some embodiments, the SIRP antibodies bind the extracellular domain of SIRPγ (e.g. amino acids 1-360 of SEQ ID NO: 9).

[0096] 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. For example, a SIRP antibody that binds to SIRPγ and SIRPα may bind to SIRPβ1 with low affinity. A SIRP antibody of the disclosure with low affinity for SIRPβ1 may bind to SIRPβ1 with a KD of about 10 μM or greater, about 100 μM or greater, about 1 mM or greater, or about 10 mM or greater but retain higher binding affinity for SIRPγ and SIRPα. As a further example, a SIRP antibody that binds to SIRPγ and SIRPβ1 may bind to SIRPα with low affinity.

[0097] 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.

[0098] 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 1nM and 50 nM, or between about 5 nM and 50 nM.

[0099] 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 0.5 nM, about 1 nM, about 5 nM, about 10 nM, about 50 nM, about 100 nM, about 500 nM, about 1μM, about 2μM, about 3μM, about 5 μM, or about 10 μM.

[00100] In some embodiments, provided herein are SIRP antibodies comprising a binding affinity (KD) to SIRPβ1 of between about 0.05 nM and 10 μM, between about 0.5 nM and 10 μM, between about 1 nM and 10 μM, between about 5 nM and 10 μM, between about 10 nM and 10 μM, between about 50 nM and 10 μM, between about 100 nM and 10 μM, 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 10 nM and 1 μM, between 50 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 10nM and 500 nM, between about 0.001 nM and 50 nM, between about 0.005nM and 50 nM, between about 0.05nM 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.

[00101] In some embodiments, provided herein are SIRP antibodies comprising a binding affinity (KD) to SIRPγ of about 0.0001 nM, about 0.0005 nM, about 0.001 nM, about 0.005 nM, about 0.1nM, 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, about 1 μM, about 2 μM or about 3 μM.

[00102] In some embodiments, provided herein are SIRP antibodies comprising a binding affinity (KD) to SIRPγ of between about 0.0001 nM and 5 μM, between about 0.0005 nM and 5 μM, between about 0.05 nM and 5 μM, between about 0.5 nM and 5 μM, between about 1nM and 5 μM, between about 5 nM and 5 μM, 0.0001 nM and 2 μM, between about 0.0005 nM and 2 μM, between about 0.05 nM and 2 μM, between about 0.5 nM and 2 μM, between about 1nM and 2 μM, between about 5 nM and 2 μM,0.0001 nM and 1 μM, between about 0.0005 nM and 1 μM, between about 0.05 nM and 1μM, between about 0.5 nM and 1μM, between about 1nM and 1μM, between about 5 nM and 1 μM, between about 0.0001 nM and 500 nM, between about 0.0005 nM and 500 nM, 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 0.0001 nM and 50 nM, between about 0.0005 nM and 50 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.

[00103] In some embodiments, a SIRP antibody of the disclosure competes with CD47 for binding to SIRPα or SIRPγ on a cell or other surface. In some embodiments, a SIRP antibody of the disclosure partially competes with CD47 for binding to SIRPα or SIRPγ on a cell or other surface. In other embodiments, a SIRP antibody of the disclosure does not compete with CD47 for binding to SIRPα or SIRPγ on a surface, e.g a cell. Exemplary antibodies of the disclosure that do not compete with CD47 binding of SIRPα include Antibodies 1 and 13 referring to Table 11. Exemplary antibodies of the disclosure that partially inhibit the binding of CD47 to SIRPα include Antibodies 3 and 7, referring to Table 11.

[00104] 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.

[00105] 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 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.

[00106] 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, 19-22, 25-26, 41, 50-53, 55, 57-58, 66-69, 71, and 73-74.

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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
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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: 19)

1 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: 41)

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 LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 50)

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: 51)

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: 52)

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: 53)

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: 55)

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: 57)

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: 58)

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: 66)

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: 67)

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: 68)

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: 69)

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: 71)

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: 73)

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: 74)

[00107] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 20, 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: 20)

[00108] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 21, 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$_1$EP KSCDKTHTCP PCPAPELLX$_2$G
121 PX$_3$VFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPX$_4$EKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 21)

[00109] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 22, wherein X_1 is V or A.

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX$_1$EP 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: 22)

[00110] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 25, wherein X_1 is V or A; X_2 is M or L; and X_3 is N or S.

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX$_1$EP 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 X$_2$HEALHX$_3$HYT QKSLSLSPGK (SEQ ID NO: 25)

[00111] In some embodiments, the human IgG1 Fc domain sequence is SEQ ID NO: 26, 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 NTKVDKX$_1$VEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRX$_2$E

241 X_3TKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 26)

[00112] 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: 34-35, 37, 82-85 and 87.

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 34)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 35)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 82)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 83)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEALGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 84)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL

PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQID NO: 85)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTQKSLSLSLGK (SEQ ID NO: 87)

[00113] 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: 37)

[00114] 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 IgG1 or IgG2b. In some embodiments, the rat constant region is 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 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.

[00115] 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.

[00116] In some embodiments, the Fc domain of a SIRP antibody is an IgG1 Fc domain (e.g. SEQ ID NOS: 3-4, 19-22 or 25-26) or IgG4 human Fc domain (e.g. SEQ ID NOS: 34, 35 or 37), 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.

[00117] In some embodiments, the Fc domain of a SIRP antibody comprises SEQ ID NOS: 3-4, 19-22 or 25-26, 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.

[00118] In some embodiments, the Fc domain of a SIRP antibody is a human IgG1 (e.g. SEQ ID NO: 3-4, 19-22 or 25-26), 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.

[00119] In some embodiments, the Fc domain of a SIRP antibody is a human IgG1 (e.g. SEQ ID NO: 3-4, 19-22 or 25-26), 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.

[00120] In some embodiments, the Fc domain of a SIRP antibody is human IgG4 (e.g. SEQ ID NOS: 34, 35 or 37), 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.

[00121] 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.

[00122] In some embodiments, the Fc domain of a SIRP antibody is an IgG4 human Fc domain (e.g. SEQ ID NOS: 34, 35 or 37), 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.

[00123] In some embodiments, the Fc domain of a SIRP antibody is human IgG4 (e.g. SEQ ID NO: 34, 35 or 37), 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.

[00124] 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

[00125] The SIRP antibodies that contain Fc domains provided herein are capable of targeting a variety of cell types and inducing the depletion of those cells. An exemplary non-limiting list of

antibodies of the disclosure that exhibit cell depletion include Antibodies 23, 25, and 28-31, as provided in Table 11.

[00126] In some embodiments, the SIRP antibodies containing Fc domains provided herein are capable of depleting SIRPγ expressing cells. In some embodiments, the SIRP antibodies provided herein are capable of inducing the depletion of lymphocytes. In some embodiments, the SIRP antibodies 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, basophil, and neutrophils. In some embodiments, for example wherein the SIRP antibody binds to SIRPγ and SIRPα, the SIRP antibody is capable of inducing the depletion of SIRPα as well as SIRPγ expressing cells. In some embodiments, for example wherein the SIRP antibody binds to SIRPβ1, the SIRP antibody is capable of inducing the depletion of SIRPβ1 as well as SIRPγ expressing cells. In some embodiments, for example where the SIRP antibody binds to SIRPγ , SIRPα and SIRPβ1, the SIRP antibody is capable of inducing the depletion of SIRPα and SIRPβ1 expressing cells, as well as SIRPγ expressing cells.

[00127] 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 cell depletion involves antibody dependent cellular cytotoxicity (ADCC). In some embodiments, the cell depletion involves antibody dependent cellular phagocytosis (ADCP). In some embodiments, 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

[00128] 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 SIRPα 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:
QSLLHGNGFNY	5
QGISGY	7
QDFSNY	8
NIGSKS	11
KLGDKY	12
KLGDRY	13
QDISSW	14
QSVSSN	15
QSVSRN	16
QTVLNSSNNKNY	17
QDINRY	18

Table 2: Exemplary SIRP antibody CDR-L2 Sequences

CDR-L2	SEQ ID NO:
LGS	23
AAS	24
DDS	27
HDD	28
QDD	29
QDT	30
GAS	31
WAS	32
RAN	33

Table 3: Exemplary SIRP antibody CDR-L3 Sequences

CDR-L3	SEQ ID NO:
MQGLQTPRT	36
QQFTSDLIT	38
QQYDNLPYT	39

CDR-L3	SEQ ID NO:
QVWDSSSDHYV	42
QTWDSSTVV	43
QAWDSSTAV	44
QACDSSTAV	45
QEANSFPYT	46
QQYNNWPYT	47
QQYYNTPPWT	48
LQYDEFPFT	49

Table 4: Exemplary SIRP antibody CDR-H1 Sequences

CDR-H1	SEQ ID NO:
GGSISSSNW	54
DYSISSGYY	56
GFTFSKFG	59
GGSFSGYY	60
GGSFSTYY	61
GFTFSSYA	62
GFTFSSYW	63
GFIFSNYG	64
GYTFRNFG	65

Table 5: Exemplary SIRP antibody CDR-H2 Sequences

CDR-H2	SEQ ID NO:
IYHSGST	70
IYHSGNT	72
ISYDGNNK	75
INHSGST	76
ISGSGGDT	77
IHNDGSRT	78
ISGSGSST	79
ISYDGRNE	80
IDTNTGEP	81

Table 6: Exemplary SIRP antibody CDR-H3 Sequences

CDR-H3	SEQ ID NO:
ARRGIWFGVGP	86
AREGIEGYYFYYGMDV	88
ARDKCSTTTCSFDY	89
WAAAGAFYI	92
SRVDSGSYPYYYDGLDV	93
ASSHYGSGSFPDSYGMDV	94
AKDGGSYYPPFDY	95
TRDPPPYDILTGYPFDY	96
AAYSGSYYYYGMDV	97
AKGSGSYYFDY	98
ARSRGNYFAMEY	99

Table 7: Exemplary SIRP antibody Light Chain CDR Triplets

CDR-L1	SEQ ID NO:	CDR-L2	SEQ ID NO:	CDR-L3	SEQ ID NO:
QSLLHGNGFNY	5	LGS	23	MQGLQTPRT	36
QGISGY	7	AAS	24	QQFTSDLIT	38
QDFSNY	8	AAS	24	QQYDNLPYT	39
NIGSKS	11	DDS	27	QVWDSSSDHYV	42
KLGDKY	12	HDD	28	QTWDSSTVV	43
KLGDRY	13	QDD	29	QAWDSSTAV	44
KLGDRY	13	QDT	30	QACDSSTAV	45
QDISSW	14	GAS	31	QEANSFPYT	46
QSVSSN	15	GAS	31	QQYNNWPYT	47
QSVSRN	16	GAS	31	QQYNNWPYT	47
QTVLNSSNNKNY	17	WAS	32	QQYYNTPPWT	48
QDINRY	18	RAN	33	LQYDEFPFT	49

Table 8: Exemplary SIRP antibody Heavy Chain CDR Triplets

CDR-H1	SEQ ID NO:	CDR-H2	SEQ ID NO:	CDR-H3	SEQ ID NO:
GGSISSSNW	54	IYHSGST	70	ARRGIWFGVGP	86
GGSISSSNW	54	IYHSGNT	72	AREGIEGYYFYYGMDV	88
DYSISSGYY	56	IYHSGNT	72	ARDKCSTTTCSFDY	89
GFTFSKFG	59	ISYDGNNK	75	WAAAGAFYI	92
GGSFSGYY	60	INHSGST	76	SRVDSGSYPYYYDGLDV	93
GGSFSTYY	61	INHSGST	76	ASSHYGSGSFPDSYGMDV	94
GFTFSSYA	62	ISGSGGDT	77	AKDGGSYYPPFDY	95

CDR-H1	SEQ ID NO:	CDR-H2	SEQ ID NO:	CDR-H3	SEQ ID NO:
GFTFSSYW	63	IHNDGSRT	78	TRDPPPYDILTGYPFDY	96
GFTFSSYA	62	ISGSGSST	79	AAYSGSYYYYGMDV	97
GFIFSNYG	64	ISYDGRNE	80	AKGSGSYYFDY	98
GYTFRNFG	65	IDTNTGEP	81	ARSRGNYFAMEY	99

Table 9: Exemplary SIRP antibody CDR Combinations, Antibodies 1, 3-4 and 7-15

Antibody No.	CDR-L1	CDR-L2	CDR-L3	CDR-H1	CDR-H2	CDR-H3
Antibody 1	QSLLHGNGFNY (SEQ ID NO: 5)	LGS (SEQ ID NO: 23)	MQGLQTPRT (SEQ ID NO: 36)	GGSISSSNW (SEQ ID NO: 54)	IYHSGST (SEQ ID NO: 70)	ARRGIWFGVGP (SEQ ID NO: 86)
Antibody 3	QGISGY (SEQ ID NO: 7)	AAS (SEQ ID NO: 24)	QQFTSDLIT (SEQ ID NO: 38)	GGSISSSNW (SEQ ID NO: 54)	IYHSGNT (SEQ ID NO: 72)	AREGIEGYYFYYGMDV (SEQ ID NO: 88)
Antibody 4	QDFSNY (SEQ ID NO: 8)	AAS (SEQ ID NO: 24)	QQYDNLPYT (SEQ ID NO: 39)	DYSISSGYY (SEQ ID NO: 56)	IYHSGNT (SEQ ID NO: 72)	ARDKCSTTTCSFDY (SEQ ID NO: 89)
Antibody 7	NIGSKS (SEQ ID NO: 11)	DDS (SEQ ID NO: 27)	QVWDSSSDHYV (SEQ ID NO: 42)	GFTFSKFG (SEQ ID NO: 59)	ISYDGNNK (SEQ ID NO: 75)	WAAAGAFYI (SEQ ID NO: 92)
Antibody 8	KLGDKY (SEQ ID NO: 12)	HDD (SEQ ID NO: 28)	QTWDSSTVV (SEQ ID NO: 43)	GGSFSGYY (SEQ ID NO: 60)	INHSGST (SEQ ID NO: 76)	SRVDSGSYPYYDGLDV (SEQ ID NO: 93)
Antibody 9	KLGDRY (SEQ ID NO: 13)	QDD (SEQ ID NO: 29)	QAWDSSTAV (SEQ ID NO: 44)	GGSFSTYY (SEQ ID NO: 61)	INHSGST (SEQ ID NO: 76)	ASSHYGSGSFPDSYGMDV (SEQ ID NO: 94)
Antibody 10	KLGDRY (SEQ ID NO: 13)	QDT (SEQ ID NO: 30)	QACDSSTAV (SEQ ID NO: 45)	GFTFSSYA (SEQ ID NO: 62)	ISGSGGDT (SEQ ID NO: 77)	AKDGGSYYPPFDY (SEQ ID NO: 95)
Antibody 11	QDISSW (SEQ ID NO: 14)	GAS (SEQ ID NO: 31)	QEANSFPYT (SEQ ID NO: 46)	GFTFSSYW (SEQ ID NO: 63)	IHNDGSRT (SEQ ID NO: 78)	TRDPPPYDILTGYPFDY (SEQ ID NO: 96)
Antibody 12	QSVSSN (SEQ ID NO: 15)	GAS (SEQ ID NO: 31)	QQYNNWPYT	GFTFSSYA (SEQ ID NO: 62)	ISGSGSST (SEQ ID NO: 79)	AAYSGSYYYYGMDV

Antibody No.	CDR-L1	CDR-L2	CDR-L3	CDR-H1	CDR-H2	CDR-H3
			(SEQ ID NO: 47)			(SEQ ID NO: 97)
Antibody 13	QSVSRN (SEQ ID NO: 16)	GAS (SEQ ID NO: 31)	QQYNNWPYT (SEQ ID NO: 47)	GFTFSSYA (SEQ ID NO: 62)	ISGSGSST (SEQ ID NO: 79)	AAYSGSYYYYGMDV (SEQ ID NO: 97)
Antibody 14	QTVLNSSNNKNY (SEQ ID NO: 17)	WAS (SEQ ID NO: 32)	QQYYNTPPWT (SEQ ID NO: 48)	GFIFSNYG (SEQ ID NO: 64)	ISYDGRNE (SEQ ID NO: 80)	AKGSGSYYFDY (SEQ ID NO: 98)
Antibody 15	QDINRY (SEQ ID NO: 18)	RAN (SEQ ID NO: 33)	LQYDEFPFT (SEQ ID NO: 49)	GYTFRNFG (SEQ ID NO: 65)	IDTNTGEP (SEQ ID NO: 81)	ARSRGNYFAMEY (SEQ ID NO: 99)

[00129] 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.

[00130] 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: 5, 7-8 or 11-18 as set forth in Table 1;

(b) any one of the CDR-L2 amino acid sequences of SEQ ID NOS: 23-24, or 27-33 as set forth in Table 2;

(c) any one of the CDR-L3 amino acid sequences of SEQ ID NOS: 36, 38-39 or 42-49 as set forth in Table 3;

(d) any one of the CDR-H1 amino acid sequences of SEQ ID NOS: 54, 56, or 59-65 as set forth in Table 4;

(e) any one of the CDR-H2 amino acid sequences of SEQ ID NOS: 70, 72, or 75-81 as set forth in Table 5; and/or

(f) any one of the CDR-H3 amino acid sequences of SEQ ID NOS: 86, 88-89 or 92-99 as set forth in Table 6.

[00131] 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: 5, 7-8, or 11-18;

(h) a CDR-L2 comprising any one of the amino acid sequences of SEQ ID NOs: 23-24, or 27-33; and

(i) a CDR-L3 comprising any one of the amino acid sequences of SEQ ID NOs: 36, 38-39, or 42-49.

[00132] 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: 54, 56, or 59-65;

(k) a CDR-H2 comprising any one of the amino acid sequences of SEQ ID NOs: 70, 72, or 75-81; and

(l) a CDR-H3 comprising any one of the amino acid sequences of SEQ ID NOs: 86, 88-89, or 92-99.

[00133] 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: 54, 56, or 59-65;

(n) a CDR-H2 comprising any one of the amino acid sequences of SEQ ID NOs: 70, 72, or 75-81; and

(o) a CDR-H3 comprising any one of the amino acid sequences of SEQ ID NOs: 86, 88-89, or 92-99.

[00134] 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: 5, 7-8, or 11-18;

(q) a CDR-L2 comprising any one of the amino acid sequences of SEQ ID NOs: 23-24, or 27-33; and

(r) a CDR-L3 comprising any one of the amino acid sequences of SEQ ID NOs: 36, 38-39, or 42-49.

[00135] 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: 5, SEQ ID NO: 23, and SEQ ID NO: 36;
b. SEQ ID NO: 7, SEQ ID NO: 24, and SEQ ID NO: 38;
c. SEQ ID NO: 8, SEQ ID NO: 24, and SEQ ID NO: 39;
d. SEQ ID NO: 11, SEQ ID NO: 27, and SEQ ID NO: 42;
e. SEQ ID NO: 12, SEQ ID NO: 28, and SEQ ID NO: 43;
f. SEQ ID NO: 13, SEQ ID NO: 29, and SEQ ID NO: 44;
g. SEQ ID NO: 13, SEQ ID NO: 30, and SEQ ID NO: 45;
h. SEQ ID NO: 14, SEQ ID NO: 31, and SEQ ID NO: 46;
i. SEQ ID NO: 15, SEQ ID NO: 31, and SEQ ID NO: 47;
j. SEQ ID NO: 16, SEQ ID NO: 31, and SEQ ID NO: 47;
k. SEQ ID NO: 17, SEQ ID NO: 32, and SEQ ID NO: 48; or
l. SEQ ID NO: 18, SEQ ID NO: 33, and SEQ ID NO: 49.

[00136] 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: 54, SEQ ID NO: 70, and SEQ ID NO: 86;
b. SEQ ID NO: 54, SEQ ID NO: 72, and SEQ ID NO: 88;
c. SEQ ID NO: 56, SEQ ID NO: 72, and SEQ ID NO: 89;
d. SEQ ID NO: 59, SEQ ID NO: 75, and SEQ ID NO: 92;
e. SEQ ID NO: 60, SEQ ID NO: 76, and SEQ ID NO: 93;
f. SEQ ID NO: 61, SEQ ID NO: 76, and SEQ ID NO: 94;
g. SEQ ID NO: 62, SEQ ID NO: 77, and SEQ ID NO: 95;
h. SEQ ID NO: 63, SEQ ID NO: 78, and SEQ ID NO: 96;
i. SEQ ID NO: 62, SEQ ID NO: 79, and SEQ ID NO: 97;
j. SEQ ID NO: 62, SEQ ID NO: 79, and SEQ ID NO: 97;
k. SEQ ID NO: 64, SEQ ID NO: 80, and SEQ ID NO: 98; or
l. SEQ ID NO: 65, SEQ ID NO: 81, and SEQ ID NO: 99.

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

a. SEQ ID NO: 5, SEQ ID NO: 23, SEQ ID NO: 36, SEQ ID NO: 54, SEQ ID NO: 70, and SEQ ID NO: 86;
b. SEQ ID NO: 7, SEQ ID NO: 24, SEQ ID NO: 38, SEQ ID NO: 54, SEQ ID NO: 72, and SEQ ID NO: 88;
c. SEQ ID NO: 8, SEQ ID NO: 24, SEQ ID NO: 39, SEQ ID NO: 56, SEQ ID NO: 72, and SEQ ID NO: 89;
d. SEQ ID NO: 11, SEQ ID NO: 27, SEQ ID NO: 42, SEQ ID NO: 59, SEQ ID NO: 75, and SEQ ID NO: 92;
e. SEQ ID NO: 12, SEQ ID NO: 28, SEQ ID NO: 43, SEQ ID NO: 60, SEQ ID NO: 76, and SEQ ID NO: 93;
f. SEQ ID NO: 13, SEQ ID NO: 29, SEQ ID NO: 44, SEQ ID NO: 61, SEQ ID NO: 76, and SEQ ID NO: 94;
g. SEQ ID NO: 13, SEQ ID NO: 30, SEQ ID NO: 45, SEQ ID NO: 62, SEQ ID NO: 77, and SEQ ID NO: 95;
h. SEQ ID NO: 14, SEQ ID NO: 31, SEQ ID NO: 46, SEQ ID NO: 63, SEQ ID NO: 78, and SEQ ID NO: 96;
i. SEQ ID NO: 15, SEQ ID NO: 31, SEQ ID NO: 47, SEQ ID NO: 62, SEQ ID NO: 79, and SEQ ID NO: 97;
j. SEQ ID NO: 16, SEQ ID NO: 31, SEQ ID NO: 47, SEQ ID NO: 62, SEQ ID NO: 79, and SEQ ID NO: 97;
k. SEQ ID NO: 17, SEQ ID NO: 32, SEQ ID NO: 48, SEQ ID NO: 64, SEQ ID NO: 80, and SEQ ID NO: 98; or
l. SEQ ID NO: 18, SEQ ID NO: 33, SEQ ID NO: 49, SEQ ID NO: 65, SEQ ID NO: 81, and SEQ ID NO: 99.

iv. Exemplary SIRP Antibodies - Variable Region Sequences

[00137] 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).

[00138] 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: 104, 106-107, and 110-118, 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: 123, 125-126, and 129-137, 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: 104, 106-107, and 110-118, or at least 80% sequence identity thereto and comprises a variable light chain comprising an amino acid sequence selected from SEQ ID NOS: 123, 125-126, and 129-137, or at least 80% sequence identity thereto.

[00139] In some embodiments, a SIRP antibody of the disclosure comprises the combination of VH/VL variable chain sequences of any one Antibodies 1, 3-4 and 7-15 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
1	QVQLQESGPGLVKPSGTLSLTCAVSGG SISSSNWWSWVRQPPGKGLEWIGEIY HSGSTNYNPSLKSRVTISVDKSKNQFSL KLSSVTAADTAVYYCARRGIWFGVGP WGQGTLVTVSS (SEQ ID NO: 104)	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHG NGFNYLDWYLQKPGQSPQLLIYLGSNRASG VPDRFTGSGSGTDFTLKISRVEAEDVGVYYC MQGLQTPRTFGQGTKVEIK (SEQ ID NO: 123)
3	QVQLQESGPGLVKPSGTLSLTCAVSGG SISSSNWWSWVRQPPGKGLEWIGEIY HSGNTNYNPSLKSRVTISVDKSKNQFS LKLSSVTAADTAVYYCAREGIEGYYFYY GMDVWGQGTTVTVSS (SEQ ID NO: 106)	DIQLTQSPSFLSASVGDRVTITCRASQGISGY LDWYQQKPGKAPKLLIYAASTLQRGVPSRFS GSGSGTDFNLTISSLQPEDFATYYCQQFTSD LITFGQGTRLEIK (SEQ ID NO: 125)
4	QVQLQESGPGLLKPSETLSLTCAVSDYS ISSGYYWGWIRQPPGKGLEWIGSIYHS GNTYYNPSLKSRVTILVDTSKNQFSLKL SSVTAADTAVYYCARDKCSTTTCSFDY WGQGTLVTVSS (SEQ ID NO: 107)	DIQMTQSPSSLSASVGDRVTITCQASQDFS NYLNWYQQKPGKAPKLLIYAASNLETGVPS RFSGSGSGTDFTFTISSLQPEDIAVYYCQQYD NLPYTFGQGTKLEIK (SEQ ID NO: 126)
7	QVQLVESGGGVVQPGRSLRLSCAASG FTFSKFGMHWVRQAPGKGLEWVAVI SYDGNNKYYTDSVKGRFTISRDNSRNT LYLQMDSVKPEDTAVYYSWAAAGAFY IWGQGTMVTVSS (SEQ ID NO: 110)	SYVLTQPPSVSVAPGQTARITCGGYNIGSKS VHWYQQKAGQAPVLVVYDDSGRPSGIPER LSGSKSGNTATLTISRVEAGDEADYYCQVW DSSSDHYVFGTGTKVTVL (SEQ ID NO: 129)
8	QVQLQQWGAGLLKPSETLSLTCAVYG GSFSGYYWSWIRQPPGKGLEWIGEIN	SSELTQPPSVSVSPGQTASITCSGDKLGDKY VYWYQQKPGQSPVLVIYHDDRRPAGIPERF

	HSGSTNFNPSLKSRVTISVDTSKNQFSL KLRSVTAADTAVYYCSRVDSGSYPYYD GLDVWGQGTTVTVSS (SEQ ID NO: 111)	AGSASGNTATLTISGTQAMDEADYYCQTW DSSTVVFGGGTKLTVL (SEQ ID NO: 130)
9	QVQLQQWGAGLLKPSETLSLTCAVYG GSFSTYYWNWIRQPPGKGLEWIGEIN HSGSTNYNPSLKSRVIISVDTSKNQFSL KLSSVTAADTAVYYCASSHYGSGSFPD SYGMDVWGQGTTVTVSA (SEQ ID NO: 112)	SYELTQSPSVSVSPGQTASITCSGDKLGDRY AWWYQQKPGQSPVLVIYQDDKRPSGIPER FSGSNSGNTATLTISGTQAMDEADYYCQA WDSSTAVFGGGTKLTVL (SEQ ID NO: 131)
10	EVQLLESGGGLVQPGGSLRLSCAASGF TFSSYAMSWVRQAPGKGLEWVSAISG SGGDTYYADSVKGRFTISRDNSKSTLYL QMNSLRAEDTAVYYCAKDGGSYYPPF DYWGQGTLVTVSS (SEQ ID NO: 113)	SYELTQPPSVSVSPGQTASITCSGDKLGDRY ACWYQQKPGQSPVLVIYQDTKRPSGIPERF SGSNSGNTATLTISGTQAMDEADYYCQACD SSTAVFGGGTKLTVL (SEQ ID NO: 132)
11	EVQLVESGGGLVQPGGSLRLSCAASGF TFSSYWMHWVRQAPGKGLVWVSRI HNDGSRTSYADSVKGRFTISRDNAKNT LYLQMSSLRAEDTAVYYCTRDPPPYDIL TGYPFDYWGQGTLVTVSS (SEQ ID NO: 114)	DIQMTQSPSSVSASVGDRVTITCRASQDISS WLAWFQQKPGKAPKLLIYGASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQEANS FPYTFGQGTKLEIK (SEQ ID NO: 133)
12	EVQVLESGGGLVQPGGSLRLSCAASGF TFSSYAMSWVRQAPGKGLEWVSAISG SGSSTHYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAAYSGSYYYYG MDVWGQGTTVTVSS (SEQ ID NO: 115)	EIVMTQSPATLSVSPGERATLSCRASQSVSS NLAWYQQKSGQAPRLLIYGASTRATGIPAR FSGSGSGTEFTLTISSLQSEDFAGYYCQQYN NWPYTFGQGTKLEIK (SEQ ID NO: 134)
13	EVQMLESGGGLVQPGGSLRLSCAASG FTFSSYAMSWVRQAPGKGLEWVSAIS GSGSSTHYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCAAYSGSYYYY GMDVWGQGTTVTVSS (SEQ ID NO: 116)	EIVMTQSPATLSVSPGERATLSCRASQSVSR NLAWYQQKSGQAPRLLIYGASTRATGIPAR FSGSGSGTEFTLTISSLQSEDFAGYYCQQYN NWPYTFGQGTKLEIK (SEQ ID NO: 135)
14	QVQLVESGGGVVQPGRSLRLSCVASG FIFSNYGMHWVRQAPGKGLEWVAVI SYDGRNEDHVDSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKGSGSYY FDYWGQGTLVTVSS (SEQ ID NO: 117)	DIVLTQSPDSLAVSLGERATINCKSSQTVLNS SNNKNYLAWYQQKPGQPPKLLIYWASIRES GVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CQQYYNTPPWTFGQGTKVEIK (SEQ ID NO: 136)
15	QIQLVQSGPELKKPGETVKISCKGSGYT FRNFGMNWVKQAPGMGLKWMVWI DTNTGEPTYAEEFKGRFAFSLETSASTA YLQINNLKNEDTATYFCARSRGNYFA MEYWGQGTSVTVSS (SEQ ID NO: 118)	DIKMTQSPSSMYASLGERVTVTCKASQDIN RYLSWFQQKPGKSPKTLIYRANRLVDGVPSR FSGSGSGQDYSLTISSLEYEDMGFYYCLQYD EFPFTFGSGTKLEIK (SEQ ID NO: 137)

[00140] 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: 104 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: 123, 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: 104, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 123. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 5, 23 and 36, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 54, 70 and 86.

[00141] 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: 106 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: 125, 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: 106, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 125. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 7, 24 and 38, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 54, 72 and 88.

[00142] 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: 107 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: 126, 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: 107, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 126. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 8, 24 and 39, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 56, 72 and 89.

[00143] 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: 110 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: 129, 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: 110, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 129. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 11, 27 and 42, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 59, 75 and 92.

[00144] 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: 111 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: 130, 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: 111, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 130. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 12, 28 and 43, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 560, 76 and 93.

[00145] 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: 112 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: 131, 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: 112, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 131. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 13, 29 and 44, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 61, 76 and 94.

[00146] 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: 113 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: 132, 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: 113, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 132. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 13, 30 and 45, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 62, 77 and 95.

[00147] 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: 114 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: 133, 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: 114, and the light chain variable domain of

the antibody comprises the amino acid sequence of SEQ ID NO: 133. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 14, 31 and 46, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 63, 78 and 96.

[00148] 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: 115 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: 134, 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: 115, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 134. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 15, 31 and 47, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 62, 79 and 97.

[00149] 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: 116 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: 135, 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: 116, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 135. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 16, 31 and 47, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 62, 79 and 97.

[00150] 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: 117 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: 136, 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: 117, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 136. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 17, 32 and 48, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 64, 80 and 98.

[00151] 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: 118 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: 137, 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: 118, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 137. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 18, 33 and 49, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 65, 81 and 99.

[00152] 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 1	SEQ ID NO: 104/SEQ ID NO: 123	Rat IgG2b Fc
Antibody 3	SEQ ID NO: 106/SEQ ID NO: 125	Rat IgG2b Fc
Antibody 4	SEQ ID NO: 107/SEQ ID NO: 126	Rat IgG2b Fc
Antibody 7	SEQ ID NO: 110/SEQ ID NO: 129	Rat IgG2b Fc
Antibody 8	SEQ ID NO: 111/SEQ ID NO: 130	Rat IgG2b Fc

Antibody No.	VH/VL Pair Amino Acid	Fc
Antibody 9	SEQ ID NO: 112/SEQ ID NO: 131	Rat IgG2b Fc
Antibody 10	SEQ ID NO: 113/SEQ ID NO: 132	Rat IgG2b Fc
Antibody 11	SEQ ID NO: 114/SEQ ID NO: 133	Rat IgG2b Fc
Antibody 12	SEQ ID NO: 115/SEQ ID NO: 134	Rat IgG2b Fc
Antibody 13	SEQ ID NO: 116/SEQ ID NO: 135	Rat IgG2b Fc
Antibody 14	SEQ ID NO: 117/SEQ ID NO: 136	Rat IgG2b Fc
Antibody 15	SEQ ID NO: 118/SEQ ID NO: 137	Mouse IgG2a Fc
Antibody 21	SEQ ID NO: 110/SEQ ID NO: 129	Human IgG1 Fc
Antibody 23	SEQ ID NO: 104/SEQ ID NO: 123	Human IgG1 Fc
Antibody 24	SEQ ID NO: 106/SEQ ID NO: 125	Human IgG1 Fc
Antibody 25	SEQ ID NO: 116/SEQ ID NO: 135	Human IgG1 Fc
Antibody 26	SEQ ID NO: 110/SEQ ID NO: 129	Human IgG1 Fc with increased affinity for FcγR
Antibody 28	SEQ ID NO: 104/SEQ ID NO: 123	Human IgG1 Fc with increased affinity for FcγR
Antibody 29	SEQ ID NO: 116/SEQ ID NO: 135	Human IgG1 Fc with increased affinity for FcγR
Antibody 30	SEQ ID NO: 104/SEQ ID NO: 123	Human IgG1 Fc with increased affinity for FcγR + extended half life
Antibody 31	SEQ ID NO: 116/SEQ ID NO: 135	Human IgG1 Fc with increased affinity for FcγR + extended half life
Antibody 32	SEQ ID NO: 106/SEQ ID NO: 125	Human IgG1 Fc with increased affinity for FcγR

B. Generation of SIRP Antibodies

[00153] 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.

[00154] 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.

[00155] 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.

[00156] 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: 142, 144-145, and 148-156, 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: 161, 163-164, and 167-175, 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: 142, 144-145, and 148-156, or at least 80% sequence identity thereto, and a variable light chain nucleic acid sequence selected from SEQ ID NOS: 161, 163-164, 167-175, 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
1	CAGGTGCAGCTGCAGGAGTCGGGCCC AGGACTGGTGAAGCCTTCGGGGACCCT GTCCCTCACCTGCGCTGTCTCTGGTGG CTCCATCAGCAGTAGTAACTGGTGGAG TTGGGTCCGCCAGCCCCCAGGGAAGG GGCTGGAATGGATTGGGGAAATCTATC ATAGTGGGAGCACCAACTACAACCCGT CCCTCAAGAGTCGAGTCACCATATCAG TAGACAAGTCCAAGAACCAGTTCTCCC TGAAGCTGAGTTCTGTGACCGCCGCGG ACACGGCCGTGTATTACTGTGCGAGAA GGGGGATATGGTTCGGGGTCGGTCCC TGGGGCCAGGGAACCCTGGTCACCGTC TCCTCA (SEQ ID NO: 142)	GATATTGTGATGACTCAGTCTCCACTC TCCCTGCCCGTCACCCCTGGAGAGCC GGCCTCCATCTCCTGCAGGTCTAGTCA GAGCCTCCTACATGGTAATGGATTCA ACTATTTGGATTGGTACCTGCAGAAG CCAGGGCAGTCTCCACAGCTCCTGAT CTATTTGGGTTCTAATCGGGCCTCCGG GGTCCCTGACAGGTTCACTGGCAGTG GATCAGGCACAGATTTTACACTGAAA ATCAGCAGAGTGGAGGCTGAGGATG TTGGGGTTTATTACTGCATGCAAGGTC TACAAACTCCTCGGACGTTCGGCCAA GGGACCAAGGTGGAAATCAAA (SEQ ID NO: 161)
3	CAGGTGCAGCTGCAGGAGTCGGGCCC AGGACTGGTGAAGCCTTCGGGGACCCT GTCTCTCACCTGCGCTGTCTCTGGTGGC TCCATCAGCAGTAGTAACTGGTGGAGT TGGGTCCGCCAGCCCCCAGGGAAGGG GCTGGAGTGGATTGGGGAAATCTATCA TAGTGGGAACACCAACTACAACCCGTC CCTCAAGAGTCGAGTCACCATATCAGT AGACAAGTCCAAGAACCAGTTCTCCCT GAAGCTGAGCTCTGTGACCGCCGCGG ACACGGCCGTGTATTACTGTGCGAGAG AGGGTATAGAGGGGTACTACTTCTACT ACGGTATGGACGTCTGGGGCCAAGGG ACCACGGTCACCGTCTCCTCA (SEQ ID NO: 144)	GACATCCAGTTGACCCAGTCTCCATCC TTCCTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGCCGGGCCAGTC AGGGCATTAGCGGTTATTTAGACTGG TATCAGCAAAAACCAGGGAAAGCCCC TAAGCTCCTGATCTATGCTGCATCCAC TTTACAAAGAGGGGTCCCATCAAGGT TCAGCGGCAGTGGATCTGGGACAGAT TTCAATCTCACAATCAGCAGCCTGCAG CCTGAAGATTTTGCAACTTATTACTGT CAACAGTTTACTAGTGACCTCATCACC TTCGGCCAAGGGACACGACTGGAGAT TAAA (SEQ ID NO: 163)
4	CAGGTGCAGCTGCAGGAGTCGGGCCC AGGACTGCTGAAGCCTTCGGAGACCCT GTCCCTCACCTGCGCTGTCTCTGATTAC TCCATCAGCAGTGGTTACTACTGGGGC TGGATCCGGCAGCCCCCGGGGAAGGG GCTGGAGTGGATTGGGAGTATCTATCA TAGTGGGAATACCTATTATAACCCGTC CCTCAAGAGTCGAGTCACCATATTAGT AGACACGTCCAAGAACCAGTTCTCCCT GAAGCTGAGCTCTGTGACCGCCGCAGA CACGGCCGTGTATTACTGTGCGAGAGA TAAATGTAGTACTACAACCTGCTCCTTT GACTACTGGGGCCAGGGAACCCTGGT CACCGTCTCCTCA (SEQ ID NO: 145)	GACATCCAGATGACCCAGTCTCCATCC TCCCTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGCCAGGCGAGTC AGGACTTTAGCAACTATTTAAATTGGT ATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTACGCTGCATCCAAT TTGGAAACAGGGGTCCCATCGAGGTT CAGTGGAAGTGGATCTGGGACAGATT TTACTTTCACCATCAGCAGCCTGCAGC CTGAAGATATTGCAGTATATTACTGTC AACAGTATGATAATCTCCCGTACACTT TTGGCCAGGGGACCAAGCTGGAGATC AAA (SEQ ID NO: 164)
7	CAGGTGCAGCTGGTGGAGTCTGGGGG AGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATT CACCTTCAGTAAATTTGGCATGCACTG	TCCTATGTGCTGACTCAGCCACCCTCG GTGTCAGTGGCCCCAGGACAGACGGC CAGGATTACCTGTGGGGGATACAACA TTGGAAGTAAAAGTGTGCACTGGTAC

Antibody No.	Variable Heavy Chain Nucleic Acid Sequence	Variable Light Chain Nucleic Acid Sequence
	GGTCCGCCAGGCTCCAGGCAAGGGGC TGGAGTGGGTGGCAGTTATATCATATG ATGGAAATAATAAATACTATACAGACT CCGTGAAGGGCCGATTCACCATCTCCA GAGACAATTCCAGGAACACGCTGTATC TGCAAATGGACAGCGTGAAACCTGAG GACACGGCTGTGTACTATTCCTGGGCA GCAGCTGGTGCTTTTTATATCTGGGGC CAAGGGACAATGGTCACCGTCTCTTCA (SEQ ID NO: 148)	CAGCAGAAGGCAGGCCAGGCCCCTGT GCTGGTCGTCTATGATGATAGCGGCC GGCCCTCAGGGATCCCTGAGCGATTG TCTGGCTCCAAGTCTGGGAACACGGC CACCCTGACCATCAGCAGGGTCGAAG CCGGGGATGAGGCCGACTATTACTGT CAGGTGTGGGATAGTAGTAGTGATCA TTATGTCTTCGGAACTGGGACCAAGG TCACCGTCCTA (SEQ ID NO: 167)
8	CAGGTGCAGCTACAGCAGTGGGGCGC AGGACTGTTGAAGCCTTCGGAGACCCT GTCCCTCACCTGCGCTGTCTATGGTGG GTCCTTCAGTGGTTACTACTGGAGCTG GATTCGCCAGCCCCCAGGGAAGGGGC TGGAGTGGATTGGGGAAATCAATCATA GTGGAAGCACCAACTTCAACCCGTCCC TCAAGAGTCGAGTCACCATATCAGTAG ACACGTCCAAGAACCAGTTCTCCCTGA AGCTGAGGTCTGTGACCGCCGCGGAC ACGGCTGTGTATTACTGTTCGAGAGTC GATAGTGGGAGCTATCCCTACTACGAC GGTTTGGACGTCTGGGGCCAAGGGAC CACGGTCACCGTCTCCTCA (SEQ ID NO: 149)	TCCTCTGAATTGACTCAGCCACCCTCA GTGTCCGTGTCCCCAGGACAGACAGC CAGCATCACCTGCTCTGGAGATAAATT GGGGGATAAATATGTTTACTGGTATC AACAGAAGCCAGGCCAGTCCCCTGTG TTGGTCATCTATCATGATGATCGGCG GCCCGCTGGGATCCCTGAGCGATTCG CTGGCTCCGCTTCTGGGAACACAGCC ACTCTGACCATCAGCGGGACCCAGGC TATGGATGAGGCTGACTATTACTGTC AGACGTGGGACAGCAGCACTGTGGTT TTCGGCGGAGGGACCAAGCTGACCGT CCTA (SEQ ID NO: 168)
9	CAGGTGCAGCTACAGCAGTGGGGCGC AGGACTGTTGAAGCCTTCGGAGACCCT GTCCCTCACCTGCGCTGTCTATGGTGG GTCCTTCAGTACTTACTACTGGAACTGG ATCCGCCAGCCCCCAGGGAAGGGGCT GGAGTGGATTGGGGAAATCAATCATA GTGGAAGCACCAACTACAACCCGTCCC TCAAGAGTCGAGTCATCATATCAGTAG ACACGTCCAAGAACCAGTTCTCCCTGA AGCTGAGCTCTGTGACCGCCGCGGACA CGGCTGTGTATTACTGTGCGAGCAGTC ATTATGGTTCGGGGAGTTTTCCCGACT CCTACGGTATGGACGTCTGGGGCCAAG GGACCACGGTCACCGTCTCCGCA (SEQ ID NO: 150)	TCCTATGAATTGACTCAGTCACCCTCA GTGTCCGTGTCCCCAGGACAGACAGC CAGCATCACCTGCTCTGGAGATAAATT GGGGGATAGATATGCTTGGTGGTATC AGCAGAAGCCAGGCCAGTCCCCTGTG CTGGTCATCTATCAAGATGACAAGCG GCCCTCAGGGATCCCTGAGCGATTCT CTGGCTCCAACTCTGGGAACACAGCC ACTCTGACCATCAGCGGGACCCAGGC TATGGATGAGGCTGACTATTACTGTC AGGCGTGGGACAGCAGCACTGCGGT ATTCGGCGGAGGGACCAAGCTGACC GTCCTA (SEQ ID NO: 169)
10	GAGGTGCAGCTGTTGGAGTCTGGGGG AGGCTTGGTACAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATT CACGTTTAGCAGCTATGCCATGAGCTG GGTCCGCCAGGCTCCAGGGAAGGGGC TGGAGTGGGTCTCAGCTATTAGTGGTA GTGGTGGTGACACTTACTACGCAGACT	TCCTATGAGCTGACTCAGCCACCCTCA GTGTCCGTGTCCCCAGGACAGACAGC CAGCATCACCTGCTCTGGAGATAAATT GGGGGATAGATATGCTTGCTGGTATC AGCAGAAGCCAGGCCAGTCCCCTGTA CTGGTCATCTATCAAGATACCAAGCG GCCCTCAGGGATCCCTGAGCGATTCT

Antibody No.	Variable Heavy Chain Nucleic Acid Sequence	Variable Light Chain Nucleic Acid Sequence
	CCGTGAAGGGCCGGTTCACCATCTCCA GAGACAATTCCAAGAGCACGCTGTATC TGCAAATGAACAGCCTGAGAGCCGAG GACACGGCCGTATATTACTGTGCGAAA GACGGTGGGAGCTACTACCCCCCCTTT GACTACTGGGGCCAGGGAACCCTGGT CACCGTCTCCTCA (SEQ ID NO: 151)	CTGGCTCCAACTCTGGGAACACAGCC ACTCTGACCATCAGCGGGACCCAGGC TATGGATGAGGCTGACTATTACTGTC AGGCGTGCGACAGCAGCACTGCGGT GTTCGGCGGAGGGACCAAGCTGACC GTCCTA (SEQ ID NO: 170)
11	GAGGTGCAGCTGGTGGAGTCCGGGGG AGGCTTAGTTCAGCCTGGGGGGTCCCT GAGACTCTCTTGTGCAGCCTCTGGATT CACCTTCAGTAGCTACTGGATGCACTG GGTCCGCCAAGCTCCAGGGAAGGGGC TGGTGTGGGTCTCACGTATTCATAATG ATGGGAGTAGAACAAGTTACGCGGAC TCCGTGAAGGGCCGATTCACTATCTCC AGAGACAACGCCAAGAACACGCTGTAT CTGCAAATGAGCAGTCTGCGAGCCGA GGACACGGCTGTGTATTACTGTACAAG AGATCCCCCTCCTTACGATATTTTGACT GGTTACCCCTTTGACTACTGGGGCCAG GGAACCCTGGTCACCGTCTCCTCA (SEQ ID NO: 152)	GACATCCAGATGACCCAGTCTCCGTCT TCCGTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGTCGGGCGAGTC AGGATATTAGCAGCTGGTTAGCCTGG TTTCAGCAGAAACCAGGGAAAGCCCC TAAGCTCCTGATCTATGGTGCATCCAG TTTGCAAAGTGGGGTCCCATCAAGGT TCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAG CCTGAAGATTTTGCAACTTACTATTGT CAAGAGGCTAACAGTTTCCCGTATACT TTTGGCCAGGGGACCAAGCTGGAGAT CAAA (SEQ ID NO: 171)
12	GAGGTGCAGGTGTTGGAGTCTGGGGG AGGCTTGGTACAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATT CACCTTTAGCAGCTATGCCATGAGCTG GGTCCGCCAGGCTCCAGGGAAGGGGC TGGAGTGGGTCTCAGCTATTAGTGGTA GTGGTAGTAGCACACACTACGCAGACT CCGTGAAGGGCCGGTTCACCATCTCCA GAGACAATTCCAAGAACACGCTGTATC TGCAAATGAACAGCCTGAGAGCCGAG GACACGGCCGTATATTACTGTGCGGCG TATAGTGGGAGCTACTACTACTATGGA ATGGACGTCTGGGGACAAGGGACCAC GGTCACCGTCTCCTCA (SEQ ID NO: 153)	GAAATAGTGATGACGCAGTCTCCAGC CACCCTGTCTGTGTCTCCAGGGGAAA GAGCCACCCTCTCCTGCAGGGCCAGT CAGAGTGTTAGCAGCAACTTAGCCTG GTACCAGCAGAAATCTGGCCAGGCTC CCAGGCTCCTCATCTATGGTGCATCCA CCAGGGCCACTGGTATCCCAGCCAGG TTCAGTGGCAGTGGGTCTGGGACAGA GTTCACTCTCACCATCAGCAGCCTGCA GTCTGAAGATTTTGCAGGTTATTACTG CCAGCAGTATAATAACTGGCCGTACA CTTTTGGCCAGGGGACCAAGCTGGAG ATCAAA (SEQ ID NO: 172)
13	GAGGTGCAGATGTTGGAGTCTGGGGG AGGCTTGGTTCAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATT CACCTTTAGCAGCTATGCCATGAGCTG GGTCCGCCAGGCTCCAGGGAAGGGGC TGGAGTGGGTCTCAGCTATTAGTGGTA GTGGTAGTAGCACACACTACGCAGACT CCGTGAAGGGCCGGTTCACCATCTCCA GAGACAATTCCAAGAACACGCTGTATC TGCAAATGAACAGCCTGAGAGCCGAG	GAAATAGTGATGACGCAGTCTCCAGC CACCCTGTCTGTGTCTCCAGGGGAAA GAGCCACCCTCTCCTGCAGGGCCAGT CAGAGTGTTAGTAGGAATTTAGCCTG GTACCAGCAGAAATCTGGCCAGGCTC CCAGGCTCCTCATCTATGGTGCATCCA CCAGGGCCACTGGTATCCCAGCCAGG TTCAGTGGCAGTGGGTCTGGGACAGA GTTCACTCTCACCATCAGCAGCCTGCA GTCTGAAGATTTTGCAGGTTATTACTG

Antibody No.	Variable Heavy Chain Nucleic Acid Sequence	Variable Light Chain Nucleic Acid Sequence
	GACACGGCCGTTTATTACTGTGCGGCG TATAGTGGGAGCTACTACTACTATGGA ATGGACGTCTGGGGACAGGGGACCAC GGTCACCGTCTCCTCA (SEQ ID NO: 154)	CCAGCAGTATAATAACTGGCCGTACA CTTTTGGCCAGGGGACCAAGCTGGAG ATCAAA (SEQ ID NO: 173)
14	CAGGTGCAGCTGGTGGAGTCTGGGGG AGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGTAGCCTCTGGATT CATCTTCAGTAACTATGGCATGCACTG GGTCCGCCAGGCTCCAGGCAAGGGGC TGGAGTGGGTGGCAGTTATATCATATG ATGGAAGAAATGAAGACCATGTAGAC TCCGTGAAGGGCCGATTCACCATCTCC AGAGACAATTCCAAGAACACGCTGTAT CTGCAAATGAACAGCCTGAGAGCTGA GGACACGGCTGTATATTACTGTGCGAA AGGGTCGGGGAGCTACTACTTTGACTA CTGGGGCCAGGGAACCCTGGTCACCGT CTCCTCA (SEQ ID NO: 155)	GACATCGTGCTGACCCAGTCTCCAGA CTCCCTGGCTGTGTCTCTGGGCGAGA GGGCCACCATCAACTGCAAGTCCAGC CAGACTGTTTTAAACAGCTCCAACAAT AAGAACTACCTAGCTTGGTACCAGCA GAAACCAGGACAGCCTCCTAAGCTGC TCATTTACTGGGCATCTATCCGGGAAT CCGGGGTCCCTGACCGATTCAGTGGC AGCGGGTCTGGGACAGATTTCACTCT CACCATCAGCAGCCTGCAGGCTGAAG ATGTGGCAGTTTATTACTGTCAGCAAT ATTATAATACTCCTCCGTGGACGTTCG GCCAAGGGACCAAGGTGGAAATCAA A (SEQ ID NO: 174)
15	CAGATCCAGTTGGTGCAGTCTGGACCT GAGCTGAAGAAGCCTGGAGAGACAGT CAAGATCTCCTGCAAGGGTTCTGGGTA TACCTTCAGAAACTTTGGAATGAATTG GGTGAAGCAGGCTCCAGGAATGGGTT TAAAGTGGATGGTGTGGATAGACACC AACACTGGAGAGCCAACATATGCTGAA GAGTTCAAGGGACGGTTTGCCTTCTCT TTGGAAACCTCTGCCAGCACTGCCTATT TGCAGATCAACAACCTCAAAAATGAGG ACACGGCTACATATTTCTGTGCAAGAT CGAGAGGTAACTACTTTGCTATGGAGT ATTGGGGGCAAGGAACCTCAGTCACC GTCTCCTCA (SEQ ID NO: 156)	GACATCAAGATGACCCAGTCTCCATCT TCCATGTATGCATCTCTAGGAGAGAG AGTCACTGTCACTTGCAAGGCGAGTC AGGACATTAATCGCTATTTAAGCTGGT TCCAGCAGAAACCAGGGAAATCTCCT AAGACCCTGATCTATCGTGCAAACAG ATTGGTAGATGGGGTCCCATCAAGGT TCAGTGGCAGTGGATCTGGGCAAGAT TATTCTCTCACCATCAGCAGCCTGGAG TATGAAGATATGGGATTTTATTATTGT CTACAGTATGATGAGTTTCCATTCACG TTCGGCTCGGGGACAAAGTTGGAAAT AAAA (SEQ ID NO: 175)

[00157] 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.

[00158] In some embodiments, the heavy chain variable domain of the SIRP antibodies of the disclosure are encoded by a nucleic acid by the nucleic acid sequence of SEQ ID NO: 142, 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 the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 161, 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: 142, 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: 161, 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: 142, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 161.

[00159] 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: 144, 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 the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 163, 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: 144, 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: 163, 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: 144, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 163.

[00160] 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: 145, 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 the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 164, 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: 145, 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: 164, 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: 145, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 164.

[00161] 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: 148, 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: 167, 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: 148, 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: 167, 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: 148, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 167.

[00162] 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: 149, 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: 168, 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: 149, 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: 168, 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: 149, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 168.

[00163] 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: 150, 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: 169, 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: 150, 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: 169, 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: 150, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 169.

[00164] 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: 151, 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: 170, 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: 151, 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: 170 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: 151, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 170.

[00165] 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: 152, 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: 171, 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: 152, 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: 171, 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: 152, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 171.

[00166] 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: 153, 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: 172, 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: 153, 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: 172, 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: 153, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 172.

[00167] 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: 154, 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: 173, 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: 154, 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: 173, 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: 154, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 173.

[00168] 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: 155, 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: 174, 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: 155, 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: 174, 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: 155, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 174.

[00169] 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: 156, 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: 175, 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: 156, 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: 175, 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: 156, and the light chain variable domain of the antibody is encoded by the nucleic acid sequence of SEQ ID NO: 175.

[00170] 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.

[00171] 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

[00172] Provided herein are methods of inducing cell depletion, the method comprising contacting the cell with any of the Fc containing SIRP antibodies of the disclosure. 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.

[00173] In some embodiments, the cells are SIRPγ-expressing cells. In some embodiments, the cells comprise a first population of SIRPγ-expressing cells, and a second population of SIRPα- and/or SIRPβ1-expressing cells. In some embodiments, the cells comprise a first population of

SIRPγ-expressing cells, second population of SIRPα-expressing cells, and a third population of SIRPβ1-expressing cells.

[00174] In some embodiments, the SIRPγ-expressing cells comprise lymphocytes. In some embodiments, the lymphocytes comprise B cells, T cells or natural killer (NK) cells. In some embodiments, the SIRPγ-expressing cell is a T cell. In some embodiments, the T cell is a cytotoxic T cell, helper T cell, a memory T cell, a regulatory T cell, a natural killer T cell, a mucosal associated invariant T cell or a gamma delta T cell. In some embodiments, the SIRPγ-expressing cell is an NK cell. In some embodiments, the SIRPγ-expressing cell is an activated T cell or an activated NK cell. In some embodiments, the SIRPγ-expressing cell is a fibroblast. In some embodiments, the SIRPγ-expressing cell is not a myeloid cell. Markers for identifying T cells, NK cells, and B cells, as well as specific populations of T cells, will be known to persons of ordinary skill in the art. For example, cytotoxic T cells express CD8, helper T cells express CD4, regulatory T cells express CD4 as well as additional markers such as CTLA-4, CCR4 or CXCR4, and memory T cells express CD8, as well as CD95. B cells express IgM and CD19, and activated B cells express CD19, CD25 and CD30. NK cells can be identified based on high CD56 expression.

[00175] 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, or monocytes. In some embodiments, the SIRPα-expressing 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.

[00176] In some embodiments, the SIRPβ1-expressing cells are myeloid cells. In some embodiments, the SIRPβ1-expressing cells are granulocytes, for example eosinophils or neutrophils. In some embodiments, the SIRPβ1-expressing cells are monocytes. In some embodiments, the monocytes are classical, intermediate, non-classical, or a combination thereof. In some embodiments, the SIRPβ1-expressing cells are macrophages. In some embodiments, the SIRPβ1-expressing cells are Kupffer cells or Hofbauer cells. In some embodiments, the SIRPβ1-expressing cells are dendritic cells. In some embodiments, the SIRPβ1-expressing cells are alveolar cells.

[00177] In some embodiments, the depleted cells comprise lymphocytes. In some embodiments, for example those embodiments where the antibody is specific to SIRPγ and SIRPα and/or SIRPβ1, the depleted cells comprise lymphocytes and at least one other cell type. In some embodiments, the depleted cells comprise lymphocytes and myeloid cells. In some embodiments, the depleted cells comprise lymphocytes and granulocytes, monocytes and/or dendritic cells. In some embodiments, cell depletion is antibody dose-dependent. Exemplary antibodies of the disclosure that induce cell depletion include Antibodies 23, 25, and 28-31, referring to Table 11.

[00178] Also provided herein are methods of depleting a population of cells in a subject, comprising administering to a subject any of the Fc containing SIRP antibodies of the disclosure. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, and 28-31, referring to Table 11. 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 SIRPγ-expressing cells. In some embodiments, the SIRPγ-expressing cells comprise lymphocytes. In some embodiments, the lymphocytes comprise B cells, T cells or NK cells. In some embodiments, the cells further 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, but are depleted by the SIRP antibodies of the disclosure. 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, basophils 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 cells are circulating cells. In some embodiments, the cell depletion is antibody dose-dependent.

[00179] 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%. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, 28, and 31-32, referring to Table 11.

[00180] 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%. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, 25, and 28-31, referring to Table 11.

[00181] 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%. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, 25, and 28-32, referring to Table 11.

[00182] In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPγ-expressing lymphocytes 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%.

[00183] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPγ-expressing lymphocytes *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%.

[00184] In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of SIRPγ-expressing lymphocytes *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%.

[00185] In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPγ-expressing T 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%.

[00186] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPγ-expressing T 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%.

[00187] In some embodiments, SIRP antibodies of the disclosure induce ADCC and/or ADCP of SIRPγ-expressing T 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%.

[00188] In some embodiments, SIRP antibodies of the disclosure induce ADCC of SIRPγ-expressing NK 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%.

[00189] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPγ-expressing NK 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%.

[00190] In some embodiments, SIRP antibodies of the disclosure induce ADCC and/or ADCP of SIRPγ-expressing NK cells *in vitro*. In some embodiments, the ADCC and 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%.

[00191] In some embodiments, SIRP antibodies bind SIRPα and also induce ADCC of SIRPα-expressing 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%.

[00192] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC of SIRPα-expressing myeloid cells *in vitro*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, 28, and 31-32, referring to Table 11. 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%.

[00193] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCP of SIRPα-expressing myeloid cells *in vitro*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, 25, and 28-31, referring to Table 11. 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%.

[00194] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCP and ADCC of SIRPα-expressing myeloid cells *in vitro*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, 25, and 28-32, referring to Table 11. 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%.

[00195] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC of SIRPα-expressing monocyte cells *in vitro*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, 28, 31-32, referring to Table 11. 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%.

[00196] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCP of SIRPα-expressing monocyte cells *in vitro*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, 25, and 28-31, referring to Table 11. 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%.

[00197] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC and ADCP of SIRPα-expressing monocyte cells *in vitro*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, 25, and 28-32, referring to Table 11. 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%.

[00198] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC of SIRPα-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%.

[00199] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCP of SIRPα-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%.

[00200] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC and ADCP of SIRPα-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%.

[00201] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC of SIRPα-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%.

[00202] In some embodiments, SIRP antibodies of the disclosure induce ADCP of SIRPα-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%.

[00203] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC and ADCP of SIRPα-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%.

[00204] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC of SIRPα-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%.

[00205] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCP of SIRPα-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%.

[00206] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC and ADCP of SIRPα-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%.

[00207] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also 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%.

[00208] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also 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%.

[00209] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also 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%.

[00210] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC of SIRPα-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%.

[00211] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCP of SIRPα-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%.

[00212] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC and ADCP of SIRPα-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%.

[00213] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCC of SIRPα-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%.

[00214] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCP of SIRPα-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%.

[00215] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce ADCP and ADCC of SIRPα-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%.

[00216] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also 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%.

[00217] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also 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%.

[00218] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also 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%.

[00219] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce ADCC and/or ADCP of SIRPβ1-expressing 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%.

[00220] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce ADCC and/or ADCP of 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%.

[00221] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce ADCC and/or ADCP of SIRPβ1-expressing granulocytes *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, the granulocytes are eosinophils, neutrophils or a combination thereof.

[00222] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce ADCC and/or ADCP of SIRPβ1-expressing monocytes *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, the monocytes are classical, intermediate, non-classical, or a combination thereof.

[00223] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce ADCC and/or ADCP of 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%.

[00224] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce ADCC and/or ADCP of 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%.

[00225] 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, SIRP antibodies of the disclosure induce ADCC of lymphocytes *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCP of lymphocytes *in vitro*. In some embodiments, SIRP antibodies of the disclosure induce ADCC and ADCP of lymphocytes *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%.

[00226] 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%.

[00227] 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%.

[00228] 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%.

[00229] 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%. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, and 28-31, referring to Table 11.

[00230] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPγ-expressing 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%.

[00231] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPγ-expressing lymphocytes *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%.

[00232] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPγ-expressing T 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%.

[00233] In some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of SIRPγ-expressing NK 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%.

[00234] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing myeloid cells *in vivo*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, and 28-31, referring to Table 11. 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%.

[00235] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing monocyte cells *in vivo*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, and 28-31, referring to Table 11. 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%.

[00236] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing neutrophils *in vivo*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, and 28-31, referring to Table 11. 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%.

[00237] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing eosinophils *in vivo*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, and 28-31, referring to Table 11. 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%.

[00238] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-expressing basophils *in vivo*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, and 28-31, referring to Table 11. 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%.

[00239] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also 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. lymphocytes). Accordingly, in some embodiments, SIRP antibodies of the disclosure induce cell depletion (e.g. ADCC and/or ADCP) of lymphocytes *in vivo*. Exemplary antibodies of the disclosure that exhibit such an effect include Antibodies 23, and 28-31, referring to Table 11. 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%.

[00240] In some embodiments, SIRP antibodies of the disclosure induce are also specific to SIRPα and also cell depletion (e.g. ADCC and/or ADCP) of SIRPα-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%.

[00241] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-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%.

[00242] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPα-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%.

[00243] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPα and also 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%.

[00244] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPβ1-expressing 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%.

[00245] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce cell depletion (e.g. ADCC and/or ADCP) of 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%.

[00246] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPβ1-expressing granulocytes 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%. In some embodiments, the granulocytes comprise eosinophils, neutrophils or a combination thereof.

[00247] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce cell depletion (e.g. ADCC and/or ADCP) of SIRPβ1-expressing monocytes 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%.

[00248] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce cell depletion (e.g. ADCC and/or ADCP) of 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%.

[00249] In some embodiments, SIRP antibodies of the disclosure are also specific to SIRPβ1 and also induce cell depletion (e.g. ADCC and/or ADCP) of 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%.

B. Therapeutic SIRP Antibodies

[00250] As discussed in Section IA above, provided herein are antibodies that recognize and bind to SIRPγ, in combination with SIRPα and/or SIRPβ1. The antibodies disclosed herein may be used for therapeutics in a subject.

[00251] 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 a 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

[00252] 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. SIRPγ-expressing cells (e.g. lymphocyte cells), optionally in combination with SIRPα and/or SIRPβ1 expressing cells (e.g., myeloid cells) as a part of the pathology.

[00253] 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 SIRPγ-expressing cells. In some embodiments, the SIRPγ-expressing cells are lymphocytes. In some embodiments, the SIRPγ-expressing lymphocytes are selected from the group consisting of B cells, T cells and NK cells. 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.

[00254] 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 cells are overactivated or hyperproliferative. 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 and neutrophils.

[00255] In some embodiments, the disease or condition is characterized by overactivation and/or hyperproliferation of lymphocytes cells (including lymphoblast cells). In some embodiments, the disease or condition is characterized by overactivation and/or hyperproliferation of myeloid cells (including myeloid progenitor cells), and other SIRPα and/or SIRPβ1-expressing cells. Exemplary diseases associated with overactivation and/or hyperproliferation include, but are not limited to, histiocytic disorders, cytokine release

syndrome (CRS), granulomatous diseases, autoimmune disorders, and hematological malignancies.

[00256] In some embodiments, the disease or disorder comprises a disease or disorder associated with lymphocytes. In some embodiments, the disease or disorder comprises a disease or disorder associated with myeloid cells. In some embodiments, the disease or disorder comprises a disease or disorder associated with both lymphocytes and myeloid cells.

[00257] In some embodiments, the disease or disorder comprises a disease or disorder associated with both lymphocytes and myeloid cells. In some embodiments, the disease or condition is a type of histiocytoses, for example hemophagocytic lymphohistiocytosis (HLH) (including primary and secondary HLH), macrophage activation syndrome, Langerhans cell histiocytosis (LCH), indeterminate cell histiocytosis, Erdheim-Chester disease (ECD), mixed LCH/ECD, Rosai Dorfman disease, malignant histiocytosis, cutaneous non-LCH histiocytoses, juvenile xanthogranuloma, virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, fungal-associated (fungal induced) HLH, autoimmune disease associated HLH, or malignancy-triggered HLH.

[00258] In some embodiments, the disease or condition is associated with a non-mendelian secondary HLH (sHLH). In some embodiments, such sHLH is an infection-associated HLH, such as virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, or fungal-associated HLH. Examples of virus-associated HLH include, but are not limited to, EBV-associated HLH, CMV-associated HLH, HLH associated with other defined herpes virus infections, HIV-associated HLH, Influenza-associated HLH, and HLH associated with other virus infections. In exemplary embodiments, the infection-associated sHLH is associated with an infection from a coronavirus (e.g. COVID19, SARS (*SARS*-CoV), MERS), or Ebola. Examples of bacteria-associated HLH include mycobacterium associated HLH. Examples of parasite-associated HLH include Leishmania-associated or Plasmodium-associated HLH. Examples of fungal-induced HLH include Histoplasmosis-associated HLH.

[00259] In other embodiments, such sHLH is a malignancy-associated HLH, such as a malignancy-triggered HLH (HLH at onset of malignancy) and include hematological malignancies (e.g. T-cell lymphoblastic lymphoma/leukemia, T-cell non-lymphoblastic lymphomas, B-cell leukemias, B-cell lymphomas (non-Hodgkin's), Hodgkin's lymphomas, NK-

cell lymphomas/leukemias, myeloid neoplasia, other hematological malignancies), as well as solid tumors. In other embodiments, such sHLH is a HLH occurring during chemotherapy (not associated with initial diagnosis of malignancy).

[00260] In other embodiments, such sHLH is associated with defined rheumatologic conditions (e.g. Macrophage Activation Syndrome-HLH, or MAS-HLH). These include, but are not limited to HLH associated with systemic-onset juvenile idiopathic arthritis (SoJIA), HLH associated with adult-onset Still's disease, HLH associated with systemic lupus erythematosus (SLE), HLH associated with vasculitis, HLH associated with rheumatoid arthritis, as well as HLH associated with other defined autoimmune conditions and HLH associated with an undefined autoimmune condition.

[00261] In other embodiments, such sHLH is a transplant-related HLH, such as HLH associated with a kidney transplant, or hematologic stem cell transplants.

[00262] In some embodiments, the disease or condition comprises comprises a sHLH or a cytokine release syndrome (CRS). In some embodiments, the disease or condition comprises CRS. In some embodiments, the sHLH or CRS is associated with iatrogenic immune activation, e.g. associated with checkpoint inhibitors for the treatment of malignancies, associated with T cell therapy, for example chimeric antigen receptor – T cell therapy (CAR-T) or T cell receptor T cell therapy (TCR-T), associated with NK cell activating bispecific monoclonal antibody therapy, or associated with T cell activating bispecific monoclonal antibody therapy. In other embodiments, such sHLH or CRS is associated with iatrogenic immune suppression. In other embodiments, the sHLH or CRS is associated with an infection, such as a viral infection, for example COVID-19.

[00263] In other embodiments, the therapeutic SIRP antibodies provided herein are useful for treating a granulomatous disease or condition, or a disease characterized by the presence of multinucleated giant cells. In some embodiments, the granulomatous diseases or conditions, or giant cell diseases or conditions, comprise sarcoidosis, inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, Takayasu arteritis, giant cell arteritis, psoriatic arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis), giant cell myocarditis, chronic granulomatous disease, eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome), or chronic beryllium disease (berylliosis).

[00264] In some embodiments, the disease or condition comprises a T-cell mediated disorder, including, but not limited to, aplastic anemia, cell mediated rejection of solid organ transplant, graft failure post-HSCT (hematopoietic stem cell transplant), lymphocyte-variant hypereosinophilia, atopic dermatitis, lymphocytic myocarditis, axial spondyloarthritis, celiac disease, or Rasmussen's encephalitis.

[00265] 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 eosinophils, basophils, mast cells or neutrophils.

[00266] In some embodiments, the disease or condition comprises a disease or condition is characterized by the aberrant activity and/or proliferation of eosinophils. In some embodiments, the disease or condition comprises hypereosinophilic syndrome (including primary, secondary, and idiopathic), acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, lymphocyte-variant hypereosinophilia, eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome), eosinophilic cardiomyopathy/Loeffler endocarditis, Löffler syndrome or episodic angioedema with eosinophilia/Gleich syndrome or lymphocyte-variant hypereosinophilia.

[00267] In some embodiments, the disease or condition comprises a disease or condition that is 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, chronic urticaria or severe allergic conjunctivitis.

[00268] In some embodiments, the disease or condition comprises 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.

[00269] 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 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.

[00270] In some embodiments, the therapeutic SIRP antibodies provided herein are useful for treating an autoimmune or inflammatory (chronic or acute) disorder such as acute disseminated encephalomyelitis, acute respiratory distress syndrome, Addison's disease, Adult-Onset Still's disease, ankylosing spondylitis, antibody-mediated rejection (AMR), anti-glomerular basement membrane disease (Goodpasture Syndrome), catastrophic antiphospholipid syndrome, antiphospholipid syndrome, aplastic anemia, allograft transplant rejection, atopic dermatitis, atherosclerosis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune lymphoproliferative syndrome, autoimmune neutropenia, axial spondyloarthritis, Behcet's disease, bullous pemphigoid, Castleman disease, catastrophic antiphospholipid syndrome, celiac disease, cell mediated rejection of solid organ transplant, chronic obstructive pulmonary disease (COPD), Chediak-Higashi syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic neutrophilic leukemia, chronic urticaria, coronary artery disease (CAD)/ peripheral artery disease (PAD), COVID-19, cutaneous mastocytosis, eosinophilic cardiomyopathy/Loeffler endocarditis, Crohn's disease, epidermolysis bullosa acquisita, Evans syndrome, eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome), Felty's syndrome, general pustular psoriasis, giant cell myocarditis, graft failure post-HSCT (hematopoietic stem cell transplant), graft vs. host disease, Graves' disease, Graves ophthalmopathy, granulomatosis with polyangiitis (Wegener's Granulomatosis), Guillain-Barre syndrome, Hashimoto's thyroiditis, hereditary alpha tryptasemia syndrome, hyper IgE syndrome, Idiopathic interstitial pneumonia, idiopathic pulmonary fibrosis, IgA nephropathy, immune/idiopathic thrombocytopenia purpura, inclusion body myositis, inflammatory bowel disease, Kawasaki disease, Lambert-Eaton myasthenic syndrome (LEMS), myasthenia gravis (MG), linear IgA disease, Löffler syndrome, lupus nephritis, lupus vasculitis, systemic lupus erythematosus (SLE), mast cell activation syndrome, mastocytic enterocolitis, membranous nephropathy, microscopic polyangiitis (MPA), multiple sclerosis, myelodysplastic syndromes,

myelofibrosis, myocarditis, neuromyelitis optica (NMO), neutrophilic dermatoses, paraneoplastic syndrome, pemphigus foliaceus, pemphigus vulgaris, primary biliary cholangitis, primary biliary cirrhosis, primary sclerosing cholangitis, psoriatic arthritis, pyoderma gangrenosum, Rasmussen's encephalitis, rheumatoid arthritis, rheumatoid vasculitis, Schmidt syndrome, scleroderma (systemic sclerosis), Sjögren's syndrome, severe allergic conjunctivitis, Sjogren syndrome, Susac syndrome, systemic inflammatory response syndrome, systemic juvenile idiopathic arthritis, systemic lupus erythematosus, systemic mastocytosis, type 1 diabetes, ulcerative colitis, uveitis, vitiligo or X-linked lymphoproliferative disease.

[00271] In some embodiments, the therapeutic SIRP antibodies provided herein are useful for treating a hematological malignancy. In some embodiments, the hematological malignancy is selected from the group consisting of acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, chronic neutrophilic leukemia, juvenile myelomonocytic leukemia, chronic eosinophilic leukemia, large granular lymphocyte leukemia, T-cell prolymphocytic leukemia, hepatosplenic lymphoma, Hodgkin's lymphomas, T-cell lymphoblastic lymphoma or leukemia, T-cell non-lymphoblastic lymphoma, NK-cell lymphoma/leukemia, myeloid neoplasia, chronic neutrophilic leukemia, and other hematological malignancies.

[00272] In other embodiments, the therapeutic SIRP antibodies provided herein are useful for treating a disease or condition associated with pathological alloantibodies or autoantibodies including myasthenia gravis, Guillain-Barre syndrome, autoimmune hemolytic anemia, immune/idiopathic thrombocytopenia purpura, Evans syndrome, Felty's syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), Lambert-Eaton myasthenic syndrome (LEMS), neuromyelitis optica (NMO), bullous pemphigoid, epidermolysis bullosa acquisita, pemphigus foliaceus, pemphigus vulgaris, anti-glomerular basement membrane disease (Goodpasture Syndrome), membranous nephropathy, rheumatoid vasculitis, lupus vasculitis, scleroderma (systemic sclerosis), Behcet's disease, microscopic polyangiitis (MPA), Kawasaki disease, antiphospholipid syndrome, catastrophic antiphospholipid syndrome, Graves ophthalmopathy, Castleman disease and antibody-mediated rejection (AMR).

[00273] In some embodiments, the disease or condition comprises the disease or condition comprises hemophagocytic lymphohistiocytosis (HLH) (including primary and secondary HLH), macrophage activation syndrome, Langerhans cell histiocytosis (LCH), indeterminate cell

histiocytosis, Erdheim-Chester disease (ECD), mixed LCH/ECD, Rosai Dorfman disease, malignant histiocytosis, cutaneous non-LCH histiocytosis, juvenile xanthogranuloma, virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, fungal-associated/fungal-induced HLH, malignancy-triggered HLH, HLH occurring during chemotherapy, HLH associated with systemic-onset juvenile idiopathic arthritis (SoJIA), HLH associated with adult-onset Still's disease, HLH associated with systemic lupus erythematosus (SLE), HLH associated with vasculitis, HLH associated with auto-immune conditions, HLH associated with a kidney transplant, HLH associated with hematologic stem cell transplants, sHLH or CRS associated with checkpoint inhibitors for the treatment of malignancies, sHLH or 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, cytokine release syndrome (CRS), systemic mastocytosis, hypereosinophilic syndrome (including primary, secondary, and idiopathic), hyper IgE syndrome, X-linked lymphoproliferative disease, graft vs. host disease, type 1 diabetes, systemic lupus erythematosus, lupus nephritis, systemic inflammatory response syndrome, acute respiratory distress syndrome, autoimmune lymphoproliferative syndrome, X-linked hyper IgM syndrome, paraneoplastic syndrome, Susac syndrome, linear IgA disease, autoimmune neutropenia, idiopathic pulmonary fibrosis, inclusion body myositis, vitiligo, Addison's disease, Graves' disease, Hashimoto's thyroiditis, Schmidt syndrome, acute disseminated encephalomyelitis, sarcoidosis, ankylosing spondylitis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, eosinophilic granulomatosis with polyangiitis, pyoderma gangrenosum, giant cell arteritis, rheumatoid arthritis, systemic juvenile idiopathic arthritis, Sjogren's syndrome, primary sclerosing cholangitis, primary biliary cholangitis, myasthenia gravis, multiple sclerosis, Guillain-Barre syndrome, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic eosinophilic leukemia, large granular lymphocyte leukemia, T-cell prolymphocytic leukemia, hepatosplenic lymphoma, Hodgkin's lymphoma, T-cell lymphoblastic lymphoma/leukemia, T-cell non-lymphoblastic lymphoma, B-cell leukemia, B-cell lymphoma (non-Hodgkin's), NK-cell lymphoma or leukemia, myeloid neoplasia, autoimmune hemolytic anemia, immune/idiopathic thrombocytopenia purpura, Evans syndrome, Felty's syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), Lambert-Eaton myasthenic syndrome (LEMS), neuromyelitis optica (NMO), bullous pemphigoid, epidermolysis bullosa

acquisita, pemphigus foliaceus, pemphigus vulgaris, anti-glomerular basement membrane disease (Goodpasture Syndrome), membranous nephropathy, rheumatoid vasculitis, lupus vasculitis, scleroderma (systemic sclerosis), Behcet's disease, granulomatosis with polyangiitis (Wegener's Granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome), microscopic polyangiitis (MPA), Kawasaki disease, antiphospholipid syndrome, catastrophic antiphospholipid syndrome, Graves ophthalmopathy, Castleman disease, antibody-mediated rejection (AMR), acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, uveitis, giant cell myocarditis, cutaneous mastocytosis, mastocytic enterocolitis, mast cell activation syndrome, IgA nephropathy, Chediak-Higashi 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, myocarditis, episodic angioedema with eosinophilia/Gleich syndrome, idiopathic interstitial pneumonia, hereditary alpha tryptasemia syndrome, chronic urticaria, severe allergic conjunctivitis, Adult-onset Still's, aplastic Anemia, cell mediated rejection of solid organ transplant, graft failure Post-hematopoietic stem cell transplant (HSCT), lymphocyte-variant hypereosinophilia, myelodysplastic syndromes, atopic dermatitis, axial spondyloarthritis, celiac disease, hyperthyroidism, Rasmussen's encephalitis, chronic beryllium disease (Berylliosis), Takayasu arteritis, autoimmune hepatitis, neutrophilic dermatoses, psoriatic arthritis, Corona Virus Disease 2019 (COVID-19), or general pustular psoriasis.

D. Pharmaceutical Compositions

[00274] 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.

E. Combination Therapies

[00275] 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, lymphocytes, or other cells expressing SIRPα, SIRPβ1, or SIRPγ. In some embodiments, the disease or condition is an autoimmune disease or condition. In some embodiments, the disease or condition is a neoplastic disorder or malignancy. In exemplary embodiments, the disease or condition being treated is a hyper-inflammatory syndrome such as HLH, or CRS (e.g. an autoimmune related CRS, or CRS associated with adoptive cell therapy) in which a therapeutic SIRP antibody may be used in combination with corticosteroids (e.g. – dexamethasone).

[00276] In some embodiments, a therapeutic SIRP antibody is provided to treat a CRS or sHLH 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.

[00277] 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.

F. Administration of Therapeutic SIRP Antibodies

[00278] 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. In some embodiments, the SIRP antibodies of the disclosure are administered intravenously. In some embodiments, the SIRP antibodies of the disclosure are administered subcutaneously. 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.

G. Diagnostic Antibodies

[00279] The antibodies provided herein may also be used for diagnostic purposes. For example, for those SIRP antibodies which bind to SIRPα, diagnostic antibodies could be used for detecting the presence of a SIRPα mediated disorder, or for detecting SIRPα levels in a subject prior to dosing (e.g. as a companion diagnostic).

III. Kits and Articles of Manufacture

[00280] 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 SIRP Antibodies

[00281] 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. Twelve individual clones were identified (Antibodies 1, 3, 4, and 7-15). Antibodies 1, 3-4 and 7-14 have a human variable region and a rat IgG2b Fc domain. Antibody 15 has a mouse variable region and a mouse IgG2a Fc domain.

Example 2: Binding of SIRP Antibodies to SIRPα Protein

[00282] 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 Antibodies 1, 3, 4, 7-15. The data depict the relative luminescence units read by a plate-reader capable of detecting chemiluminescence.

[00283] 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 Antibodies 1, 3, 4, 7-15. The data depict the relative luminescence units read by a plate-reader capable of detecting chemiluminescence.

[00284] FIGS. 2A-2B shows binding curves of SIRP antibodies to human SIRPα V1 and cynomolgus monkey 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.

[00285] FIGS. 2C-2H 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. Select 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.

[00286] FIGS. 3A-3C show binding curves of SIRP antibodies and two isotype controls with human Fc to human SIRPα V1, human SIRPβ1, human SIRPγ and cynomolgus monkey SIRPα by ELISA. Select SIRP antibodies from Example 1 were fully made human. Isotype control 1 was an unrelated human IgG1 antibody with irrelevant CDRs. Isotype control 2 was the same as isotype control 1 but contained the same amino acid substitutions in the Fc region as some of the selected SIRP antibodies for increased FcγR binding (referring to Table 11). 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 in FIGS. 2A-2B using an anti-human IgG antibody as the detection antibody.

[00287] FIGS. 3D-3E shows binding curves of SIRP antibodies with human Fc to human SIRPα V1, human SIRPβ1, human SIRPγ, cynomolgus monkey SIRPα, cynomolgus monkey SIRPβ, and cynomolgus monkey SIRPγ by ELISA. Select SIRP antibodies from Example 1 were 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 in FIG. 2C-2H using an anti-human IgG antibody as the detection antibody.

[00288] Selected antibodies 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 these antibodies is presented in Tables 10 and 11. The affinities of these SIRP antibodies were determined using surface plasmon resonance. The SIRP antibodies were flowed onto a chip and captured by an anti-mouse IgG or 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.

[00289] Select 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). Antibodies with human Fc were digested with gingipain K enzyme to yield monomeric F(ab'), biotinylated, then coated onto streptavidin biosensors. 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. K_D affinities were calculated as k_{dis} to k_{on} ratio at each concentration of SIRP-His and averaged. This average of the K_D affinities for each antibody is presented in Table 15 below. The table shows the K_D of binding of selected antibodies to monomeric human SIRPα, SIRPβ1, and SIRPγ, as assayed by ForteBio Octet.

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

Antibody No.	Human SIRPα V1 (M)	Cyno SIRPα (M)
1	5.79E-07	5.81E-07
3	4.57E-09	5.13E-07
7	4.98E-08	5.61E-08
13	1.26E-08	1.67E-08

Table 14: Affinities (K_D) 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)
21	3.01E-08	3.66E-08	7.54E-08
23	3.23E-07	3.74E-07	3.84E-07
24	2.89E-09	2.26E-08	1.50E-08

Antibody No.	Human SIRPα V1 (M)	Human SIRPα V2 (M)	Cyno SIRPα (M)
25	1.14E-08	9.09E-09	1.26E-08
26	3.89E-08	not tested	6.60E-08
28	3.11E-07	3.73E-07	3.61E-07
29	8.32E-9	1.03E-08	1.11E-08

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

Antibody No.	Human SIRPα V1 (M)	Human SIRPβ1 (M)	Human SIRPγ (M)
1	3.71E-08	3.52E-06	9.73E-07
3	3.10E-09	7.50E-06	1.03E-07
4	4.61E-08	N/A	2.41E-08
7	3.83E-08	N/A	3.27E-07
8	4.66E-08	7.89E-08	5.00E-08
9	1.24E-09	1.36E-08	8.05E-09
10	5.76E-08	N/A	1.37E-09
11	3.74E-09	6.19E-08	1.33E-08
12	5.31E-09	N/A	<1.0E-12 [+]
13	9.22E-10	2.99E-06	<1.0E-12 [+]
14	9.84E-06	N/A	3.87E-08
15	2.44E-10	N/A	5.44E-08
28	1.49E-08	5.55E-07	1.34E-06

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

[+] No dissociation was seen in the time frame (600 seconds) of the assay

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

[00290] Selected antibodies and two isotype controls were tested for binding to human monocytes, neutrophils, T lymphocytes, and B lymphocytes. FIG. 4A shows the results of binding studies performed with SIRP antibodies to monocytes, neutrophils, T lymphocytes, and B lymphocytes in human whole blood compared to two isotype controls. 50 μg/mL fluorescent dye-conjugated SIRP antibodies or isotype controls were incubated with whole blood from two normal donors. Positive signal was detected on monocytes and neutrophils via flow cytometry. No signal was detected for T lymphocytes and B lymphocytes when compared to isotype

controls. Monocytes were identified as the CD45+ and CD14+ population. Neutrophils were identified as the CD45+, CD14-, CD19-, SSC^{high}, and CD16+ population. T lymphocytes were identified as the CD45+, CD14-, CD19-, SSC^{low}, CD3+, and CD16- population. B lymphocytes were identified as the CD45+, SSC^{low}, and CD19+ population. Graphs depict the median fluorescence intensity (MFI) of each population. Selected antibodies and two isotype controls were tested for binding to cynomolgus monkey monocytes, granulocytes, and T lymphocytes. Isotype controls used were the same as for human binding experiments. FIG. 4B shows the results of binding studies performed with SIRP antibodies and isotype controls to monocytes, granulocytes, and T lymphocytes in cyno whole blood. 50 μg/mL fluorescent dye-conjugated SIRP antibodies were incubated with whole blood from three normal donors. Positive signal was detected on monocytes, granulocytes, and T lymphocytes via flow cytometry. Monocytes were identified as the CD45+ and CD14+ population. Granulocytes were identified as the CD45+, CD14-, CD19-, and SSC^{high} population. T lymphocytes were identified as the CD45+, CD14-, CD19-, SSC^{low}, CD3+, and CD16- population. Graph depicts the median fluorescence intensity (MFI) of each population.

[00291] 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. 4C-4E shows 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. 4F shows the binding curves of SIRP antibodies to human SIRPα, SIRPβ, or SIRPγ-expressing CHO cells detected using an anti-human IgG antibody.

Example 4: Effect of SIRP Antibodies on ADCC

[00292] Antibody-dependent cell-mediated cytotoxicity (ADCC) induced by selected SIRP antibodies of a SIRPα-expressing human monocyte cell line was evaluated. An immortalized human monocyte-like cell line, THP-1, was stained using an intracellular dye (CellTracker™) and exposed to test article (SIRPα antibodies or isotype control) at various concentrations. Human NK (effector) cells were then co-incubated with the SIRP antibody-opsonized THP-1 (target) cells at an effector cell to target cell ratio of 1:1 for 4 hours at 37°C. Dead cells were stained using DAPI and samples analyzed via flow cytometry. FIG. 5 depicts percent of dual

DAPI+ and CellTracker+ THP-1 cells. The data show ADCC of THP-1 cells induced by selected antibodies of the disclosure. The ADCC effect is antibody-dose dependent. The results are presented as compared to an isotype control, an unrelated IgG1 antibody with an irrelevant CDR.

[00293] Antibody-dependent cell-mediated cytotoxicity (ADCC) induced by selected SIRP antibodies on primary monocytes was evaluated. SIRPα expressing-human primary monocyte (target) cells were exposed to test article at various concentrations, washed, and then co-incubated with human NK (effector) cells at an effector cell to target cell ratio of 1:1 for 4 hours at 37°C. Samples were stained with anti-CD14 antibody followed by DAPI and analyzed via flow cytometry. The graphs in FIG. 6A depicts percent of dual DAPI+ and CD14+ cells. FIG. 6A shows ADCC of human monocytes induced by selected antibodies of the disclosure. The ADCC effect is antibody-dose dependent. The results are presented as compared to an isotype control, l, an unrelated IgG1 antibody with an irrelevant CDR.

[00294] ADCC induced by selected SIRP antibodies on primary human and cynomolgus monkey monocytes and resting T lymphocytes were evaluated. SIRP expressing-human and cynomolgus monkey primary monocyte or resting T lymphocytes (target) cells were stained with intracellular CellTracker™ Green, washed, and exposed to SIRP antibodies at various concentrations. 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 graph in FIGS. 6B –6D depict percent of cells positive for Zombie Violet dye with respect to total cells positive for CellTracker™ Green (% ADCC). FIG. 6B shows ADCC of human and cyno monocytes induced by selected antibodies of the disclosure. FIG. 6C shows ADCC of human and cyno CD4+ T cells induced by selected antibodies. FIG. 6D shows ADCC of human and cyno CD8+ T cells induced by selected antibodies. The ADCC effect is antibody-dose dependent. The results are presented as compared to isotype controls. Isotype control 1 was an unrelated IgG1 antibody with an irrelevant CDR. Isotype control 2 was the same as isotype control 1 but contained the same high affinity substitutions in the Fc region as some of the selected SIRP antibodies.

Example 5: Effect of SIRP Antibodies on ADCP

[00295] The antibody-dependent cellular phagocytosis (ADCP) of a monocytic cell line induced by selected SIRPα antibodies was evaluated. Two human monocytic cell lines, MOLM-

13 and THP-1, were labelled with different colored intracellular dyes (CellTracker™ Green and CellTracker™ Deep Red). MOLM-13 (target) cells were opsonized with SIRP antibodies at the indicated concentrations and co-incubated with THP-1 (phagocytes) at a target cell to phagocyte ratio of 1:1 for 2 hours at 37°C. Cells were analyzed by flow cytometry. Graph depicts percent of THP-1 cells positive for two colors. FIG. 7 shows ADCP of MOLM-13 cells by THP-1 cells induced by selected antibodies of the disclosure.

[00296] The antibody-dependent cellular phagocytosis (ADCP) of primary monocytes induced by SIRPα antibodies was evaluated. Primary human CD14+ monocytes were split into two sets and labelled with different colored intracellular dyes (CellTracker™ Green and CellTracker™ Deep Red). One set (target cells) was opsonized with SIRP antibodies at the indicated concentrations and co-incubated with the other set (phagocytes) at a target cell to phagocyte ratio of 1:1 for 2 hours at 37°C. Cells were analyzed by flow cytometry. Graph depicts percent of phagocytes positive for two colors. FIG. 8 shows ADCP of human monocytes by human monocytes induced by selected antibodies of the disclosure.

Example 6: Effect of SIRP Antibodies on *in vivo* Depletion of Selected Cell Types

[00297] The effect on monocytes in cynomolgus monkeys dosed intravenously with selected SIRP antibodies was evaluated. Data were generated from whole blood samples collected at different times post-dose and processed according to test facility's Standard Operating Procedures (SOPs). Samples were analyzed on an automated hematology analyzer. Graph depicts average (n=3 monkeys) of absolute monocyte number per microliter of whole blood sample plotted against time. Depletion of monocytes was observed. The effect was transient, but reversible. FIG. 9 shows that intravenous administration of selected antibodies of the disclosure resulted in transient *in vivo* monocyte depletion in cynomolgus monkeys at the doses indicated.

[00298] The effect on neutrophils in cynomolgus monkeys dosed intravenously with selected SIRP antibodies was evaluated. Data were generated from whole blood samples collected at different times post-dose and processed according to test facility's Standard Operating Protocols (SOPs). Samples were analyzed on an automated hematology analyzer. Graph depicts average (n=3 monkeys) of absolute neutrophil number per microliter of whole blood sample plotted against time. FIG. 10 shows that intravenous administration of selected antibodies of the

disclosure resulted in transient *in vivo* neutrophil depletion in cynomolgus monkeys at the doses indicated.

[00299] The effect on lymphocytes in cynomolgus monkeys dosed intravenously with selected SIRP antibodies was evaluated. Data were generated from whole blood samples collected at different times post-dose and processed according to test facility's Standard Operating Protocols (SOPs). Samples were analyzed on an automated hematology analyzer. Graph depicts average (n=3 monkeys) of absolute lymphocyte number per microliter of whole blood sample plotted against time. FIG. 11 shows that intravenous administration of selected antibodies of the disclosure resulted in transient *in vivo* lymphocyte depletion in cynomolgus monkeys at the doses indicated.

[00300] The effect on eosinophils in cynomolgus monkeys dosed intravenously with selected SIRP antibodies was evaluated. Data was generated from whole blood samples collected at different times post-dose and processed according to test facility's Standard Operating Protocols (SOPs). Samples were analyzed on an automated hematology analyzer. Graph depicts average (n=3 monkeys) of absolute eosinophil number per microliter of whole blood sample plotted against time. FIG. 12 shows that intravenous administration of selected antibodies of the disclosure resulted in transient *in vivo* eosinophil depletion in cynomolgus monkeys at the doses indicated.

[00301] The effect on basophils in cynomolgus monkeys dosed intravenously with selected SIRP antibodies was evaluated**.** Data were generated from whole blood samples collected at different times post-dose and processed according to test facility's Standard Operating Protocols (SOPs). Samples were analyzed on an automated hematology analyzer. Graph depicts average (n=3 monkeys) of absolute basophil number per microliter of whole blood sample plotted against time. FIG. 13 shows that intravenous administration of selected antibodies of the disclosure resulted in transient *in vivo* basophil depletion in cynomolgus monkeys at the doses indicated.

Example 7: Determination of SIRP Antibody Competition with CD47 for Binding to SIRPα

[00302] 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 SIRP 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, each SIRP antibody 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. A subset of the antibodies tested and shown in FIG. 14 showed significant disruption of the CD47-Fc binding to hSIRPα. A subset of the antibodies tested and shown in FIG. 14 show no or negligible disruption of the CD47-Fc binding to hSIRPα. Antibodies 1, and 13 do not disrupt the binding of CD47, they do not compete with CD47. Antibodies 3 and 7 inhibit the binding of CD47 to SIRPα at least partially. The competition data shown in FIG. 14 show varying degrees of luminescence for the antibodies tested, suggesting some antibodies bind to different regions on SIRPα.

[00303] SIRP antibodies were tested for their ability to interfere with SIRP-CD47 binding using the biolayer interferometry (BLI) Octet system (Pall ForteBio). Streptavidin (SA) biosensors were coated with biotinylated recombinant CD47-His. Human SIRPα or SIRPγ, conjugated to an Fc region, were tested to determine their ability to bind to CD47 immobilized on the biosensors and a response value during association is generated for each. To test for inhibition of SIRP-CD47 binding, select SIRP antibodies (200 nM) were each pre-incubated at a 10-fold molar excess with SIRP-Fc protein (20 nM) and then tested for their ability to block binding of SIRPα-Fc or SIRPγ-Fc to CD47-His-biotin immobilized on the biosensors. Table 16 shows total response values calculated during association for each antibody-SIRPα-Fc or SIRPγ-Fc complex measured and compared, as percent of response, to the binding of SIRPα-Fc or SIRPγ-Fc alone to CD47. A greater than or equal to 100% response indicates no blocking of the binding of the Antibody:SIRP antigen complex to the CD47 receptor. A less than 100% Response indicates blocking or partial blocking of Antibody:SIRP antigen complex to the CD47 receptor.

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

Antibody No.	SIRPα-CD47 Response (%)	SIRPγ-CD47 Response (%)
1	130.00	109.56
3	-4.69	-7.23
4	-4.60	-6.94
7	62.40	51.68
8	-3.27	-4.94
9	-1.77	-4.72
10	-3.65	-4.29
11	-3.86	-3.80
12	126.87	120.02
13	126.98	110.72
14	52.17	14.41
15	115.26	129.39
24	-7.55	-37.86
28	173.16	144.06

Example 8: Effect of SIRP Antibodies on Germinal Centers

[00304] Preliminary histological data from non-human primate studies indicate that *in vivo* administration of a SIRP antibody resulted in decreased germinal center cellularity in the spleen, characterized by decreased size of active germinal centers, fewer numbers of larger lymphocytes and tingible body macrophages, or complete absence of germinal centers. These observations are consistent with the mechanisms of action of the antibodies described herein that are capable of depleting SIRP-expressing cells found in the germinal centers, namely dendritic cells (SIRPα and SIRPβ1) and lymphocytes (SIRPγ). These observations suggest that the antibodies described herein may provide therapeutic effect in diseases where ectopic germinal centers or ectopic lymphoid like structures contribute to pathology including autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, multiple sclerosis, Hashimoto's thyroiditis, primary sclerosing cholangitis and primary biliary cirrhosis, and Myasthenia gravis.

CLAIMS

What is claimed is:

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

2. An antibody that is specific for one or more of SIRPα and SIRPβ1, and is specific for SIRPγ, 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: 54, 56, and 59-65;

   ii. a CDR-H2 sequence selected from the group consisting of SEQ ID NOS: 70, 72, and 75-81; and

   iii. a CDR-H3 sequence selected from the group consisting of SEQ ID NOS: 86, 88-89, and 92-99; 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: 5, 7-8, and 11-18;

   ii. a CDR-L2 sequence selected from the group consisting of SEQ ID NOS: 23-24, and 27-33; and

   iii. a CDR-H3 sequence selected from the group consisting of SEQ ID NOS: 36, 38-39, and 42-49.

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: 5, SEQ ID NO: 23, SEQ ID NO: 36, SEQ ID NO: 54, SEQ ID NO: 70, and SEQ ID NO: 86;
   b. SEQ ID NO: 7, SEQ ID NO: 24, SEQ ID NO: 38, SEQ ID NO: 54, SEQ ID NO: 72, and SEQ ID NO: 88;

c. SEQ ID NO: 8, SEQ ID NO: 24, SEQ ID NO: 39, SEQ ID NO: 56, SEQ ID NO: 72, and SEQ ID NO: 89;
d. SEQ ID NO: 11, SEQ ID NO: 27, SEQ ID NO: 42, SEQ ID NO: 59, SEQ ID NO: 75, and SEQ ID NO: 92;
e. SEQ ID NO: 12, SEQ ID NO: 28, SEQ ID NO: 43, SEQ ID NO: 60, SEQ ID NO: 76, and SEQ ID NO: 93;
f. SEQ ID NO: 13, SEQ ID NO: 29, SEQ ID NO: 44, SEQ ID NO: 61, SEQ ID NO: 76, and SEQ ID NO: 94;
g. SEQ ID NO: 13, SEQ ID NO: 30, SEQ ID NO: 45, SEQ ID NO: 62, SEQ ID NO: 77, and SEQ ID NO: 95;
h. SEQ ID NO: 14, SEQ ID NO: 31, SEQ ID NO: 46, SEQ ID NO: 63, SEQ ID NO: 78, and SEQ ID NO: 96;
i. SEQ ID NO: 15, SEQ ID NO: 31, SEQ ID NO: 47, SEQ ID NO: 62, SEQ ID NO: 79, and SEQ ID NO: 97;
j. SEQ ID NO: 16, SEQ ID NO: 31, SEQ ID NO: 47, SEQ ID NO: 62, SEQ ID NO: 79, and SEQ ID NO: 97;
k. SEQ ID NO: 17, SEQ ID NO: 32, SEQ ID NO: 48, SEQ ID NO: 64, SEQ ID NO: 80, and SEQ ID NO: 98; and
l. SEQ ID NO: 18, SEQ ID NO: 33, SEQ ID NO: 49, SEQ ID NO: 65, SEQ ID NO: 81, and SEQ ID NO: 99.

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: 104, 106-107, and 110-118.

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: 123, 125-126, and 129-137.

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: 104 and SEQ ID NO: 123;
b. SEQ ID NO: 106 and SEQ ID NO: 125;
c. SEQ ID NO: 107 and SEQ ID NO: 126;

d. SEQ ID NO: 110 and SEQ ID NO: 129;

e. SEQ ID NO: 111 and SEQ ID NO: 130;

f. SEQ ID NO: 112 and SEQ ID NO: 131;

g. SEQ ID NO: 113 and SEQ ID NO: 132;

h. SEQ ID NO: 114 and SEQ ID NO: 133;

i. SEQ ID NO: 115 and SEQ ID NO: 134;

j. SEQ ID NO: 116 and SEQ ID NO: 135;

k. SEQ ID NO: 117 and SEQ ID NO: 136; and

l. SEQ ID NO: 118 and SEQ ID NO: 137.

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: 104 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: 123, 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: 106 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: 125, 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: 107 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: 126, 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: 110 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: 129, 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: 111 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: 130, 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: 112 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: 131, 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: 113 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: 132, or an amino acid sequence with at least 80% sequence identity thereto.

14. 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: 114 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: 133, or an amino acid sequence with at least 80% sequence identity thereto.

15. 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: 115 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: 134, or an amino acid sequence with at least 80% sequence identity thereto.

16. 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: 116 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: 135, or an amino acid sequence with at least 80% sequence identity thereto.

17. 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: 117 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: 136, or an amino acid sequence with at least 80% sequence identity thereto.

18. 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: 118 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: 137, or an amino acid sequence with at least 80% sequence identity thereto.

19. The antibody of any one of claims 2-18, wherein the antibody comprises an Fc domain.

20. The antibody of any one of claims 1-19, wherein the antibody is an Fc-containing antibody, and the binding of the antibody to one or more of SIRPα, SIRPβ1, and SIRPγ on a cell induces depletion of the cell.

21. The antibody of any one of claims 1-20, wherein the cell depletion involves antibody dependent cellular phagocytosis (ADCP).

22. The antibody of any one of claims 1-21, wherein the cell depletion involves antibody dependent cellular cytotoxicity (ADCC).

23. The method of any one of claims 1-22, wherein the cell depletion involves depletion of SIRPγ positive cells.

24. The antibody of any one of claims 1-23 wherein the SIRPγ cells are lymphocytes.

25. The antibody of claim 24, wherein the lymphocytes are T cells or NK cells.

26. The antibody of claim 25, wherein the T cells are cytotoxic T cells, helper T cells, memory T cells, regulatory T cells, natural killer T cells, mucosal associated invariant T cells, gamma delta T cells, or a combination thereof.

27. The antibody of any one of claims 1-22, wherein the cell depletion involves depletion of SIRPγ positive cells and SIRPα and/or SIRPβ1 positive cells.

28. The antibody of claim 27, wherein the SIRPα and/or SIRPβ1 cells are myeloid cells or myeloid progenitor cells.

29. The antibody of claim 27 or 28, wherein the SIRPα and/or SIRPβ1 cells are selected from the group consisting of myeloid cell progenitors, monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, and mast cells.

30. The antibody of any one of claims 1-29, wherein the antibody is a monoclonal antibody.

31. The antibody of any one of claims 1-29, wherein the antibody is an antibody fragment.

32. The antibody of any one of claims 1-29, wherein the antibody is a human antibody.

33. The antibody of any one of claims 1-29, wherein the antibody is a humanized antibody.

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

35. The antibody of any one of claims 1-29, wherein the antibody is a full-length antibody.

36. The antibody of any one of claims 1 or 19-35, wherein the Fc domain is selected from the group consisting of human IgG1, IgG2, IgG3, and IgG4.

37. The antibody of claim 36, wherein the Fc domain comprises SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 26.

38. The antibody of claim 36, 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: 26.

39. The antibody of 36, 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.

40. The antibody of claim 36, wherein the IgG1 Fc comprises a sequence selected from the group consisting of:

a. SEQ ID NO: 19;

b. SEQ ID NO: 20, wherein X_1 is V or A;
c. SEQ ID NO: 21, 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: 22, wherein X_1 is V or A;
e. SEQ ID NO: 25, 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: 26, wherein X_1 is K or R; X_2 is D or E; and X_3 is L or M.

41. The antibody of claim 36, wherein the IgG4 Fc comprises a sequence of SEQ ID NO: 34, 35 or 37, wherein X_1 in SEQ ID NO: 37 is S or P; and X_2 in SEQ ID NO: 37 is L or E.

42. The antibody of any one of claims 1-41, wherein the binding of the antibody does not disrupt the interaction between CD47 and SIRPα, and/or the interaction between CD47 and SIRPγ.

43. The antibody of any one of claims 1-41, wherein the binding of the antibody disrupts the the interaction between CD47 and SIRPα, and/or between CD47 and SIRPγ.

44. The antibody of any one of claims 1-43, wherein the antibody binds SIRPα, SIRPβ1 and SIRPγ.

45. The antibody of any one of claims 1-43, wherein the antibody binds SIRPα and SIRPγ and exhibits little or no binding to SIRPβ1.

46. The antibody of any one of claims 1-43, wherein the antibody binds SIRPβ1 and SIRPγ and exhibits little or no binding to SIRPα.

47. The antibody of any one of claims 1-45, wherein the antibody comprises a binding affinity to SIRPα of about 100pm, about 1nM, about 5nM, about 10nM, about 50nM, about 100nM, about 500nM, or about 1μM.

48. The antibody of any one of claims 1-47, 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, about 1 μM, about 5 μM, or about 10 μM.

49. The antibody of any one of claims 1-47, wherein the antibody comprises a binding affinity for SIRPγ of about 0.0001 nM, about 0.0005 nM, about 0.001 nM, about 0.005 nM, about 0.1 nM, 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, about 1 μM, about 2 μM or about 3 μM.

50. A pharmaceutical composition comprising any one of the antibodies of claims 1-49, and optionally a pharmaceutically acceptable carrier.

51. A nucleic acid encoding for the antibody of any one of claims 1-49.

52. The nucleic acid of claim 51, comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOS: 142, 144-145, 148-156, 161, 163-164, and 167-175.

53. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 142, 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: 161, or a nucleic acid sequence with at least 80% sequence identity thereto.

54. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 144, 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: 163, or a nucleic acid sequence with at least 80% sequence identity thereto.

55. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 145, 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: 164, or a nucleic acid sequence with at least 80% sequence identity thereto.

56. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 148, 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: 167, or a nucleic acid sequence with at least 80% sequence identity thereto.

57. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 149, 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: 168, or a nucleic acid sequence with at least 80% sequence identity thereto.

58. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 150, 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: 169, or a nucleic acid sequence with at least 80% sequence identity thereto.

59. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 151, 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: 170, or a nucleic acid sequence with at least 80% sequence identity thereto.

60. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 152, 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: 171, or a nucleic acid sequence with at least 80% sequence identity thereto.

61. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 153, 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: 172, or a nucleic acid sequence with at least 80% sequence identity thereto.

62. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 154, 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: 173, or a nucleic acid sequence with at least 80% sequence identity thereto.

63. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 155, 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: 174, or a nucleic acid sequence with at least 80% sequence identity thereto.

64. The nucleic acid of claim 51 or 52, wherein the heavy chain variable domain is encoded by the nucleic acid sequence of SEQ ID NO: 156, 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: 175, or a nucleic acid sequence with at least 80% sequence identity thereto.

65. A vector comprising the nucleic acid of any one of claims 51-64.

66. 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 1-49.

67. The method of claim 66, wherein at least a subset of the population of cells expresses SIRPγ.

68. The method of claim 66, wherein the population of cells that express SIRPγ comprise lymphocytes.

69. The method of claim 68, wherein the lymphocytes comprise T cells or NK cells.

70. The method of any one of claims 66-69, wherein at least a subset of the population of cells expresses SIRPα and/or SIRPβ1.

71. The method of claim 70, wherein the population of cells that express SIRPα and/or SIRPβ1 comprise myeloid cells or myeloid progenitor cells.

72. The method of claim 70, wherein the population of cells that express SIRPα and/or SIRPβ1 comprise monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, or mast cells.

73. The method of any one of claims 66-72, wherein the method is *in vitro*.

74. The method of any one of claims 66-72, wherein the method is *in vivo*.

75. The method any one of claims 66-74, wherein the population of cells comprises tissue-resident cells.

76. The method any one of claims 66-75, wherein the population of cells comprises circulating cells.

77. The method of any one of claims 66-76, wherein the cell depletion involves ADCC.

78. The method of any one of claims 66-77, wherein the cell depletion involves ADCP.

79. The method of any one of claims 66-78, wherein the cell depletion involves ADCC and ADCP.

80. 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 1-49 or the pharmaceutical composition of claim 50.

81. The method of claim 80, wherein the disease or condition is characterized by overactivation and/or hyperproliferation of lymphocytes, and the antibody induces depletion of lymphocytes.

82. The method of claim 81, wherein the lymphocytes are T cells.

83. The method of claim 82 or 83, wherein the disease or condition comprises aplastic anemia, cell mediated rejection of solid organ transplant, graft failure post-HSCT (hematopoietic stem cell transplant), lymphocyte-variant hypereosinophilia, atopic dermatitis, lymphocytic myocarditis, axial spondyloarthritis, celiac disease, or Rasmussen's encephalitis.

84. The method of claim 80, wherein the disease or condition is characterized by overactivation and/or hyperproliferation of myeloid cells, and the antibody induces depletion of myeloid cells.

85. The method of claim 84, wherein the myeloid cells comprise monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, or mast cells.

86. The method of claim 85, wherein the myeloid cells comprise eosinophils, and the disease or condition comprises acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, lymphocyte-variant hypereosinophilia, eosinophilic cardiomyopathy/Loeffler endocarditis, Löffler syndrome or episodic angioedema with eosinophilia/Gleich syndrome.

87. The method of claim 85, 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, chronic urticaria or severe allergic conjunctivitis.

88. The method of claim 85, 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.

89. The method of claim 80, wherein the disease or condition comprises a disease or disorder associated with both lymphocytes and myeloid cells.

90. The method of claim 89, wherein the disease or disorder comprises histiocytosis.

91. The method of claim 90, wherein the histiocytosis comprises hemophagocytic lymphohistiocytosis (HLH) (including primary and secondary HLH), macrophage activation syndrome, Langerhans cell histiocytosis (LCH), indeterminate cell histiocytosis, Erdheim-Chester disease (ECD), mixed LCH/ECD, Rosai Dorfman disease, malignant histiocytosis, cutaneous non-LCH histiocytoses, juvenile xanthogranuloma, virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, fungal-associated (fungal induced) HLH, autoimmune disease mediated HLH, or malignancy-triggered HLH.

92. The method of claim 91, wherein the malignancy-triggered HLH includes an HLH triggered by a hematological malignancy or solid tumor.

93. The method of claim 89, wherein the disease or disorder comprises a non-mendelian secondary HLH (secondary HLH, or sHLH).

94. The method of claim 93, wherein the secondary HLH comprises an infection-associated HLH.

95. The method of claim 93, wherein the sHLH is associated with a rheumatologic condition.

96. The method of claim 93, wherein the sHLH is associated with a kidney transplant or hematologic stem cell transplant.

97. The method of claim 80, wherein the disease or condition comprises cytokine release syndrome (CRS).

98. The method of claim 97, wherein the CRS is associated with iatrogenic immune activation, infection, T cell therapy, or T cell activating bispecific antibody therapy.

99. The method of claim 80, wherein the disease or condition comprises sHLH or CRS associated with iatrogenic immune activation, infection, T cell therapy, chimeric antigen receptor T cell (CAR-T) therapy, T cell receptor T cell therapy (TCR-T), T cell activating bispecific antibody therapy, or iatrogenic immune suppression.

100. The method of claim 80, wherein the disease or disorder comprises a granulomatous disease or condition, or a disease characterized by the presence of multinucleated giant cells.

101. The method of claim 100, wherein the disease or condition comprises sarcoidosis, Crohn's disease, Takayasu arteritis, giant cell arteritis, psoriatic arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis), giant cell myocarditis, chronic granulomatous disease, eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome), or chronic beryllium disease (berylliosis).

102. The method of claim 80, wherein the disease or condition comprises an autoimmune disorder or an inflammatory disorder.

103. The method of claim 102, wherein the autoimmune disorder comprises presentation of self antigens by antigen presenting dendritic cells in germinal centers of secondary lymphoid tissue of the subject.

104. The method of claim 80, wherein th disease or condition is associated with pathological alloantibodies or autoantibodies.

105. The method of claim 80, wherein the disease or disorder comprises a hematological malignancy.

106. The method of any one of claims 80-105 wherein the subject is human.

107. The method of any one of claims 80-106, wherein the antibody or pharmaceutical composition is administered intravenously.

108. The method of any one of claims 80-106, wherein the antibody or pharmaceutical composition is administered subcutaneously.

109. A cell expressing SIRPγ, wherein the cell bound is to an antibody of any one of claims 1-49, wherein the antibody is bound to the SIRPγ.

110. A kit or article of manufacture comprising an antibody of any one claims 1-49, or the pharmaceutical composition of claim 50.

111. Use of the antibody of any one claims 1-49, or the pharmaceutical composition of claim 50 for the treatment of a disease or disorder in a subject in need thereof.

112. Use of the antibody of any one claims 1-49, or the pharmaceutical composition of claim 50 for the manufacture of a medicament for the treatment of a disease or disorder in a subject in need thereof.

FIG. 1A

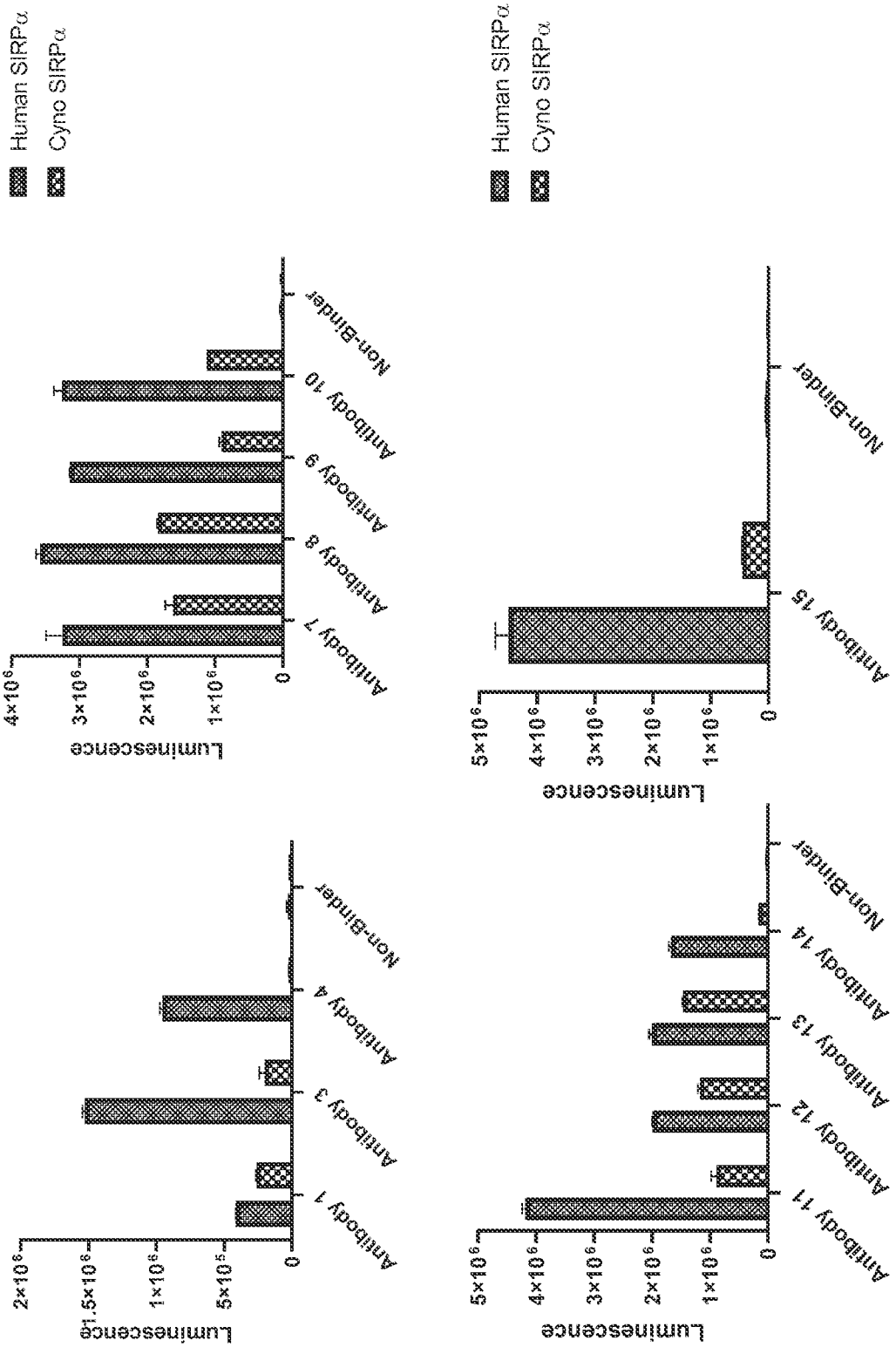

Human SIRPα
Cyno SIRPα
Luminescence
Antibody 7
Antibody 8
Antibody 9
Antibody 10
Non-Binder
Antibody 1
Antibody 3
Antibody 4
Antibody 11
Antibody 12
Antibody 13
Antibody 14
Antibody 15

FIG. 1B

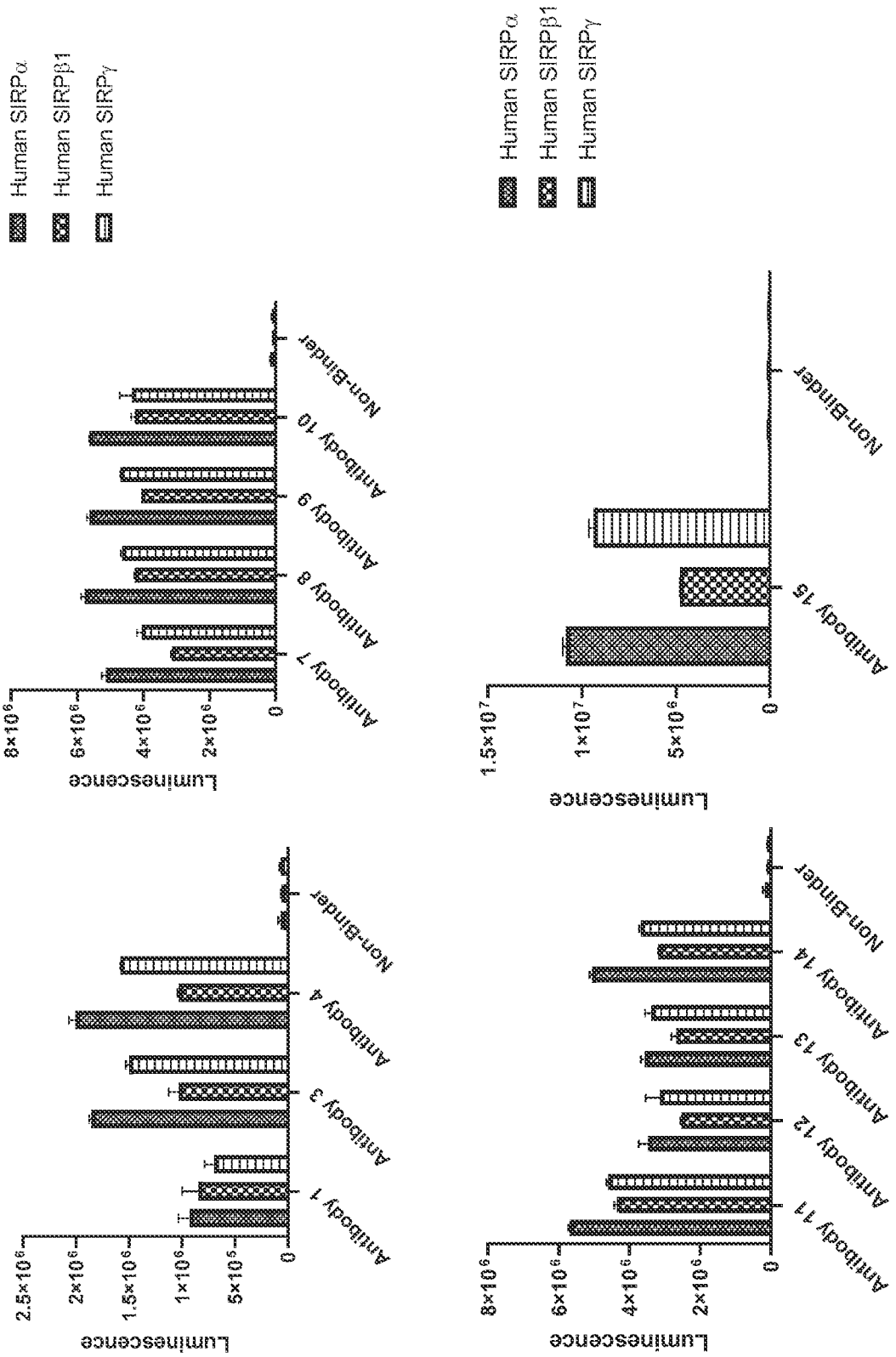

Human SIRPα
Human SIRPβ1
Human SIRPγ
Luminescence
Antibody 1
Antibody 3
Antibody 4
Non-Binder
Antibody 7
Antibody 8
Antibody 9
Antibody 10
Non-Binder
Antibody 11
Antibody 12
Antibody 13
Antibody 14
Non-Binder
Antibody 15
Non-Binder

FIG. 2A

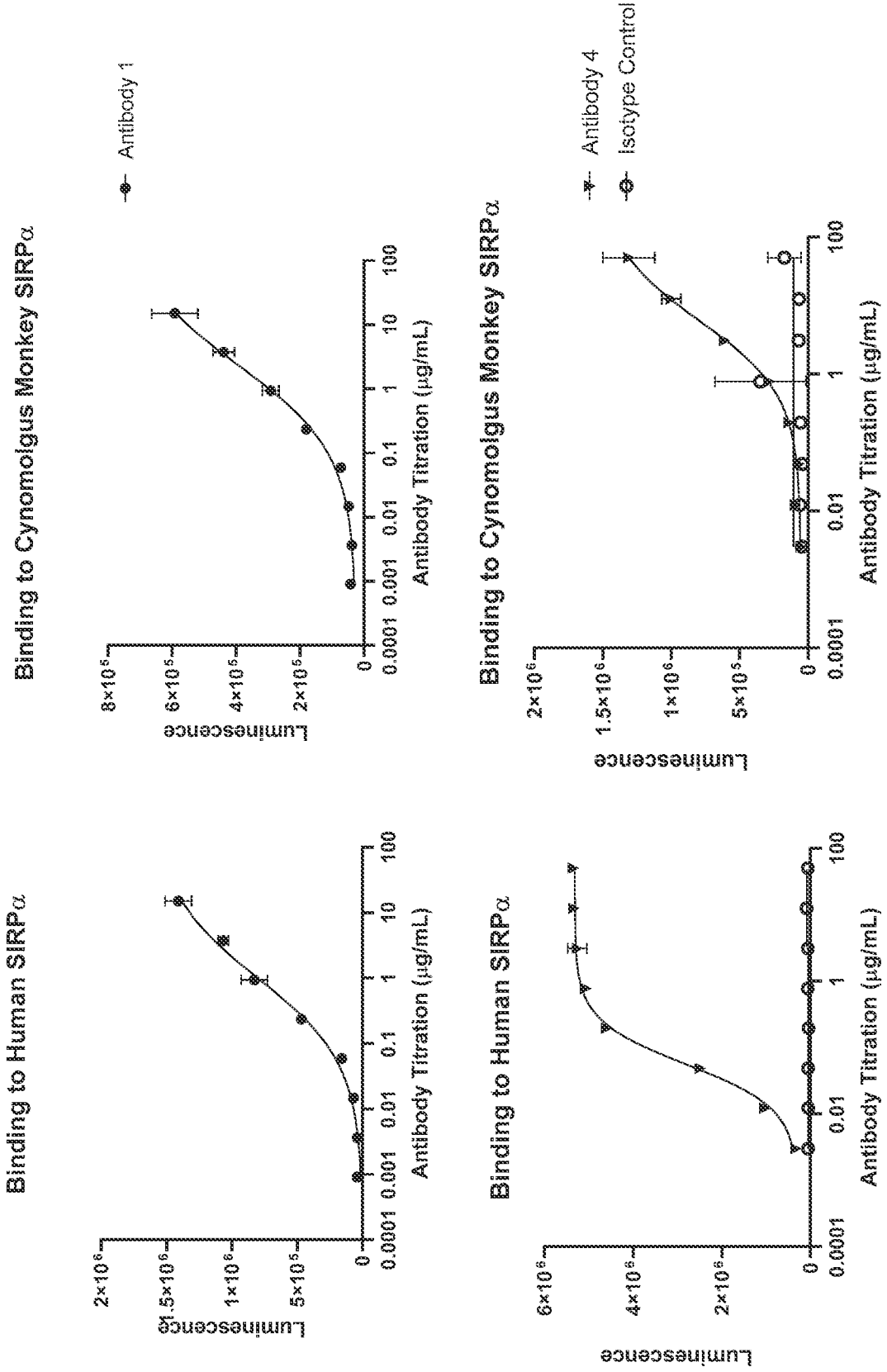

Binding to Human SIRPα
Binding to Cynomolgus Monkey SIRPα
Antibody 1
Antibody 4
Isotype Control
Luminescence
Antibody Titration (μg/mL)
0
0.0001
0.001
0.01
0.1
1
10
100
2×10^6
1.5×10^6
1×10^6
5×10^5
8×10^5
6×10^5
4×10^5
2×10^5

FIG. 2B

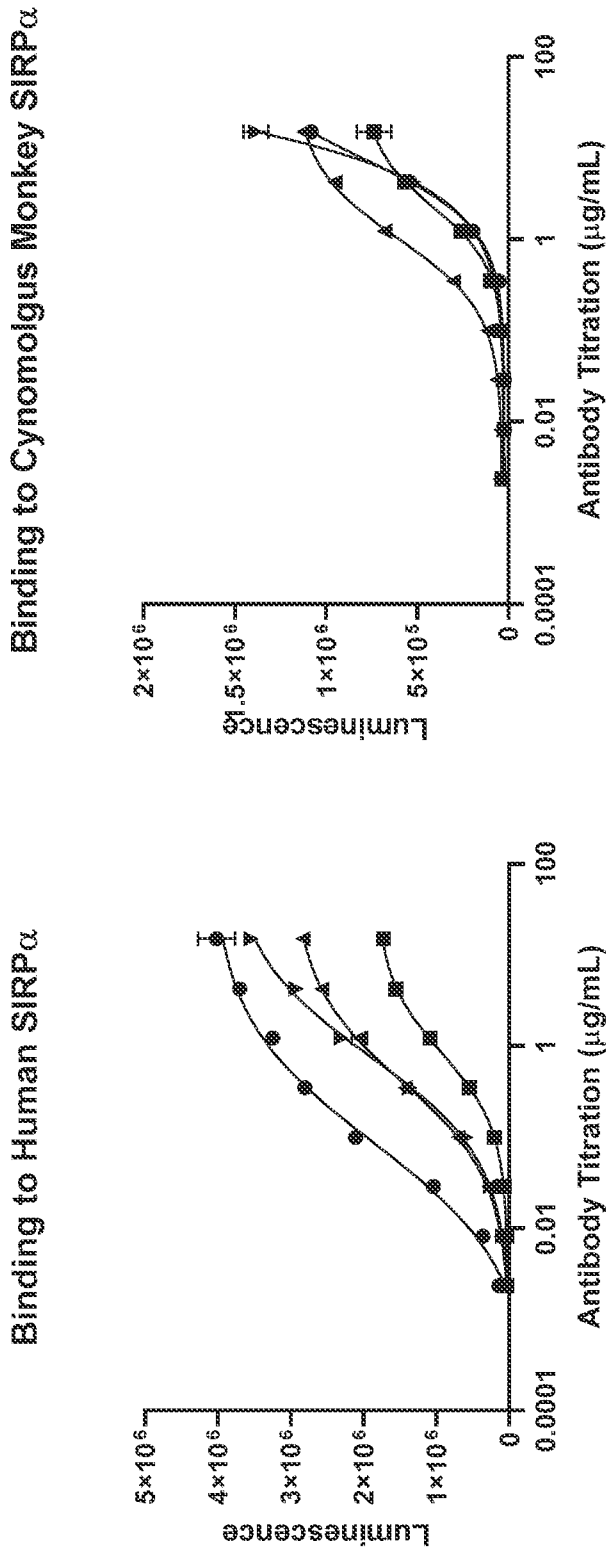

Binding to Cynomolgus Monkey SIRPα
Antibody 11
Antibody 12
Antibody 13
Antibody 14
Luminescence
2×10^6
1.5×10^6
1×10^6
5×10^5
0
0.0001
0.01
1
100
Antibody Titration (μg/mL)
Binding to Human SIRPα
Luminescence
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
0.0001
0.01
1
100
Antibody Titration (μg/mL)

FIG. 2C

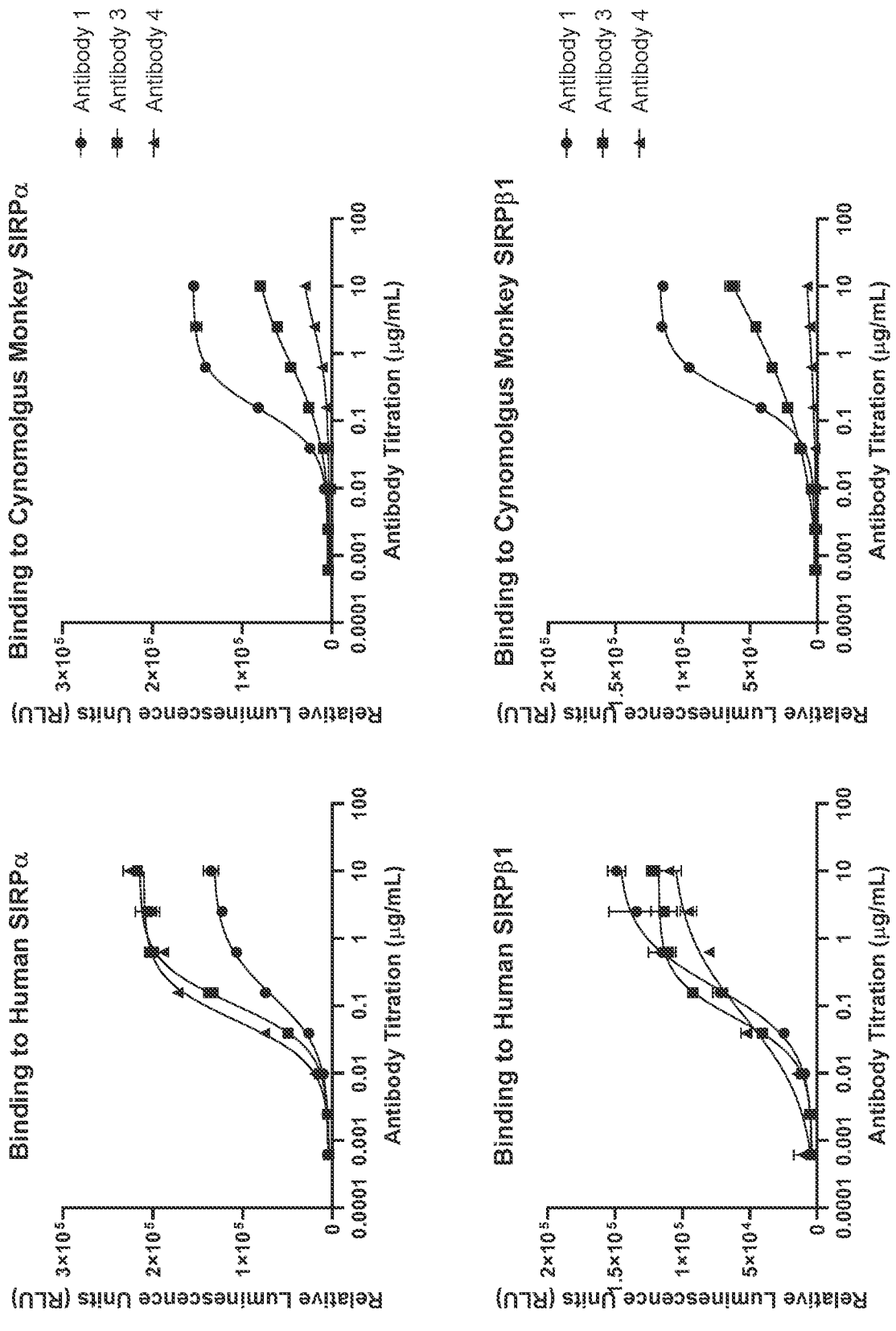

Binding to Human SIRPα
Binding to Cynomolgus Monkey SIRPα
Binding to Human SIRPβ1
Binding to Cynomolgus Monkey SIRPβ1
Relative Luminescence Units (RLU)
Antibody Titration (μg/mL)
Antibody 1
Antibody 3
Antibody 4

FIG. 2D

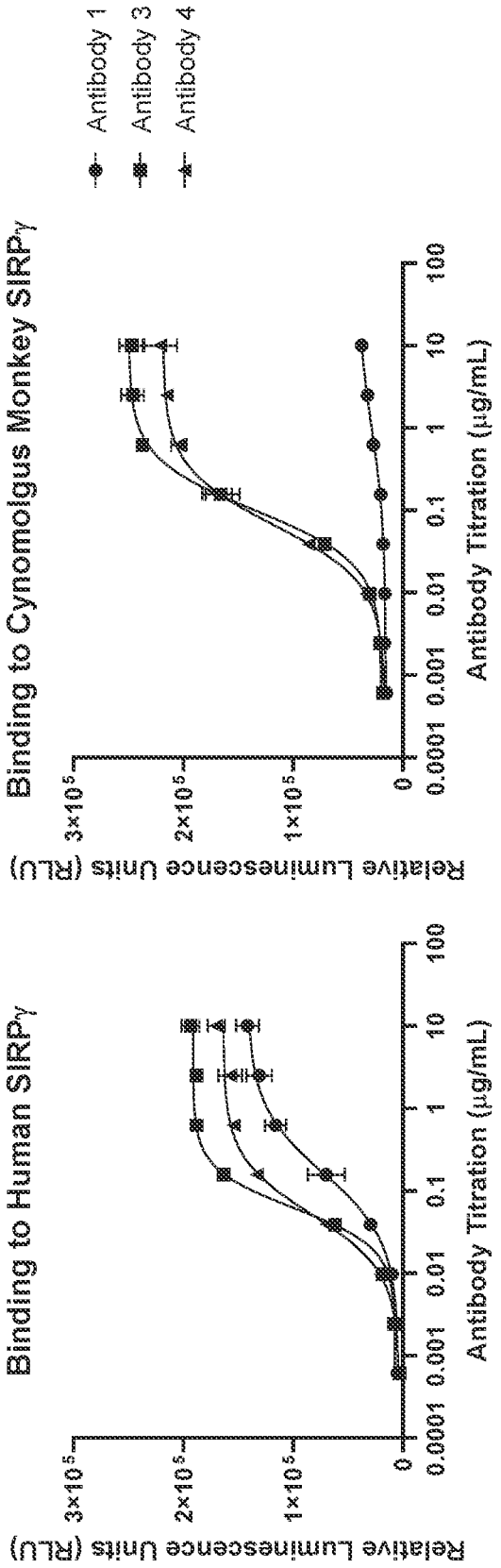

Binding to Human SIRPγ
Relative Luminescence Units (RLU)
3×10^5
2×10^5
1×10^5
0
0.0001
0.001
0.01
0.1
1
10
100
Antibody Titration (μg/mL)
Binding to Cynomolgus Monkey SIRPγ
Antibody 1
Antibody 3
Antibody 4

FIG. 2E

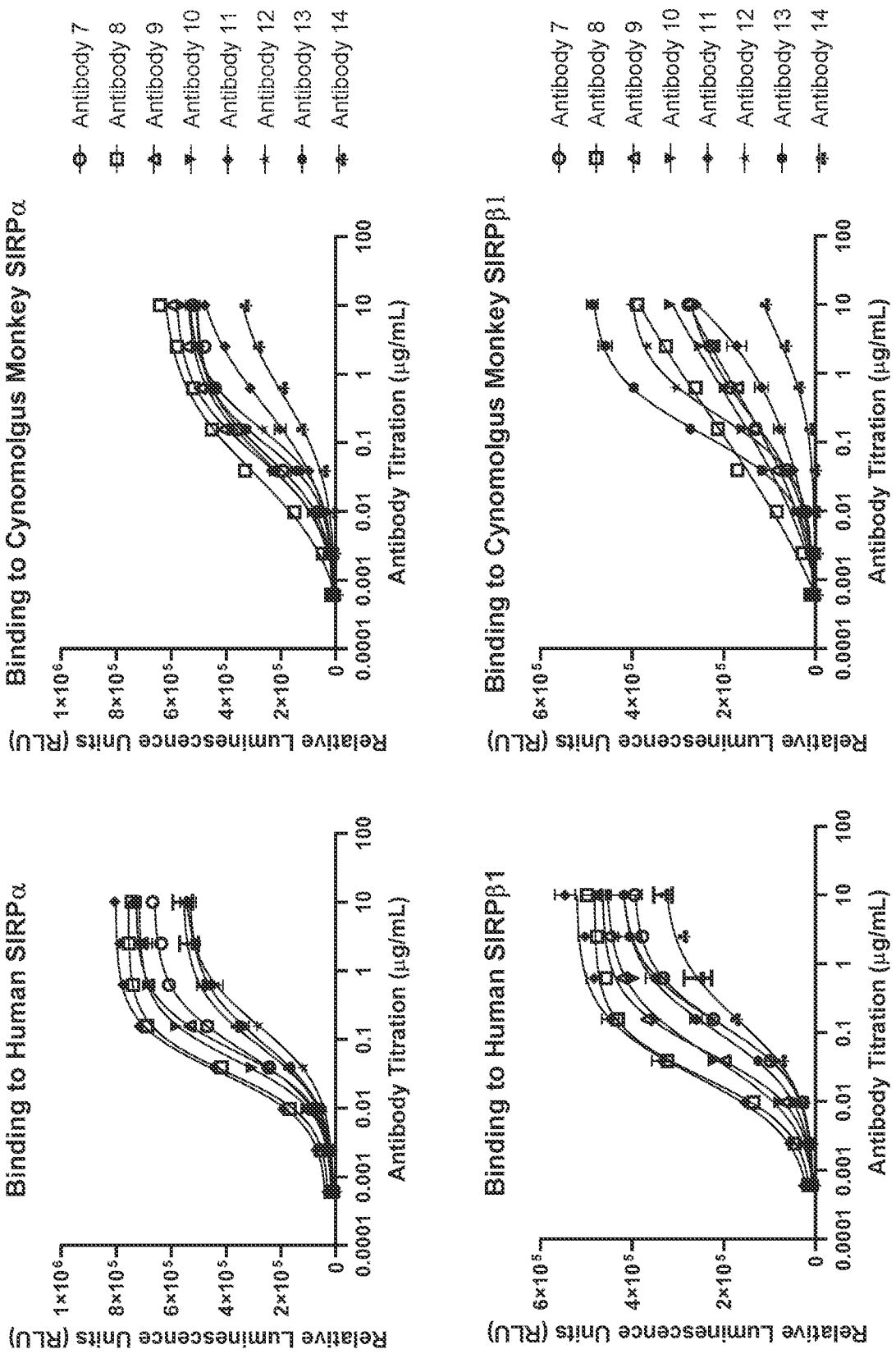

Binding to Human SIRPα
Binding to Cynomolgus Monkey SIRPα
Binding to Human SIRPβ1
Binding to Cynomolgus Monkey SIRPβ1
Relative Luminescence Units (RLU)
Antibody Titration (μg/mL)
Antibody 7
Antibody 8
Antibody 9
Antibody 10
Antibody 11
Antibody 12
Antibody 13
Antibody 14

FIG. 2F

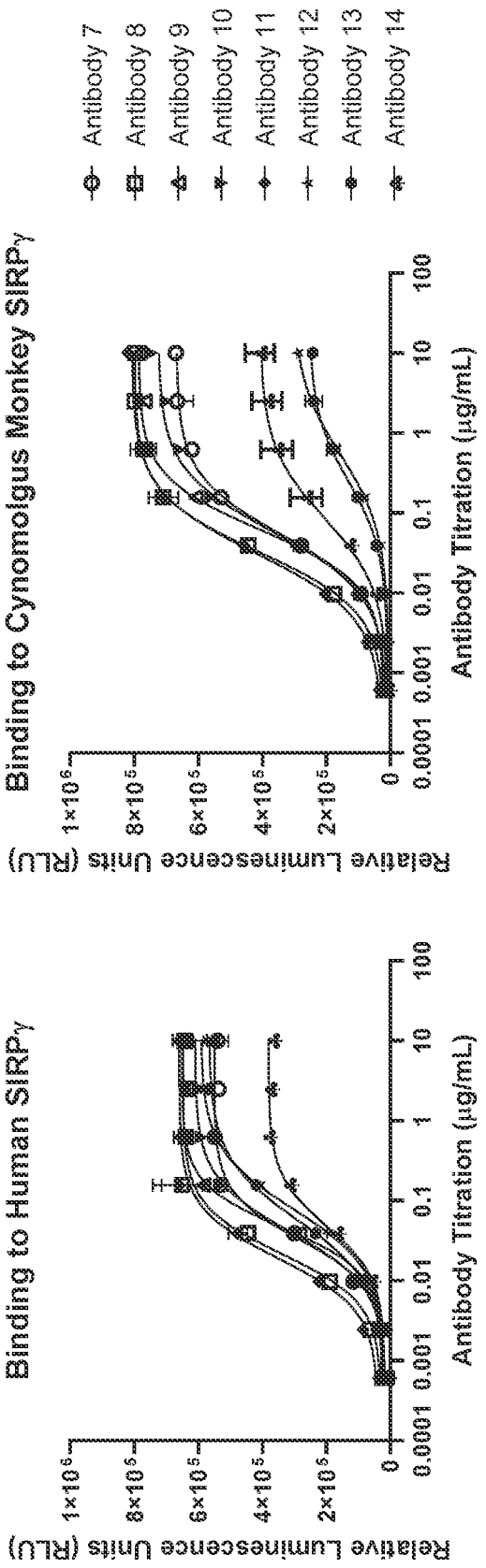

Binding to Human SIRPγ
Relative Luminescence Units (RLU)
1×10^6
8×10^5
6×10^5
4×10^5
2×10^5
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (µg/mL)
Binding to Cynomolgus Monkey SIRPγ
Relative Luminescence Units (RLU)
1×10^6
8×10^5
6×10^5
4×10^5
2×10^5
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (µg/mL)
Antibody 7
Antibody 8
Antibody 9
Antibody 10
Antibody 11
Antibody 12
Antibody 13
Antibody 14

FIG. 2G

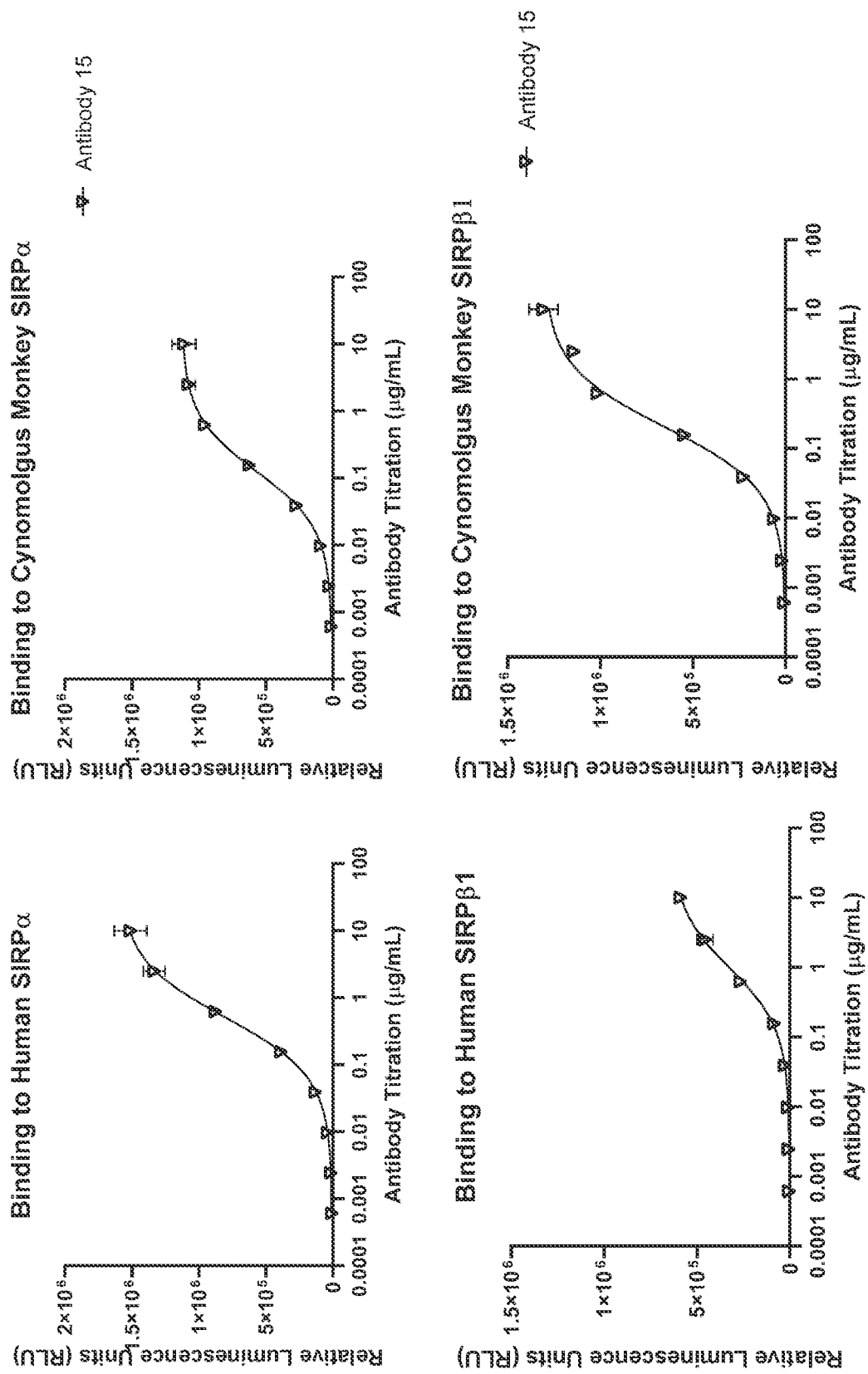

Binding to Human SIRPα
Binding to Cynomolgus Monkey SIRPα
Binding to Human SIRPβ1
Binding to Cynomolgus Monkey SIRPβ1
Antibody 15
Relative Luminescence Units (RLU)
Antibody Titration (μg/mL)
2×10^6
1.5×10^6
1×10^6
5×10^5
0
0.0001
0.001
0.01
0.1
1
10
100

FIG. 2H

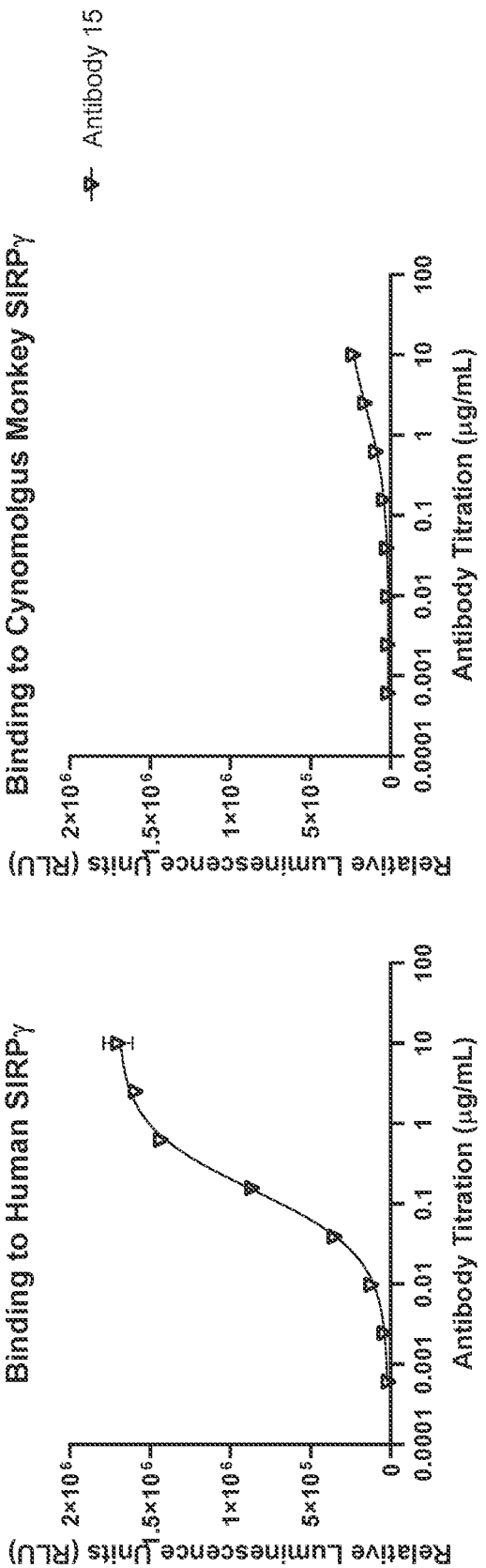

Binding to Human SIRPγ
Relative Luminescence Units (RLU)
2×10^6
1.5×10^6
1×10^6
5×10^5
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Binding to Cynomolgus Monkey SIRPγ
Antibody 15

FIG. 3A

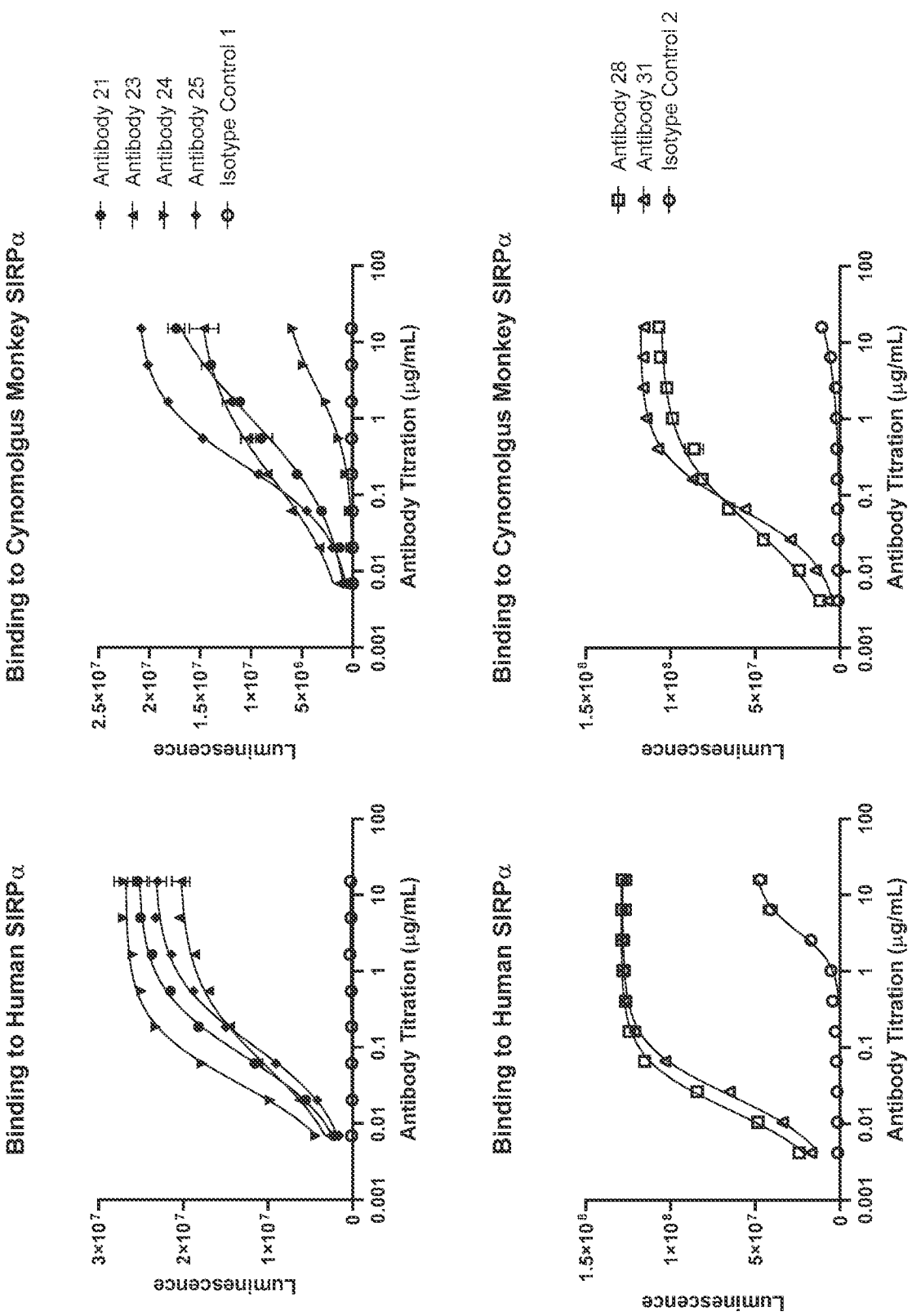

Binding to Human SIRPα
Binding to Cynomolgus Monkey SIRPα
Antibody 21
Antibody 23
Antibody 24
Antibody 25
Isotype Control 1
Antibody 28
Antibody 31
Isotype Control 2
Luminescence
Antibody Titration (μg/mL)
0
0.001
0.01
0.1
1
10
100
1×10^7
2×10^7
3×10^7
5×10^6
1.5×10^7
2.5×10^7
5×10^7
1×10^8
1.5×10^8

FIG. 3B

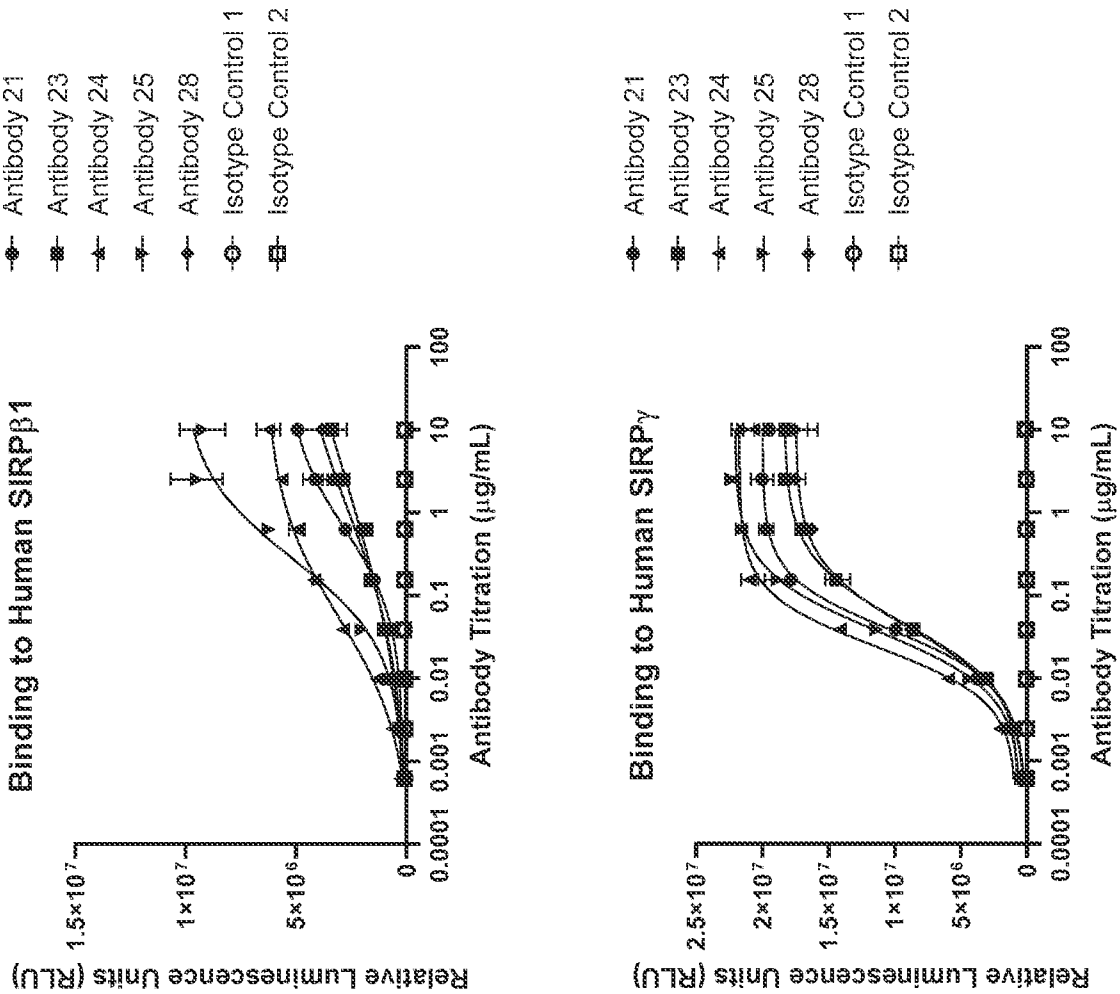

Binding to Human SIRPβ1
Antibody 21
Antibody 23
Antibody 24
Antibody 25
Antibody 28
Isotype Control 1
Isotype Control 2
Relative Luminescence Units (RLU)
1.5×10^7
1×10^7
5×10^6
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Binding to Human SIRPγ
Antibody 21
Antibody 23
Antibody 24
Antibody 25
Antibody 28
Isotype Control 1
Isotype Control 2
Relative Luminescence Units (RLU)
2.5×10^7
2×10^7
1.5×10^7
1×10^7
5×10^6
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)

FIG. 3C

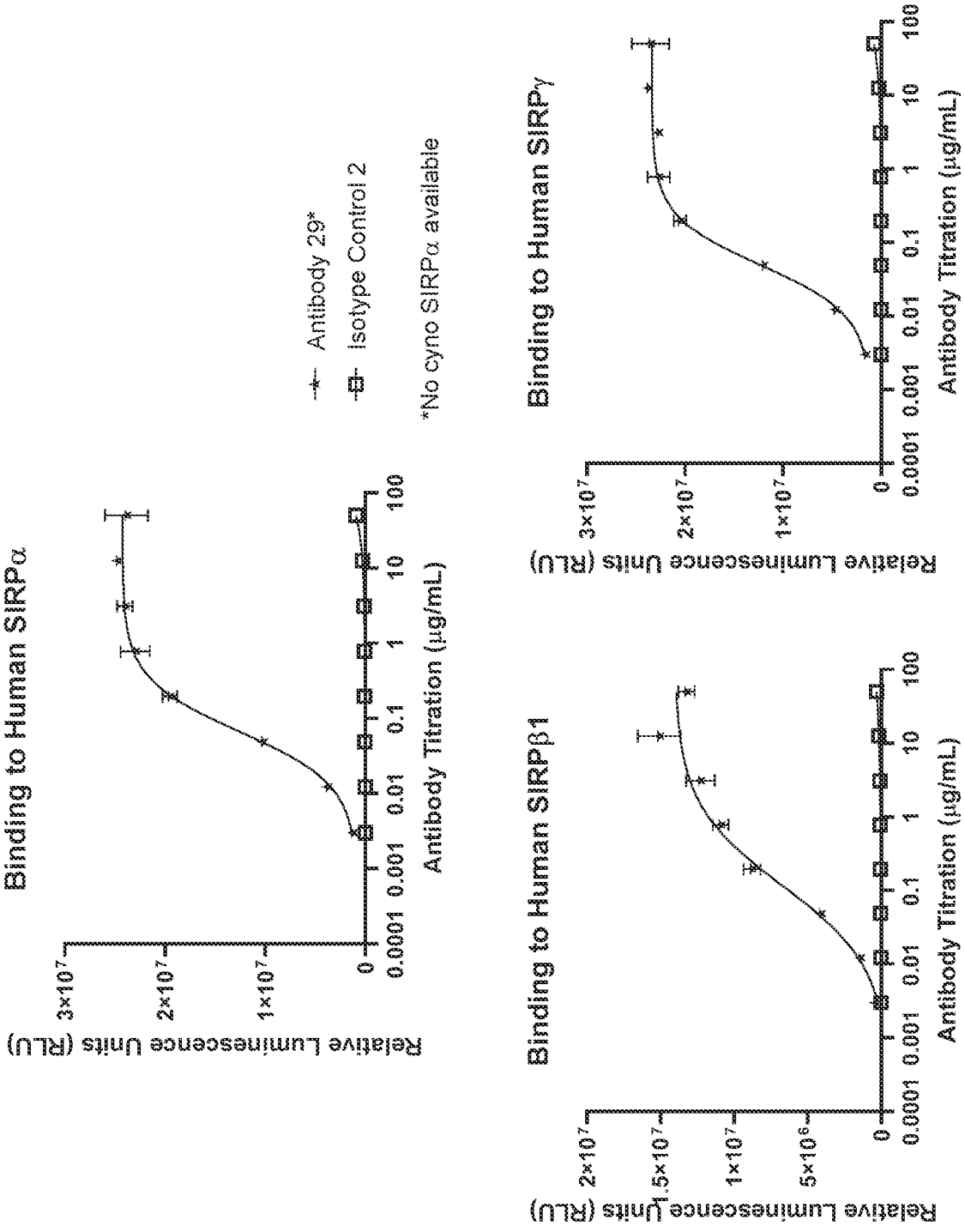

Binding to Human SIRPα
Relative Luminescence Units (RLU)
3×10^7
2×10^7
1×10^7
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Antibody 29*
Isotype Control 2
*No cyno SIRPα available
Binding to Human SIRPγ
Relative Luminescence Units (RLU)
3×10^7
2×10^7
1×10^7
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Binding to Human SIRPβ1
Relative Luminescence Units (RLU)
2×10^7
1.5×10^7
1×10^7
5×10^6
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)

FIG. 3D

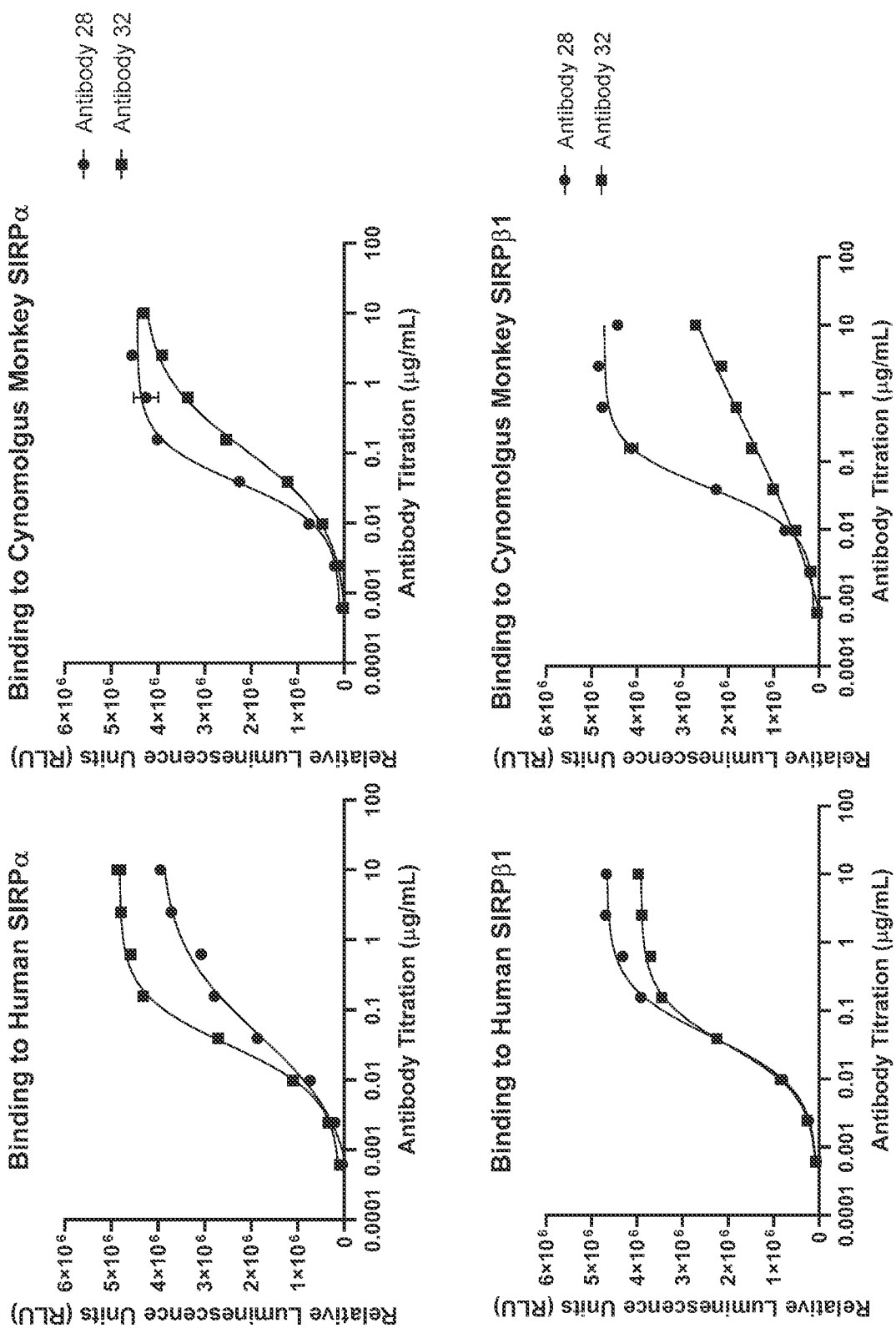

Binding to Human SIRPα
Binding to Cynomolgus Monkey SIRPα
Binding to Human SIRPβ1
Binding to Cynomolgus Monkey SIRPβ1
Relative Luminescence Units (RLU)
Antibody Titration (μg/mL)
Antibody 28
Antibody 32
0
1×10^6
2×10^6
3×10^6
4×10^6
5×10^6
6×10^6
0.0001
0.001
0.01
0.1
1
10
100

FIG. 3E

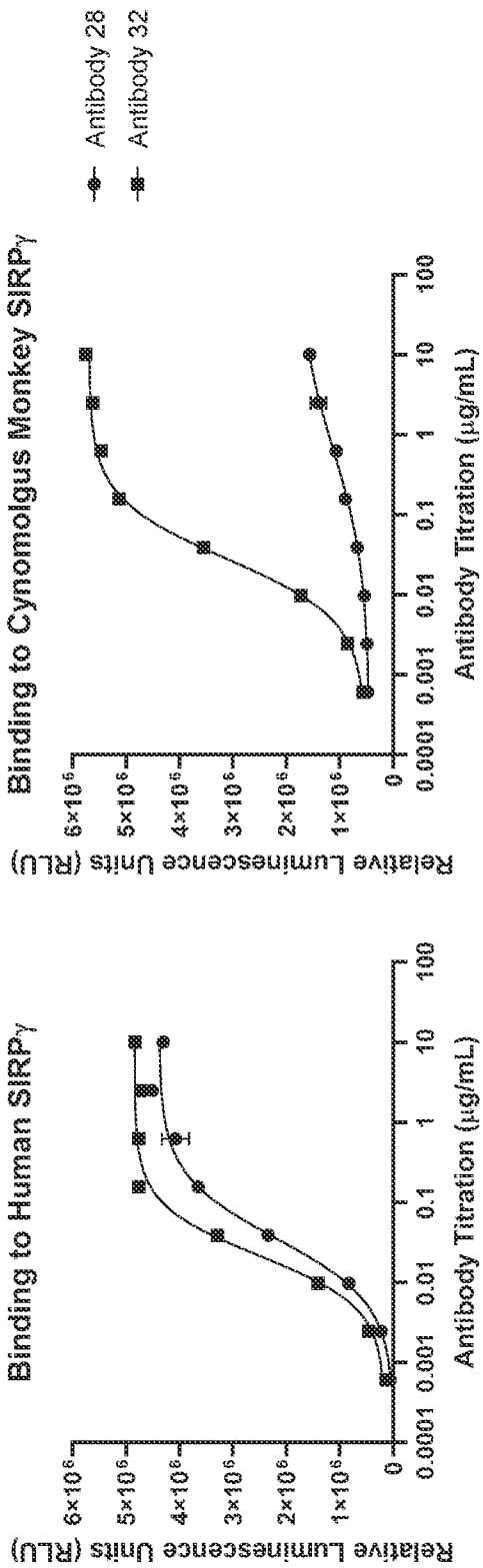

Binding to Human SIRPγ
Relative Luminescence Units (RLU)
6×10^6
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Binding to Cynomolgus Monkey SIRPγ
Relative Luminescence Units (RLU)
6×10^6
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Antibody 28
Antibody 32

FIG. 4A

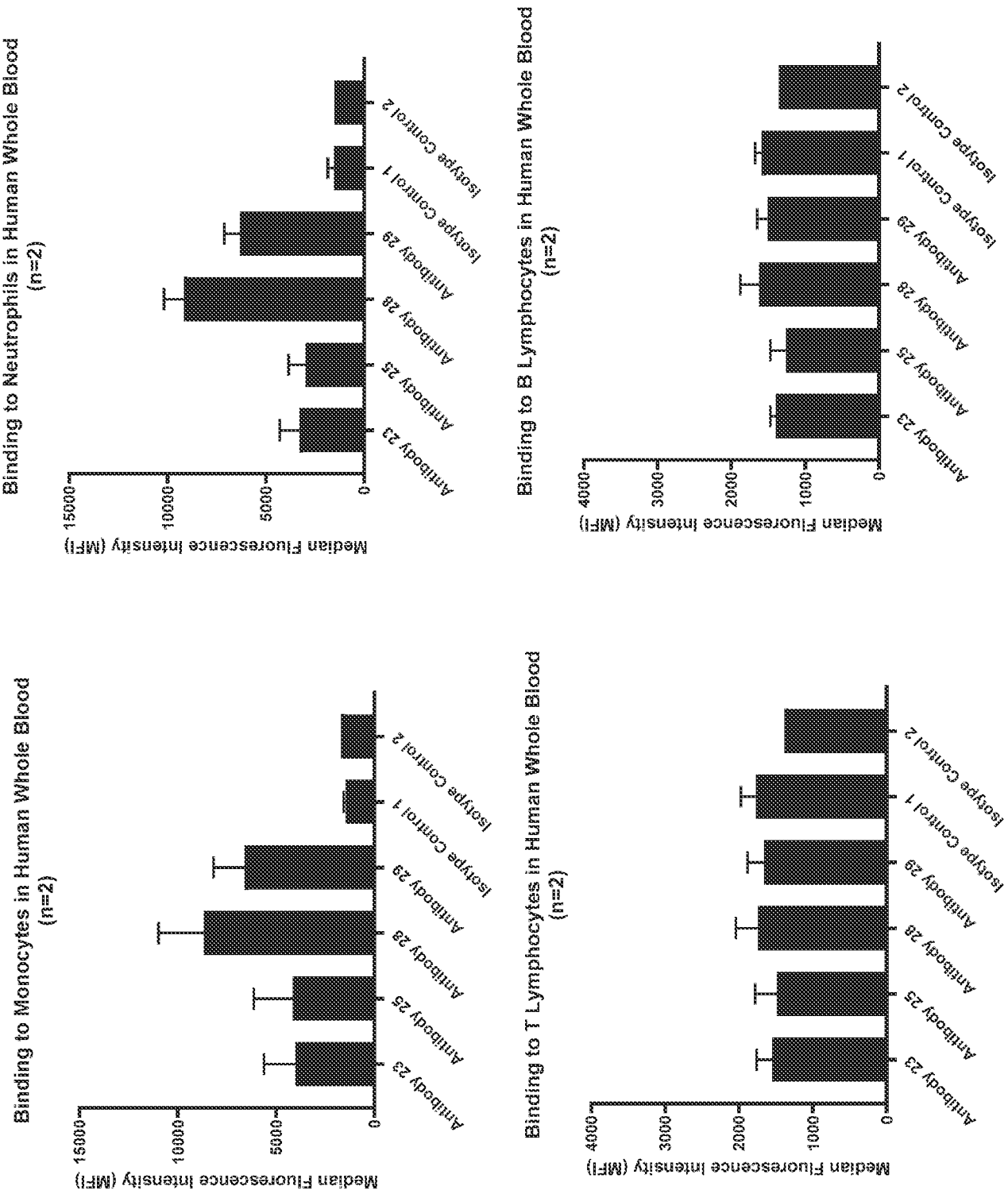

Binding to Neutrophils in Human Whole Blood
(n=2)
Median Fluorescence Intensity (MFI)
15000
10000
5000
0
Antibody 23
Antibody 25
Antibody 28
Antibody 29
Isotype Control 1
Isotype Control 2
Binding to B Lymphocytes in Human Whole Blood
(n=2)
Median Fluorescence Intensity (MFI)
4000
3000
2000
1000
0
Antibody 23
Antibody 25
Antibody 28
Antibody 29
Isotype Control 1
Isotype Control 2
Binding to Monocytes in Human Whole Blood
(n=2)
Median Fluorescence Intensity (MFI)
15000
10000
5000
0
Antibody 23
Antibody 25
Antibody 28
Antibody 29
Isotype Control 1
Isotype Control 2
Binding to T Lymphocytes in Human Whole Blood
(n=2)
Median Fluorescence Intensity (MFI)
4000
3000
2000
1000
0
Antibody 23
Antibody 25
Antibody 28
Antibody 29
Isotype Control 1
Isotype Control 2

FIG. 4B

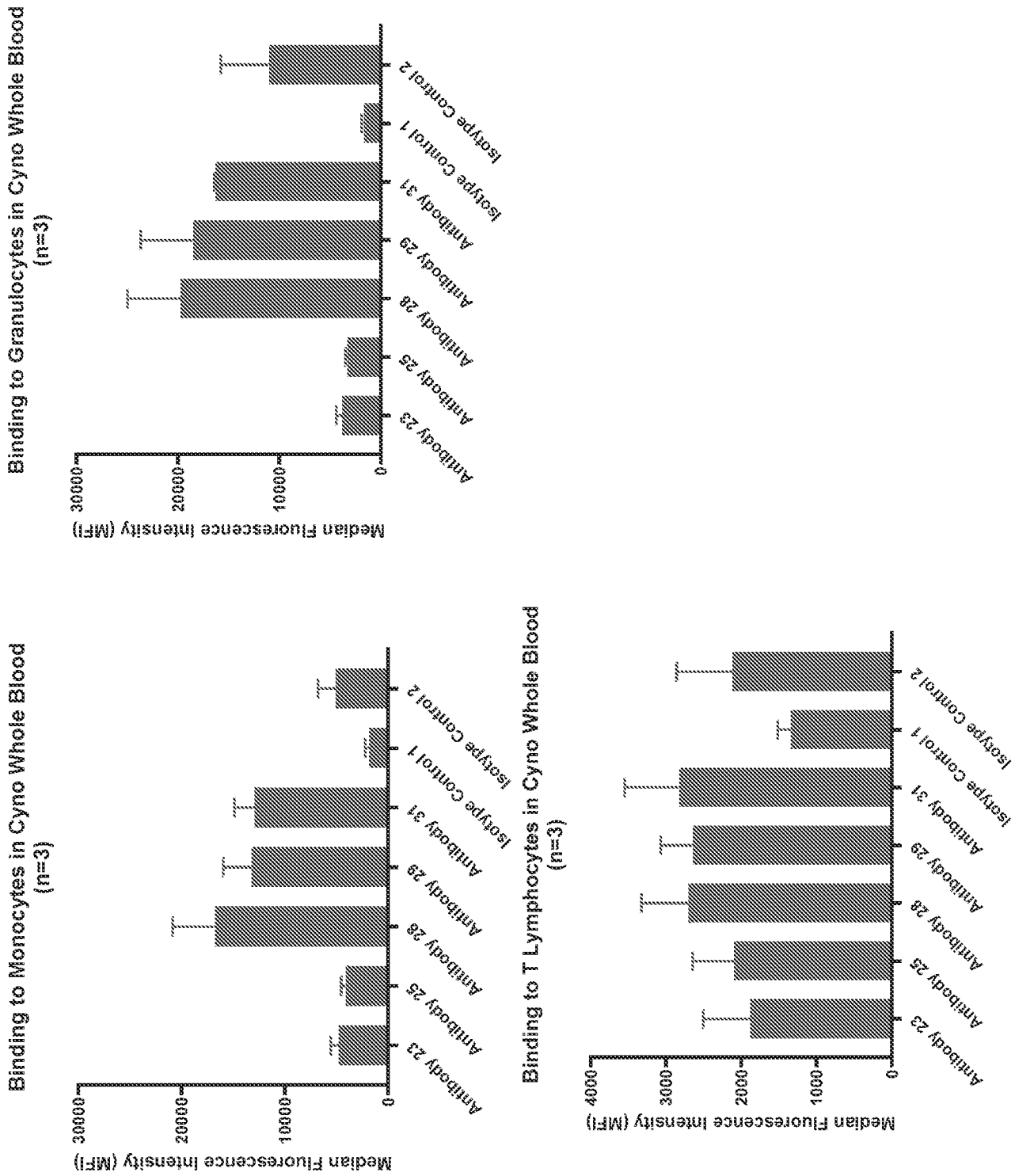

Binding to Granulocytes in Cyno Whole Blood
(n=3)
Median Fluorescence Intensity (MFI)
30000
20000
10000
0
Antibody 23
Antibody 25
Antibody 28
Antibody 29
Antibody 31
Isotype Control 1
Isotype Control 2
Binding to Monocytes in Cyno Whole Blood
(n=3)
Median Fluorescence Intensity (MFI)
30000
20000
10000
0
Antibody 23
Antibody 25
Antibody 28
Antibody 29
Antibody 31
Isotype Control 1
Isotype Control 2
Binding to T Lymphocytes in Cyno Whole Blood
(n=3)
Median Fluorescence Intensity (MFI)
4000
3000
2000
1000
0
Antibody 23
Antibody 25
Antibody 28
Antibody 29
Antibody 31
Isotype Control 1
Isotype Control 2

FIG. 4C

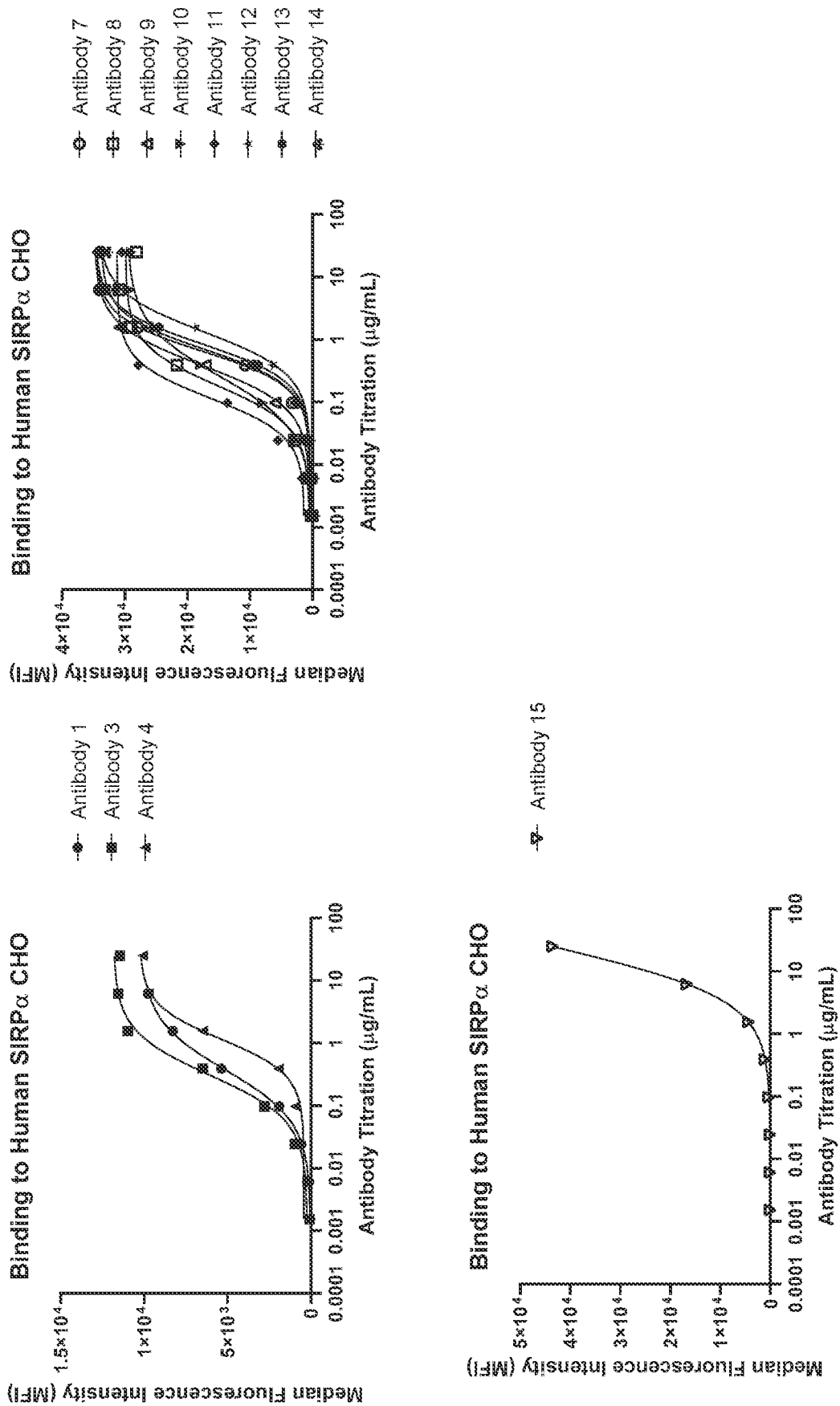

Binding to Human SIRPα CHO
Median Fluorescence Intensity (MFI)
Antibody Titration (μg/mL)
Antibody 1
Antibody 3
Antibody 4
Antibody 7
Antibody 8
Antibody 9
Antibody 10
Antibody 11
Antibody 12
Antibody 13
Antibody 14
Antibody 15

FIG.4D

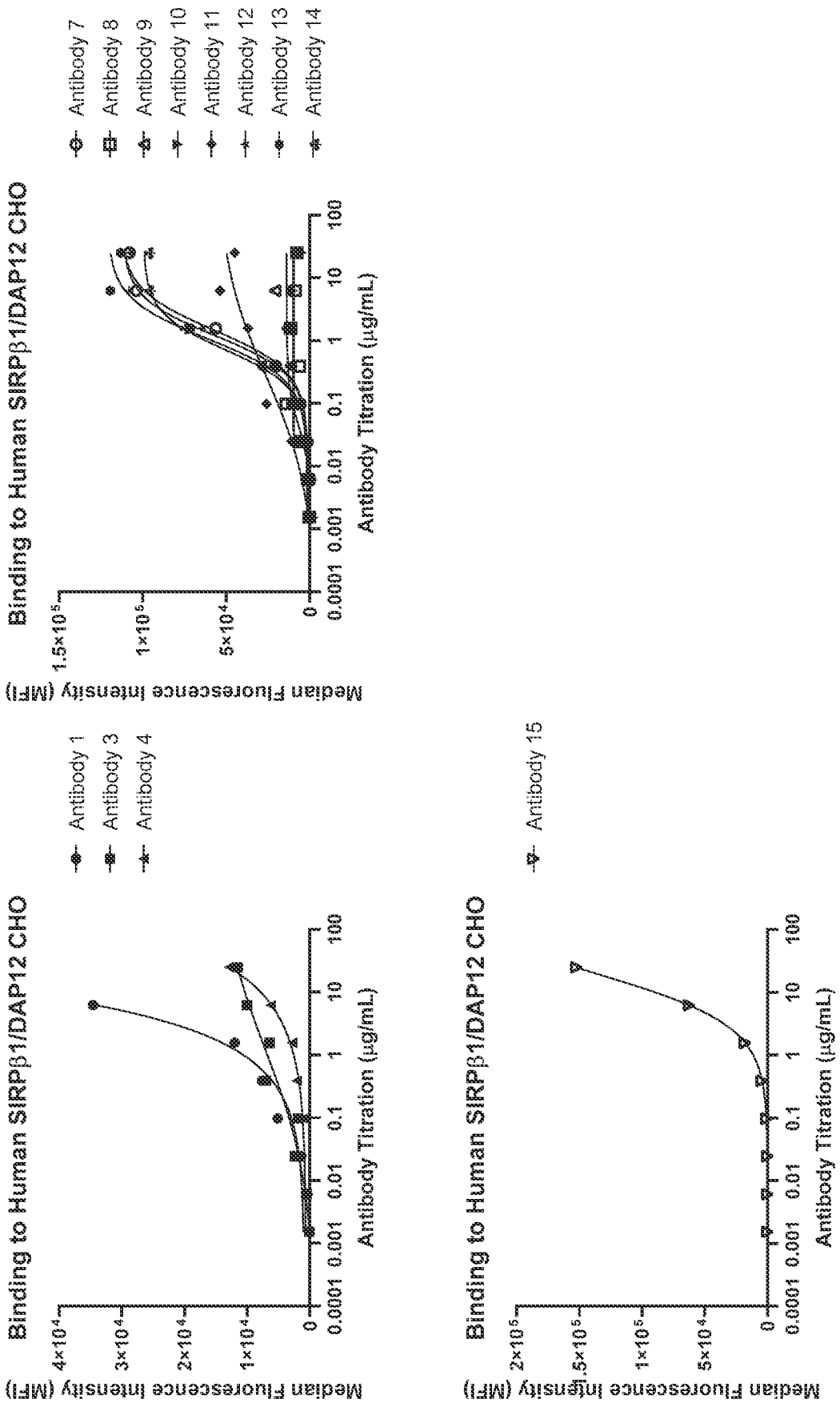

Binding to Human SIRPβ1/DAP12 CHO
Median Fluorescence Intensity (MFI)
Antibody Titration (μg/mL)
Antibody 1
Antibody 3
Antibody 4
Antibody 7
Antibody 8
Antibody 9
Antibody 10
Antibody 11
Antibody 12
Antibody 13
Antibody 14
Antibody 15

FIG. 4E

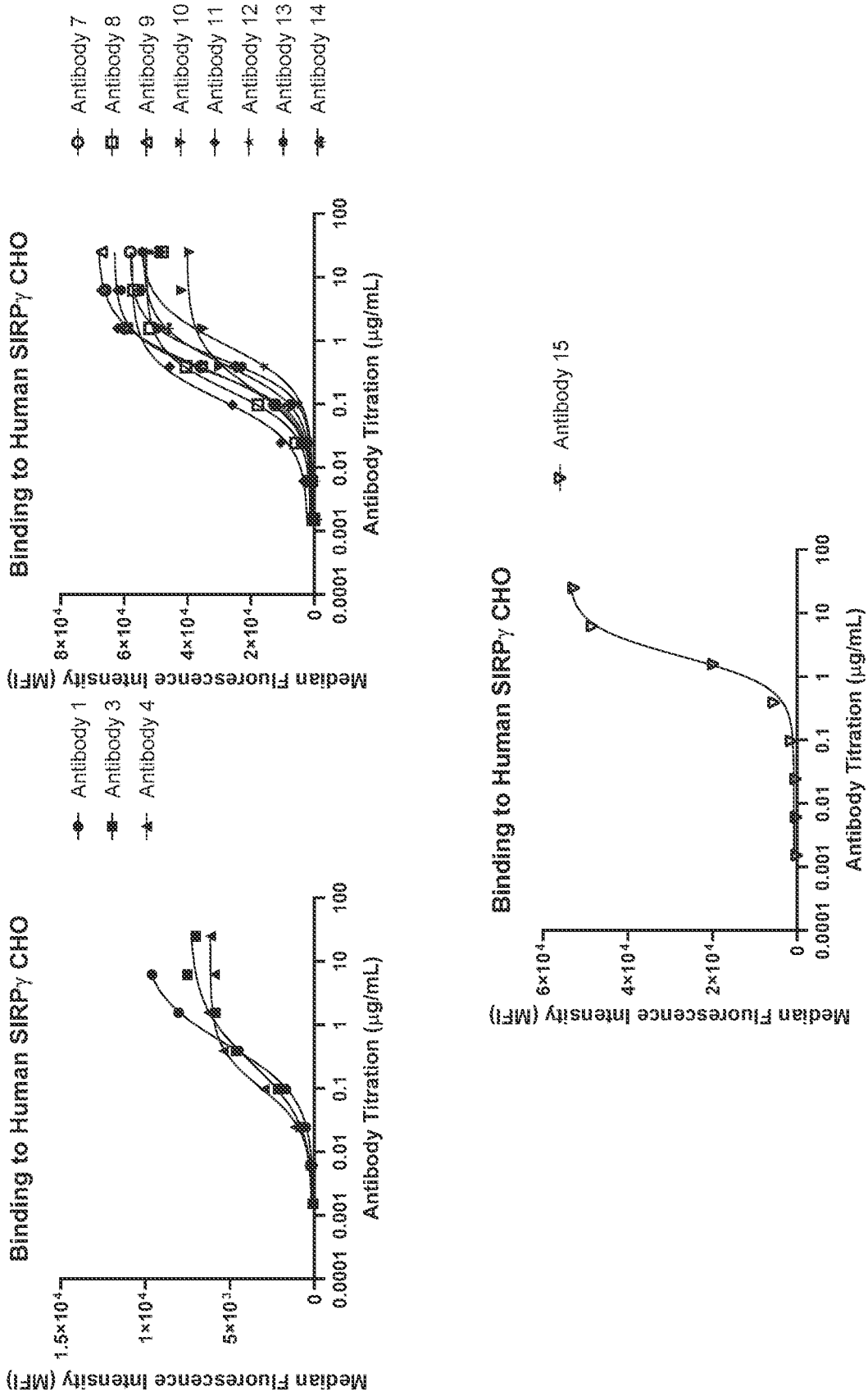

Binding to Human SIRPγ CHO
Median Fluorescence Intensity (MFI)
Antibody Titration (μg/mL)
Antibody 1
Antibody 3
Antibody 4
Antibody 7
Antibody 8
Antibody 9
Antibody 10
Antibody 11
Antibody 12
Antibody 13
Antibody 14
Antibody 15

FIG. 4F

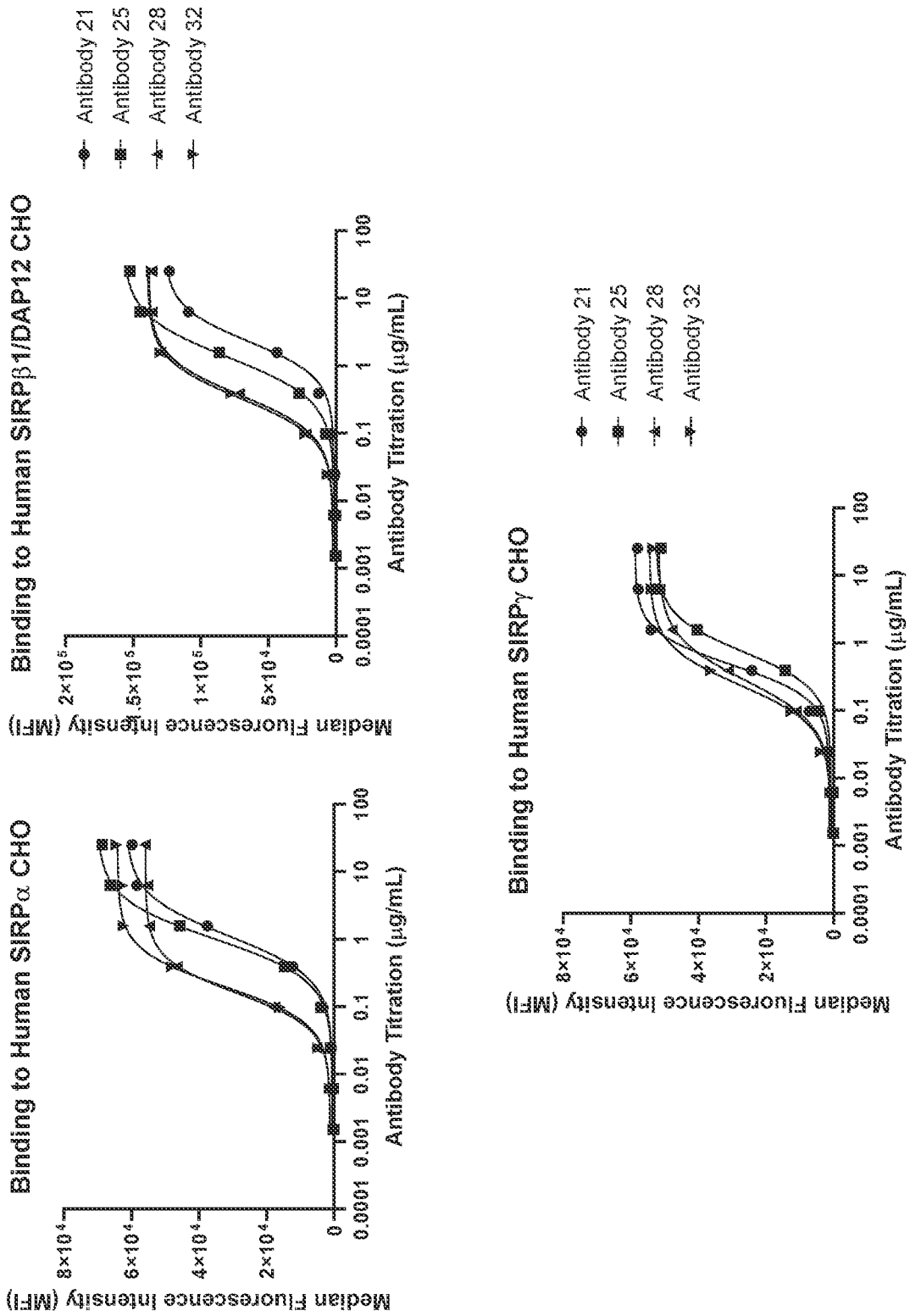

Binding to Human SIRPα CHO
Median Fluorescence Intensity (MFI)
8×10⁴
6×10⁴
4×10⁴
2×10⁴
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Binding to Human SIRPβ1/DAP12 CHO
Median Fluorescence Intensity (MFI)
2×10⁵
1.5×10⁵
1×10⁵
5×10⁴
0
0.0001 0.001 0.01 0.1 1 10 100
Antibody Titration (μg/mL)
Antibody 21
Antibody 25
Antibody 28
Antibody 32
Binding to Human SIRPγ CHO
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)
Antibody 21
Antibody 25
Antibody 28
Antibody 32

FIG. 5

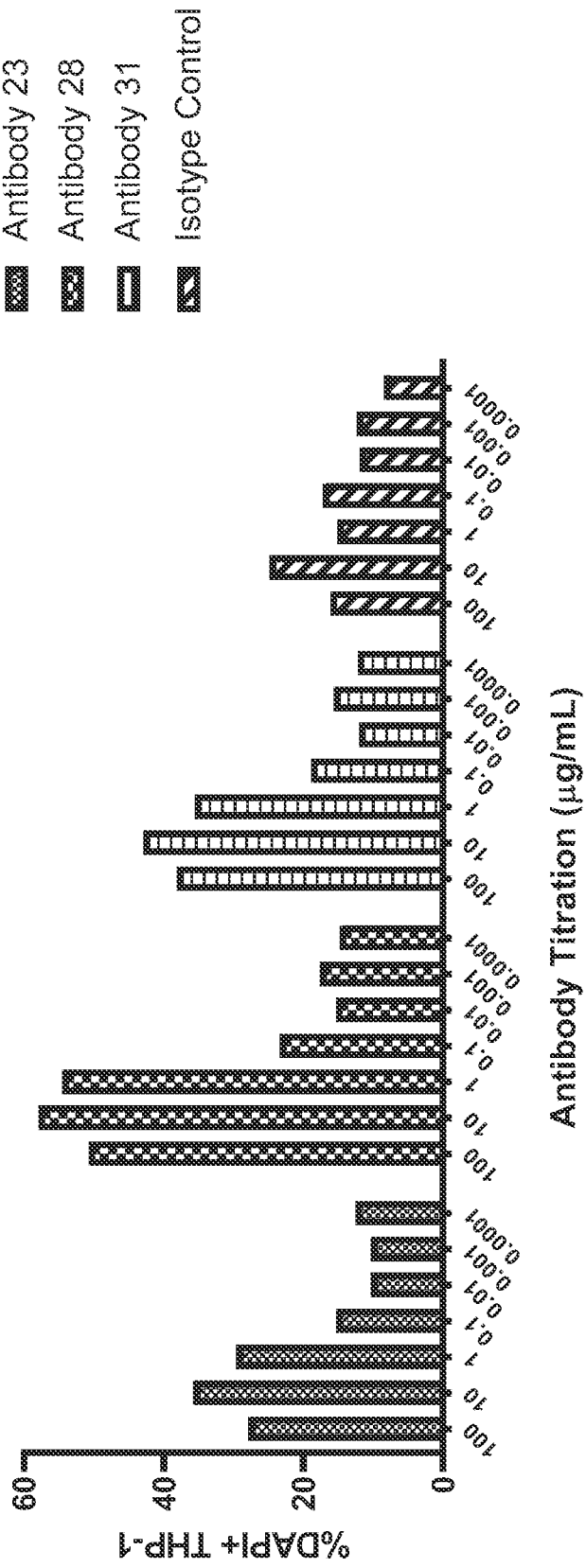

Antibody 23
Antibody 28
Antibody 31
Isotype Control
%DAPI+ THP-1
60
40
20
0
Antibody Titration (µg/mL)
100
10
1
0.1
0.01
0.001
0.0001

FIG. 6A

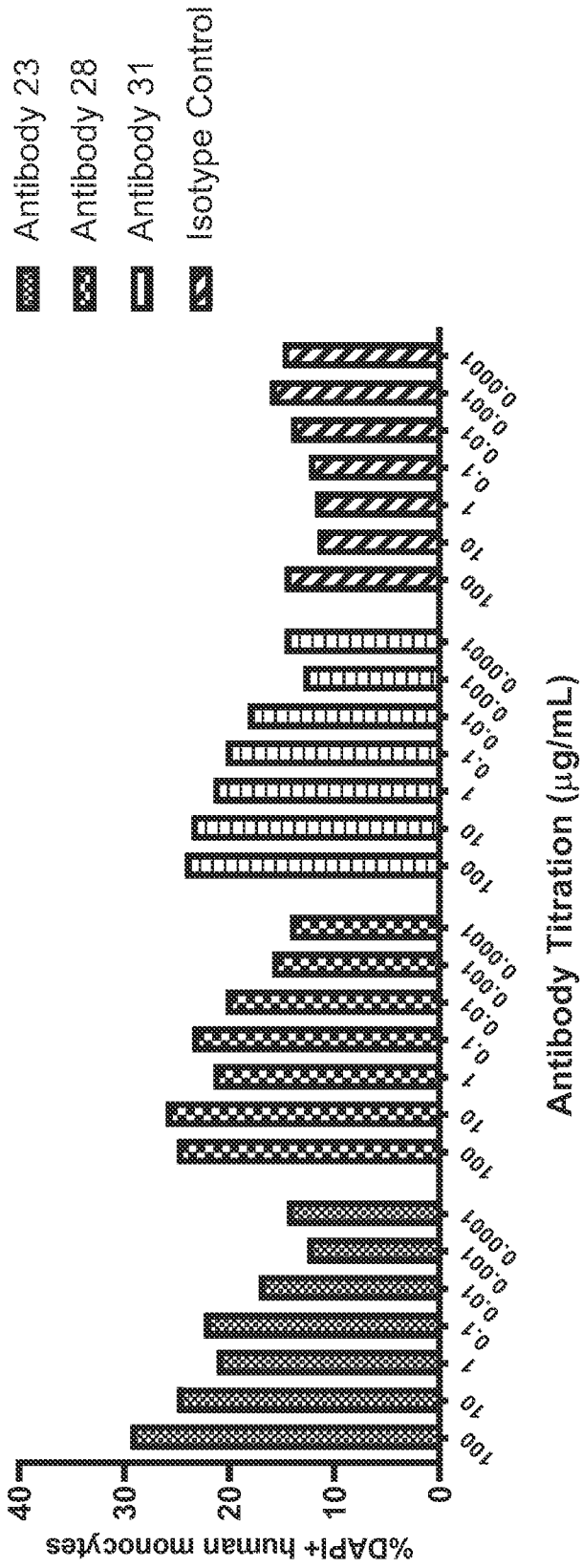

Antibody 23
Antibody 28
Antibody 31
Isotype Control
%DAPI+ human monocytes
0
10
20
30
40
100
10
1
0.1
0.01
0.001
0.0001
Antibody Titration (μg/mL)

FIG. 6B

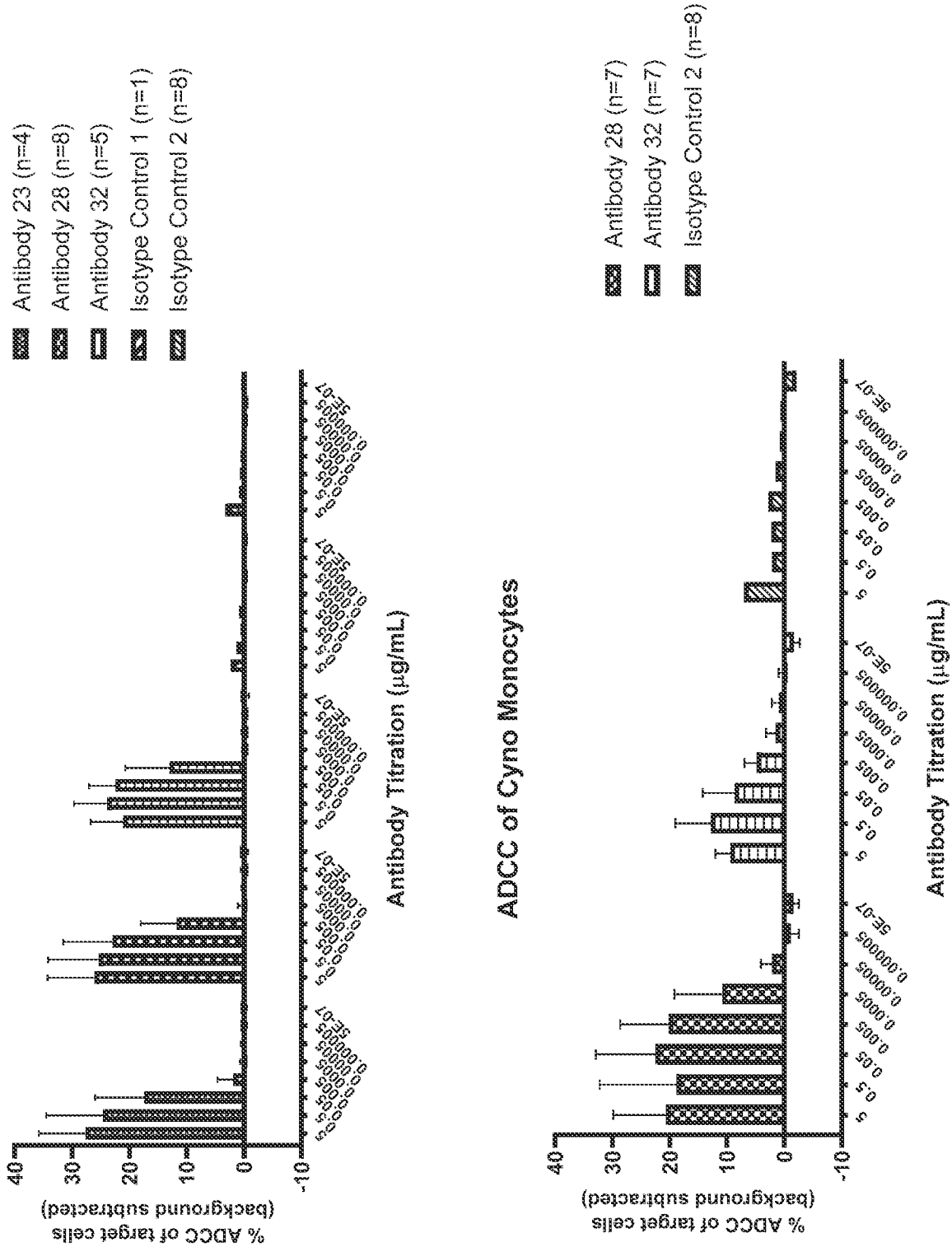

ADCC of Human Monocytes
Antibody 23 (n=4)
Antibody 28 (n=8)
Antibody 32 (n=5)
Isotype Control 1 (n=1)
Isotype Control 2 (n=8)
% ADCC of target cells (background subtracted)
Antibody Titration (µg/mL)
ADCC of Cyno Monocytes
Antibody 28 (n=7)
Antibody 32 (n=7)
Isotype Control 2 (n=8)
% ADCC of target cells (background subtracted)
Antibody Titration (µg/mL)

FIG. 6C

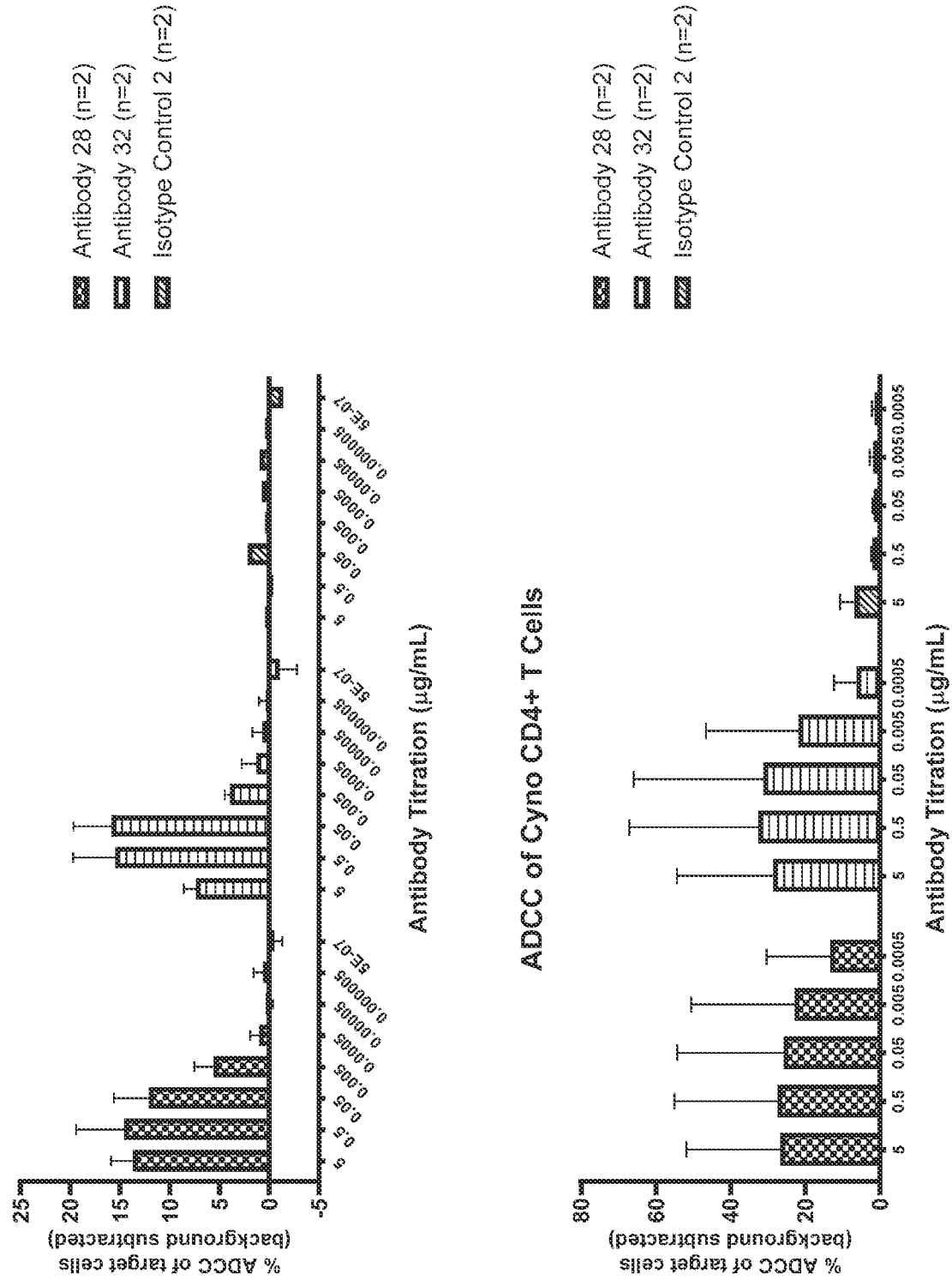

ADCC of Human CD4+ T Cells
Antibody 28 (n=2)
Antibody 32 (n=2)
Isotype Control 2 (n=2)
% ADCC of target cells (background subtracted)
Antibody Titration (µg/mL)
ADCC of Cyno CD4+ T Cells
Antibody 28 (n=2)
Antibody 32 (n=2)
Isotype Control 2 (n=2)
% ADCC of target cells (background subtracted)
Antibody Titration (µg/mL)

FIG. 6D

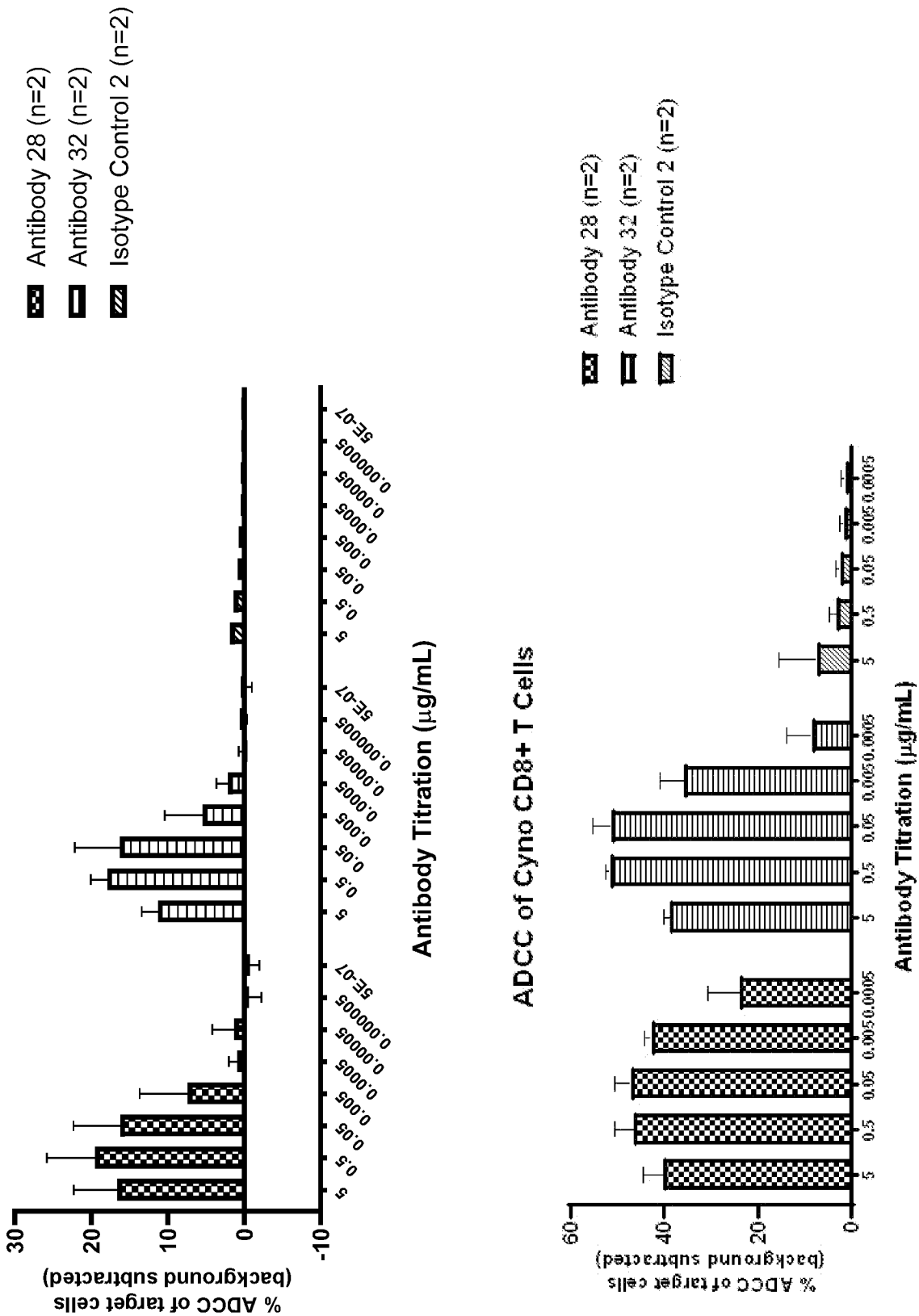

ADCC of Human CD8+ T Cells
Antibody 28 (n=2)
Antibody 32 (n=2)
Isotype Control 2 (n=2)
% ADCC of target cells (background subtracted)
Antibody Titration (µg/mL)
ADCC of Cyno CD8+ T Cells
Antibody 28 (n=2)
Antibody 32 (n=2)
Isotype Control 2 (n=2)
% ADCC of target cells (background subtracted)
Antibody Titration (µg/mL)

FIG. 7

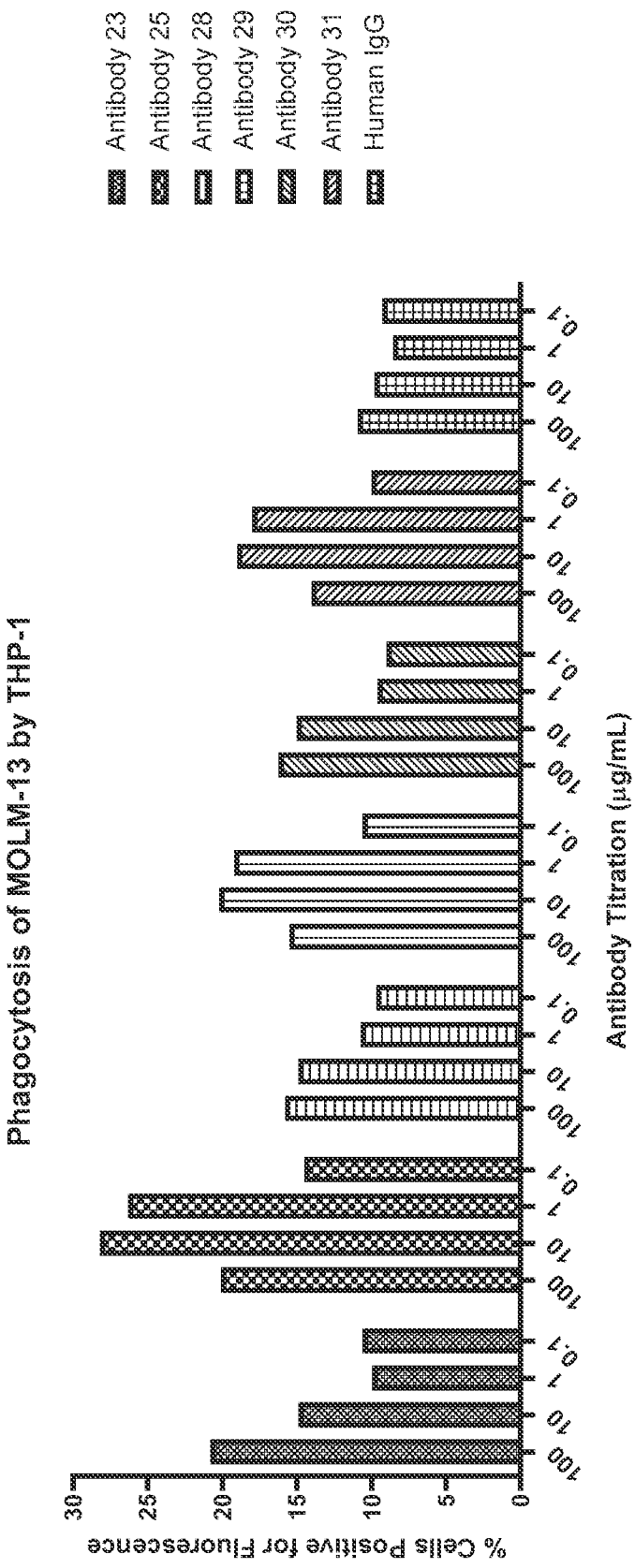

Phagocytosis of MOLM-13 by THP-1
% Cells Positive for Fluorescence
0
5
10
15
20
25
30
Antibody Titration (µg/mL)
100
10
1
0.1
Antibody 23
Antibody 25
Antibody 28
Antibody 29
Antibody 30
Antibody 31
Human IgG

FIG. 8

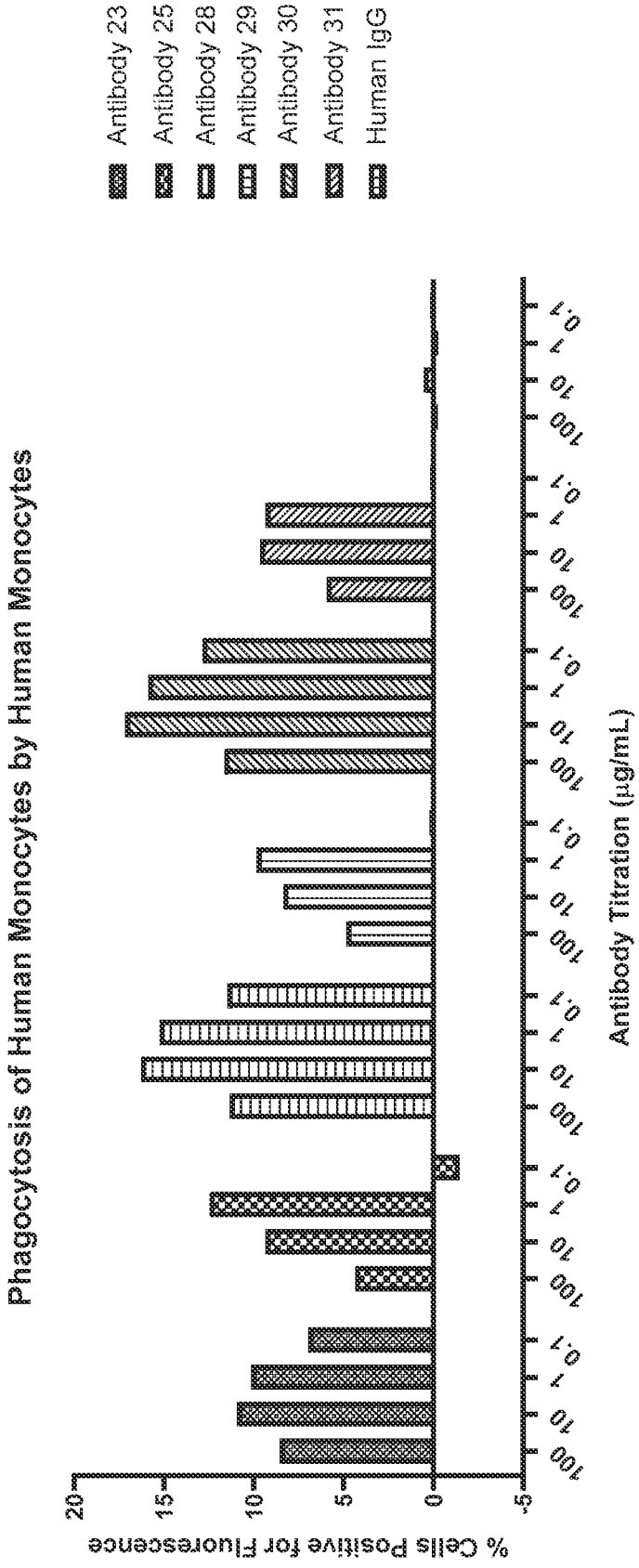

Phagocytosis of Human Monocytes by Human Monocytes
Antibody 23
Antibody 25
Antibody 28
Antibody 29
Antibody 30
Antibody 31
Human IgG
% Cells Positive for Fluorescence
20
15
10
5
0
-5
Antibody Titration (µg/mL)
100
10
1
0.1

FIG. 9A

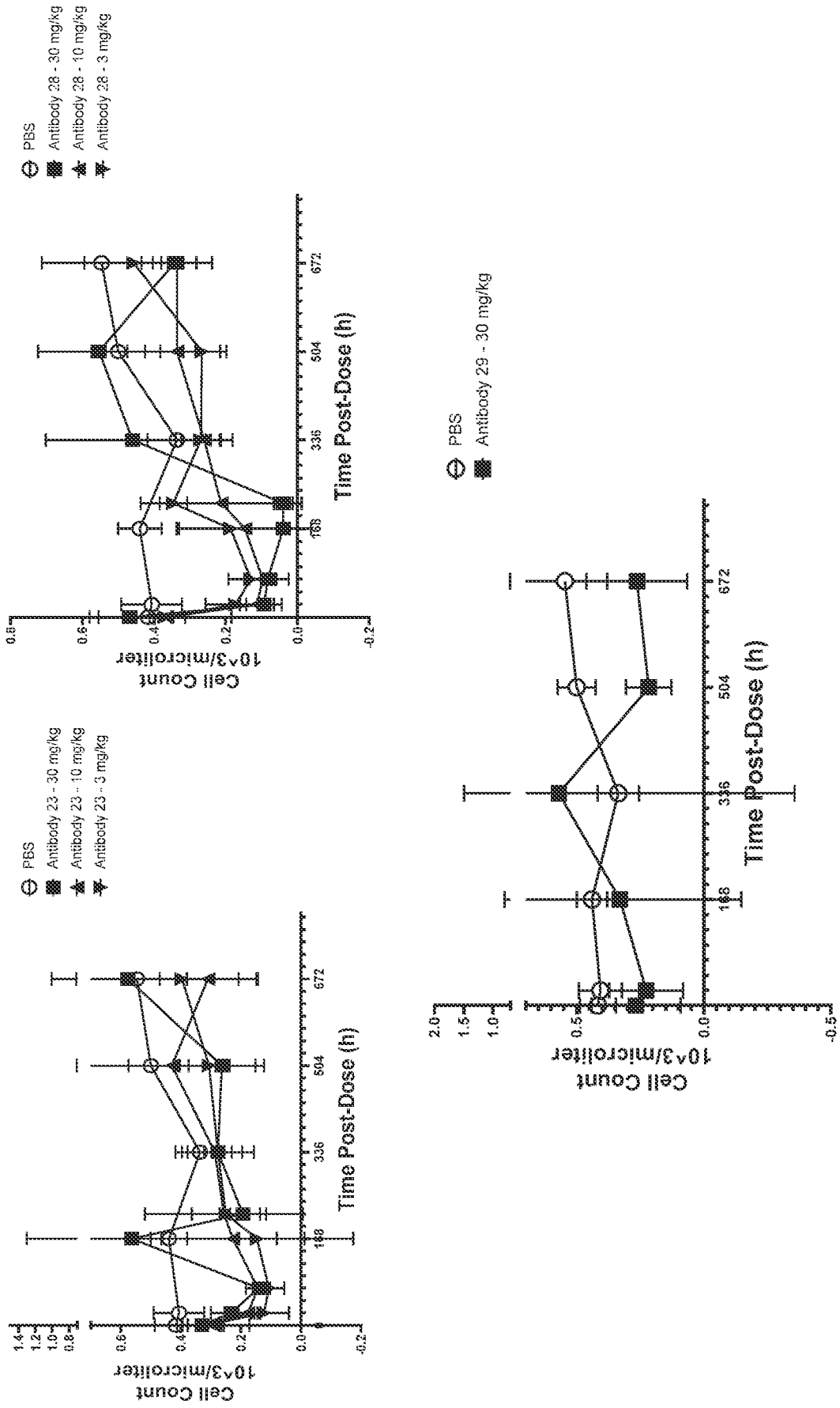

PBS
Antibody 28 - 30 mg/kg
Antibody 28 - 10 mg/kg
Antibody 28 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
PBS
Antibody 23 - 30 mg/kg
Antibody 23 - 10 mg/kg
Antibody 23 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
PBS
Antibody 29 - 30 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)

FIG. 9B

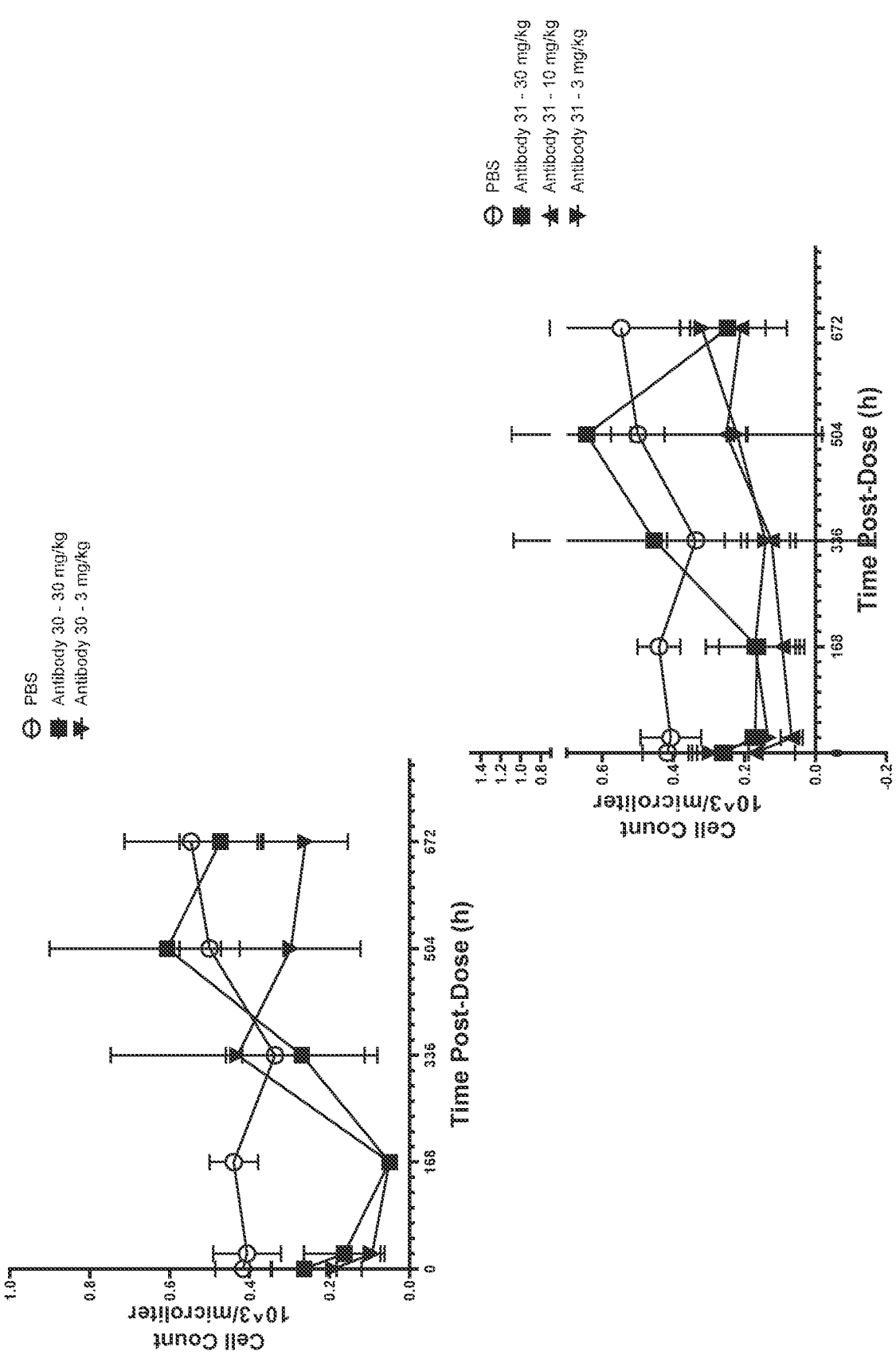

PBS
Antibody 30 - 30 mg/kg
Antibody 30 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
0
168
336
504
672
0.0
0.2
0.4
0.6
0.8
1.0
PBS
Antibody 31 - 30 mg/kg
Antibody 31 - 10 mg/kg
Antibody 31 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
0
168
336
504
672
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4

FIG. 10A

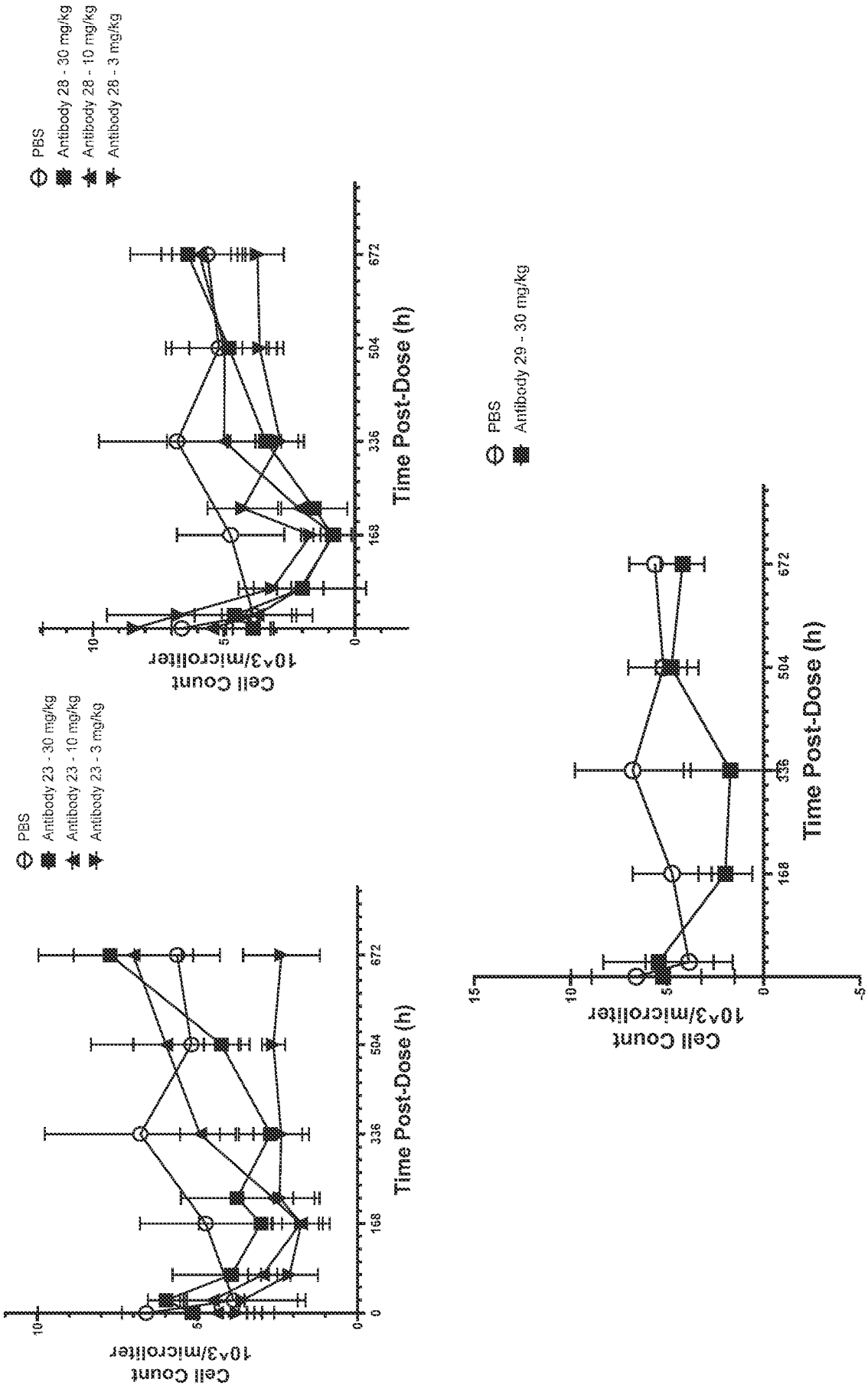

PBS
Antibody 28 - 30 mg/kg
Antibody 28 - 10 mg/kg
Antibody 28 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
0
168
336
504
672
PBS
Antibody 23 - 30 mg/kg
Antibody 23 - 10 mg/kg
Antibody 23 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
PBS
Antibody 29 - 30 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)

FIG. 10B

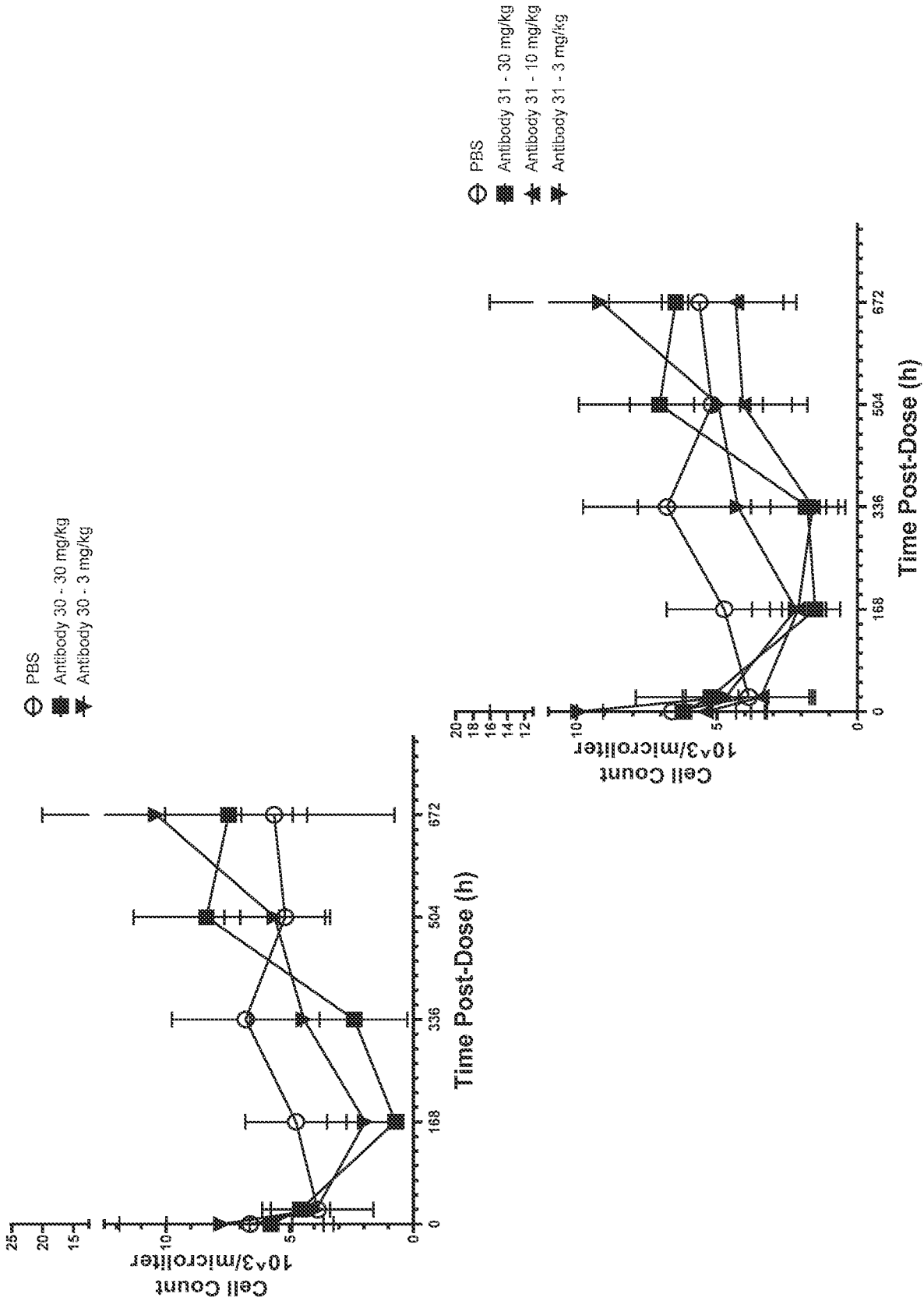

PBS
Antibody 30 - 30 mg/kg
Antibody 30 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
0
168
336
504
672
PBS
Antibody 31 - 30 mg/kg
Antibody 31 - 10 mg/kg
Antibody 31 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)

FIG. 11A

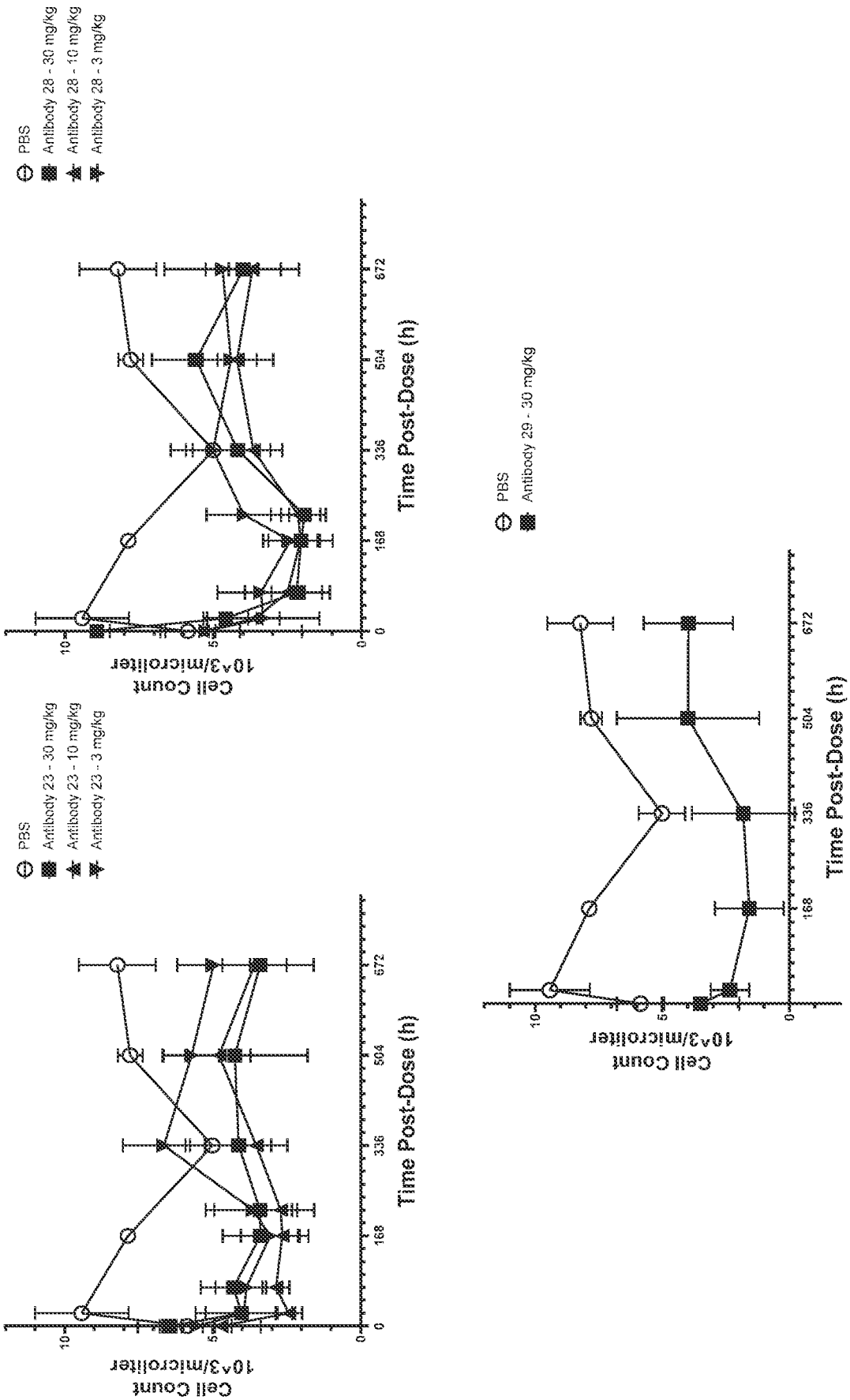

PBS
Antibody 28 - 30 mg/kg
Antibody 28 - 10 mg/kg
Antibody 28 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
0
168
336
504
672
5
10
PBS
Antibody 23 - 30 mg/kg
Antibody 23 - 10 mg/kg
Antibody 23 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
PBS
Antibody 29 - 30 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)

FIG. 11B

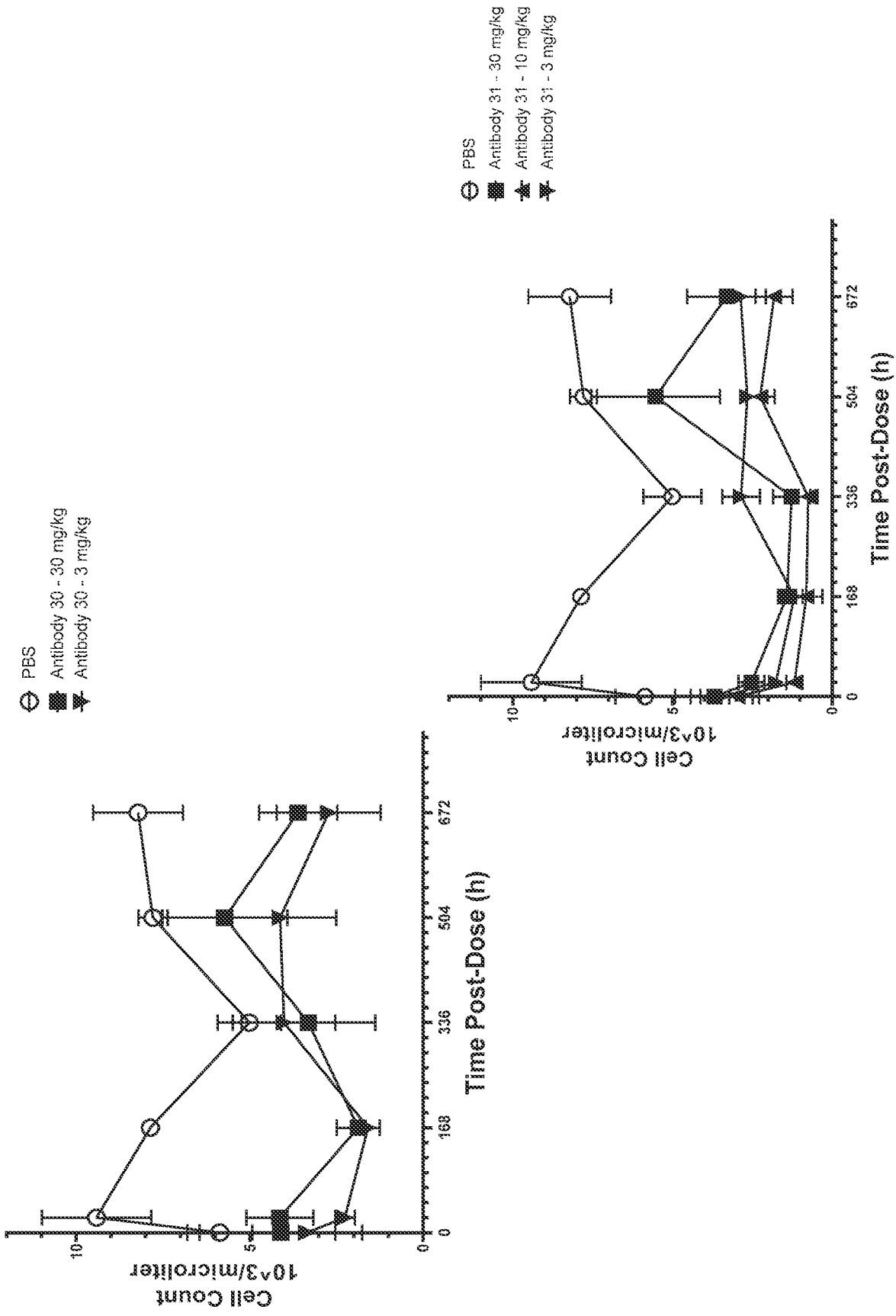

PBS
Antibody 30 - 30 mg/kg
Antibody 30 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
0
168
336
504
672
5
10
PBS
Antibody 31 - 30 mg/kg
Antibody 31 - 10 mg/kg
Antibody 31 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)

FIG. 12A

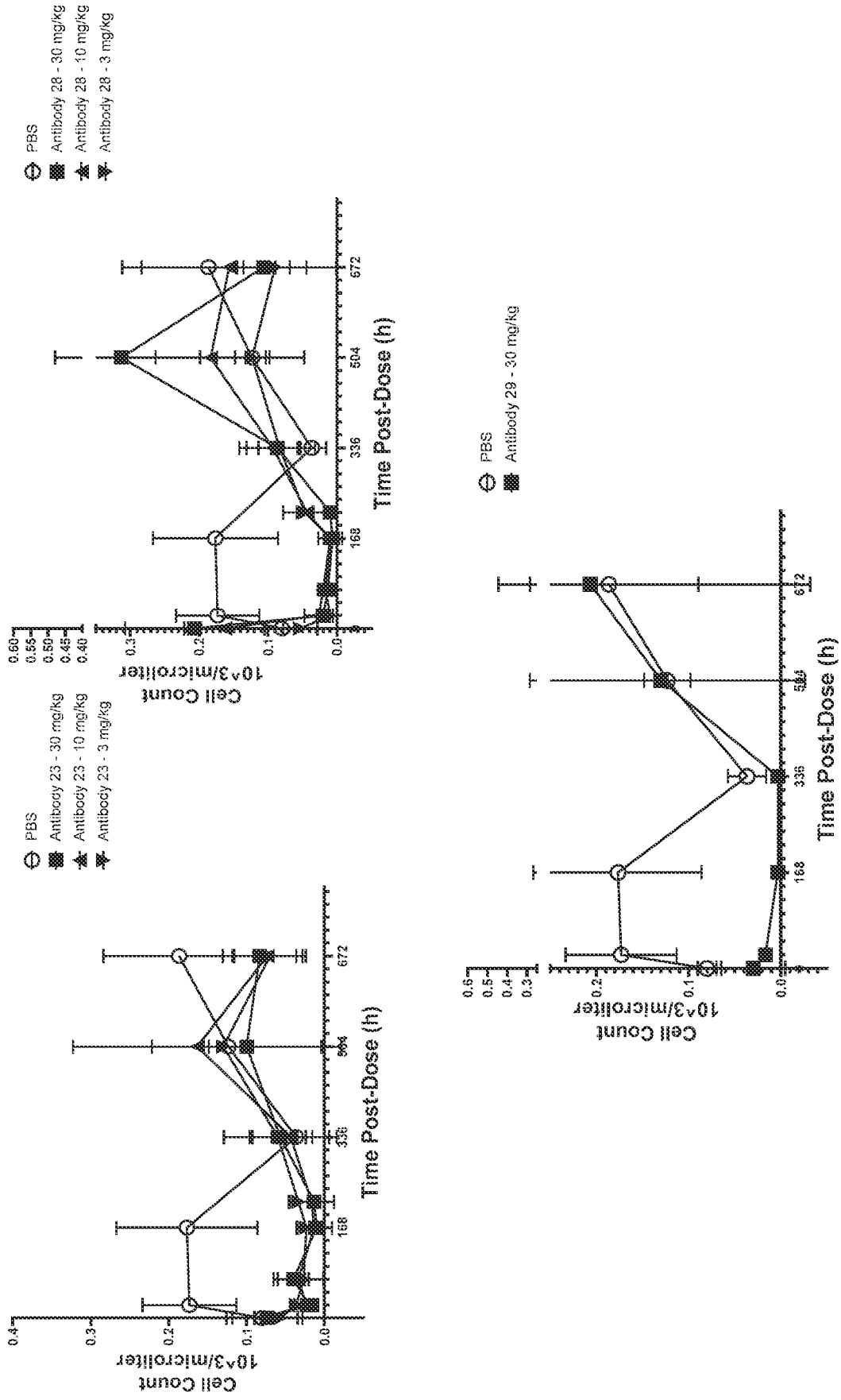

PBS
Antibody 23 - 30 mg/kg
Antibody 23 - 10 mg/kg
Antibody 23 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
PBS
Antibody 28 - 30 mg/kg
Antibody 28 - 10 mg/kg
Antibody 28 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
PBS
Antibody 29 - 30 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)

FIG. 12B

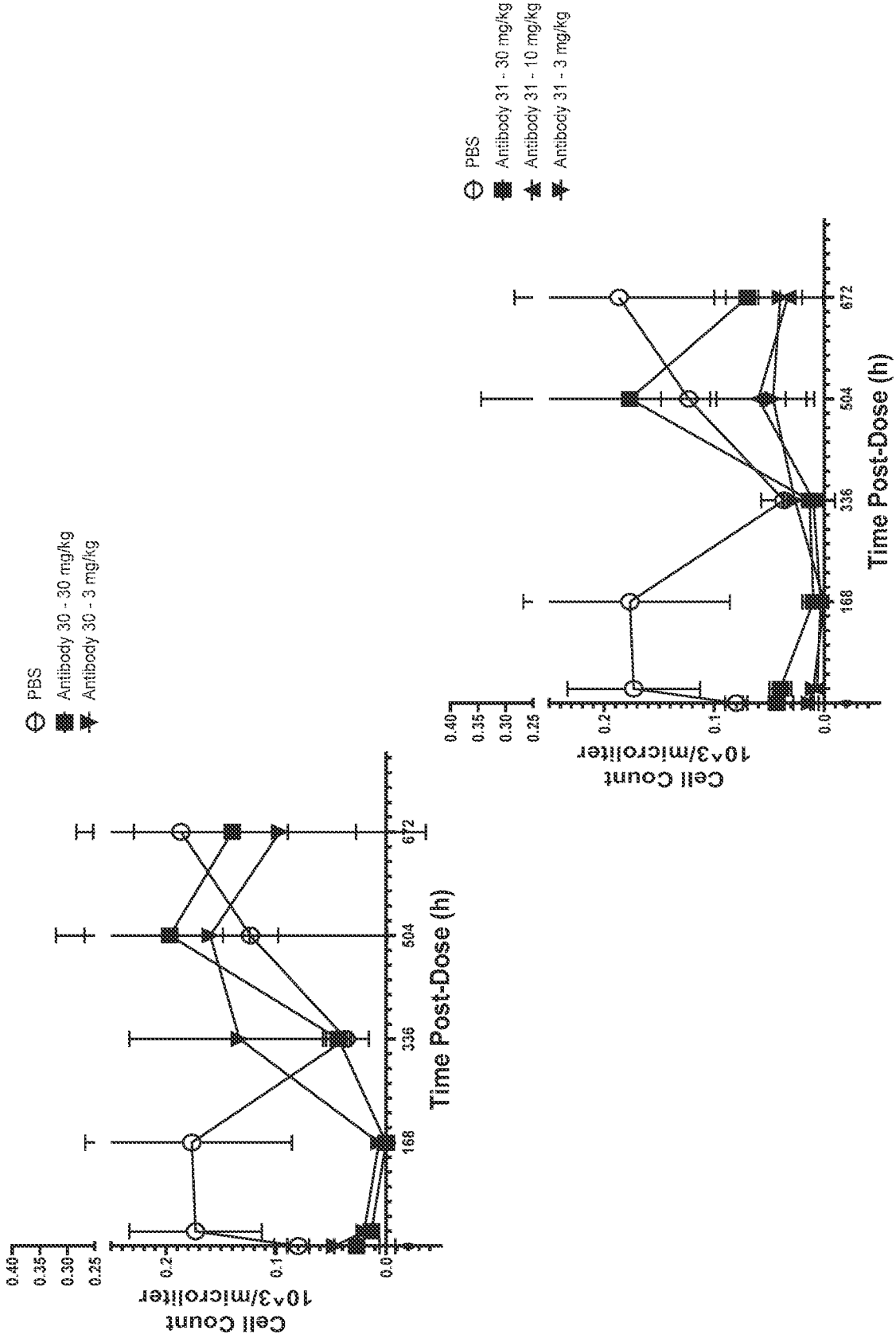

PBS
Antibody 30 - 30 mg/kg
Antibody 30 - 3 mg/kg
Cell Count
10^3/microliter
0.40
0.35
0.30
0.25
0.2
0.1
0.0
168
336
504
672
Time Post-Dose (h)
PBS
Antibody 31 - 30 mg/kg
Antibody 31 - 10 mg/kg
Antibody 31 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)

FIG. 13A

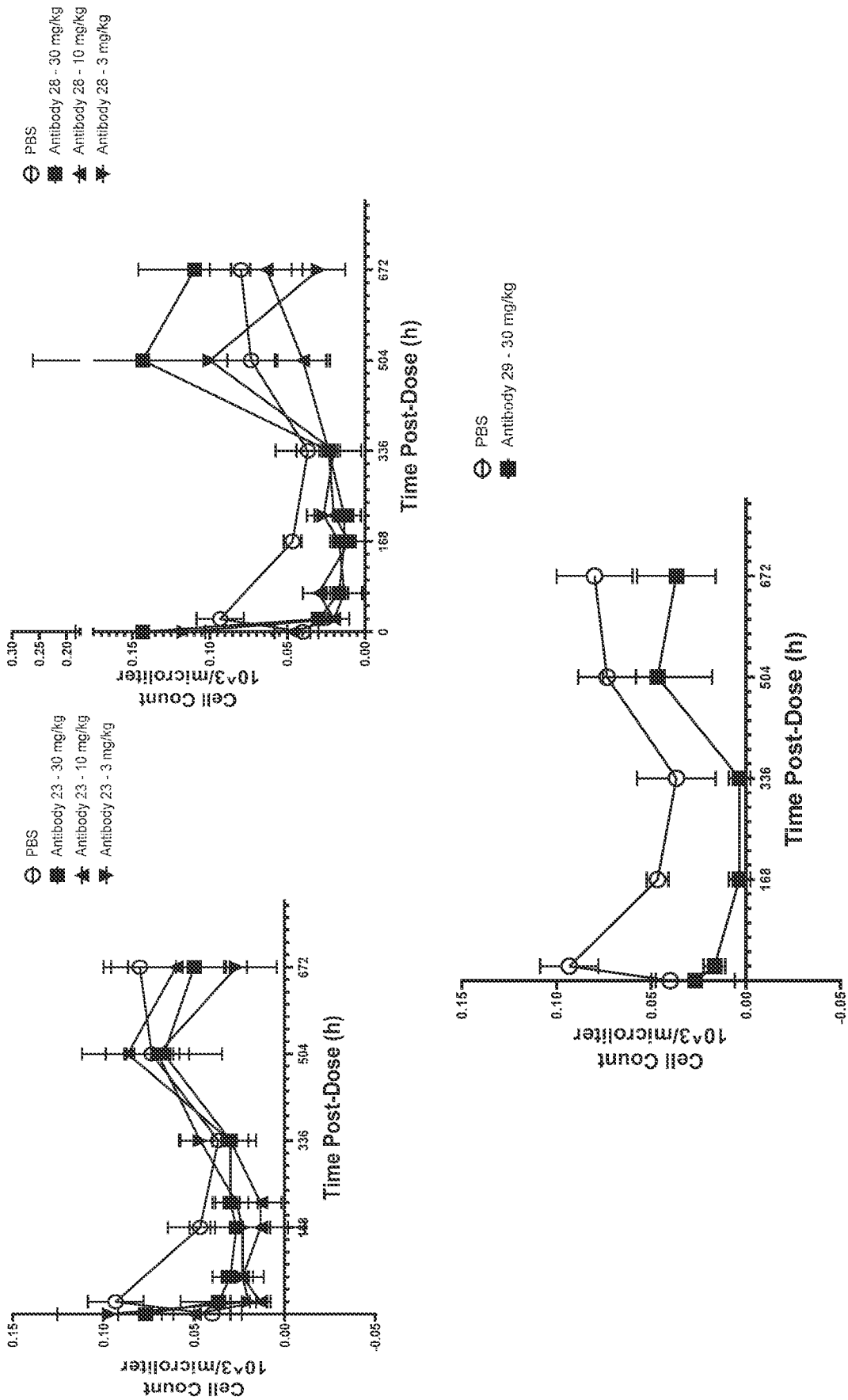

PBS
Antibody 23 - 30 mg/kg
Antibody 23 - 10 mg/kg
Antibody 23 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
0.15
0.10
0.05
0.00
-0.05
168
336
504
672
PBS
Antibody 28 - 30 mg/kg
Antibody 28 - 10 mg/kg
Antibody 28 - 3 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0
168
336
504
672
PBS
Antibody 29 - 30 mg/kg
Cell Count
10^3/microliter
Time Post-Dose (h)
0.15
0.10
0.05
0.00
-0.05
168
336
504
672

FIG. 13B

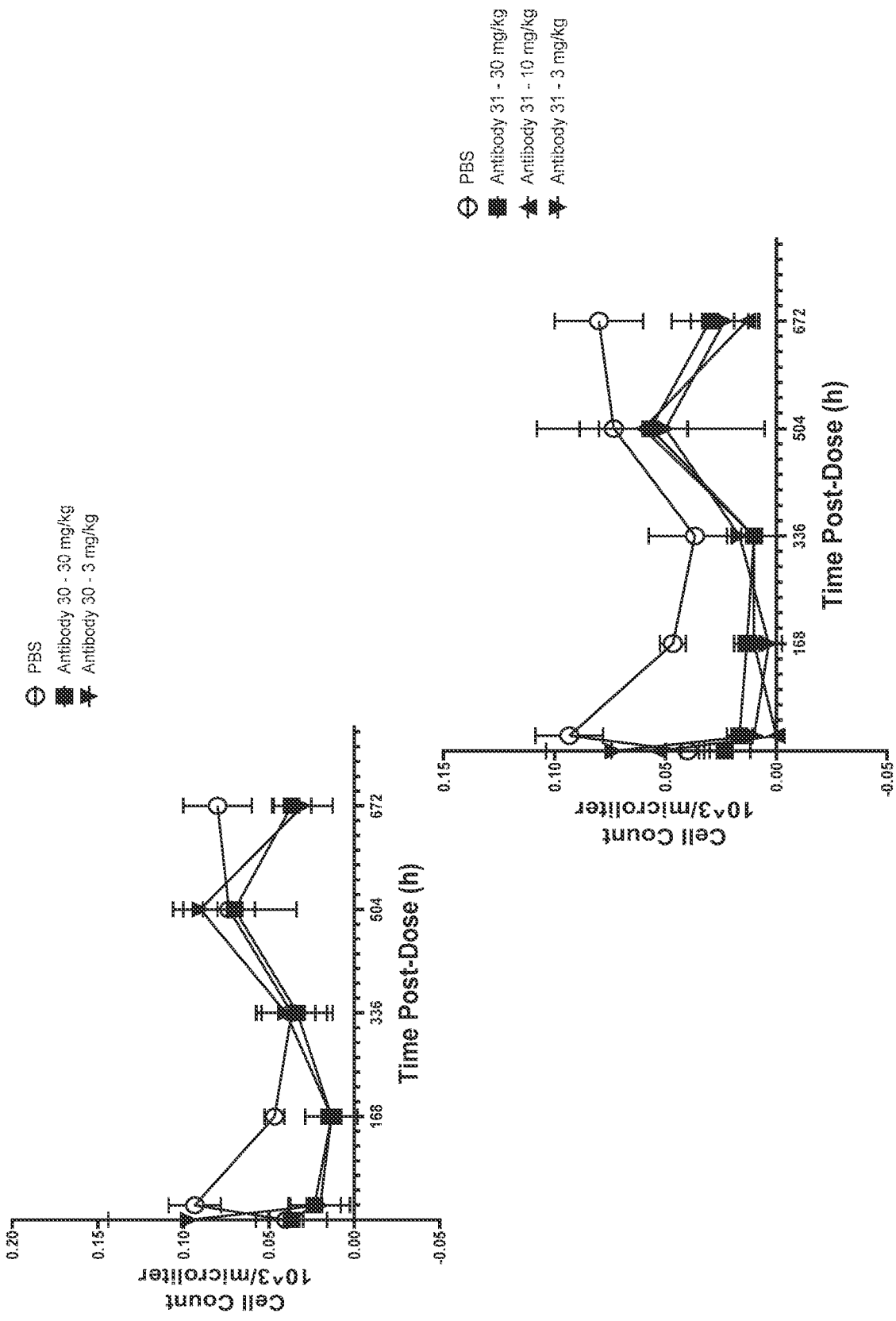
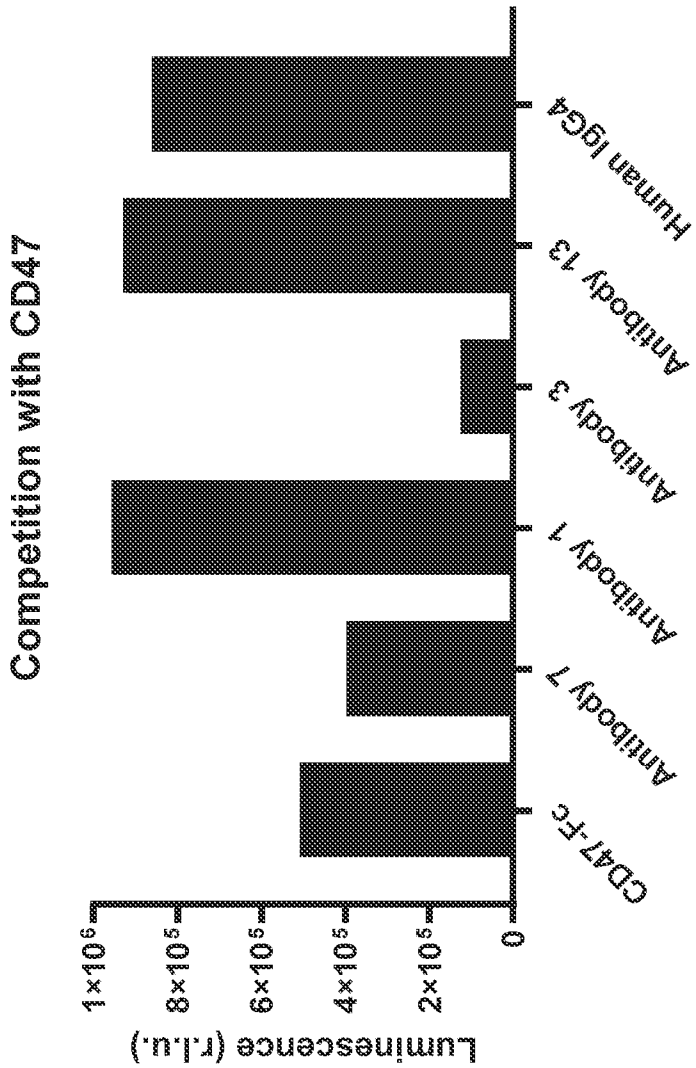

PBS
Antibody 30 - 30 mg/kg
Antibody 30 - 3 mg/kg
Cell Count
10^3/microliter
0.20
0.15
0.10
0.05
0.00
-0.05
168
336
504
672
Time Post-Dose (h)
PBS
Antibody 31 - 30 mg/kg
Antibody 31 - 10 mg/kg
Antibody 31 - 3 mg/kg
Cell Count
10^3/microliter
0.15
0.10
0.05
0.00
-0.05
168
336
504
672
Time Post-Dose (h)

FIG. 14


Competition with CD47
Luminescence (r.l.u.)
1×10⁶
8×10⁵
6×10⁵
4×10⁵
2×10⁵
0
CD47-Fc
Antibody 7
Antibody 1
Antibody 3
Antibody 13
Human IgG4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/031605

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/149938 A1 (OSE IMMUNOTHERAPEUTICS [FR]) 23 August 2018 (2018-08-23) page 31; claims 5-7; figures 4,10; examples 4,7,9 -----	1-7,16, 19-53, 62, 65-112
X	NAN GUO RING ET AL: "Anti-SIRP[alpha] antibody immunotherapy enhances neutrophil and macrophage antitumor activity", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, 20 November 2017 (2017-11-20), XP055429669, US ISSN: 0027-8424, DOI: 10.1073/pnas.1710877114 figures 5c,5d -----	1,50,51, 65,66, 80, 110-112

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2021	30/09/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lonnoy, Olivier

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/031605

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/031605

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

7, 16, 53, 62(completely); 1-6, 19-52, 65-112(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 7, 16, 53, 62(completely); 1-6, 19-52, 65-112(partially)

An antibody that is specific for one or more of SIRPa and SIRPb1, and is specific for SIRPg; A pharmaceutical composition comprising said antibody; A nucleic acid encoding said antibody; A vector comprising said nucleic acid; A method of depleting a cell population relying on said antibody; A cell expressing SIRPg and bound by said antibody; A kit comprising said antibody; Use of said antibody for treating a disease; Use of said antibody in the manufacture of a medicament.

1.1. claims: 7, 53(completely); 1-6, 19-52, 65-112(partially)

An antibody that is specific for one or more of SIRPa and SIRPb1, and is specific for SIRPg, wherein the antibody comprises a combination of heavy and light chain CDRs comprising SeqIdNo.5, 23, 36, 54, 70 and 86, as recited in claim 3(a); A pharmaceutical composition comprising said antibody; A nucleic acid encoding said antibody; A vector comprising said nucleic acid; A method of depleting a cell population relying on said antibody; A cell expressing SIRPg and bound by said antibody; A kit comprising said antibody; Use of said antibody for treating a disease; Use of said antibody in the manufacture of a medicament.

1.2. claims: 16, 62(completely); 1-6, 19-52, 65-112(partially)

As for invention 1, but wherein the antibody comprises a combination of heavy and light chain CDRs comprising SeqIdNo.16, 31, 47, 62, 79, and 97, as recited in claim 3(j).

2-11. claims: 1-6, 8-15, 17-52, 54-61, 63-112(all partially)

As for invention 1, but wherein the antibody comprises a combination of heavy and light chain CDRs as recited in claim 3(b)-3(i), 3(k) or 3(l), respectively.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/031605

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018149938 A1	23-08-2018	AU 2018221774 A1	08-08-2019
		BR 112019016356 A2	07-04-2020
		CA 3051318 A1	23-08-2018
		CN 110300764 A	01-10-2019
		EP 3583128 A1	25-12-2019
		JP 2020510643 A	09-04-2020
		KR 20190117670 A	16-10-2019
		MA 47494 A	25-12-2019
		US 2019382483 A1	19-12-2019
		WO 2018149938 A1	23-08-2018