

CLAIMS

What is claimed is:

1. An antibody that is specific for one or more of SIRP α and SIRP β 1, and is also specific for SIRP γ , wherein binding of the antibody to one or more of SIRP α , SIRP β 1, and SIRP γ does not disrupt the interaction between CD47 and SIRP α , and/or the interaction between CD47 and SIRP γ .
2. The antibody of claim 1, wherein the antibody comprises a heavy variable domain and a light variable domain, and wherein the heavy and light variable domains comprise a complementarity determining region (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: 15, SEQ ID NO: 31, SEQ ID NO: 47, SEQ ID NO: 62, SEQ ID NO: 79, and SEQ ID NO: 97;
 - c. 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; and
 - d. 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.
3. The antibody of claim 1 or 2, wherein the antibody comprises a heavy variable domain and a light variable domain, wherein:
 - a. 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;
 - b. 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;

- c. 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; or
 - d. 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.
4. The antibody of any one of claims 1-3, wherein the antibody comprises an Fc domain, optionally wherein the Fc domain is selected from the group consisting of human IgG1, IgG2, IgG3, and IgG4.
 5. The antibody of any one of claims 1-4, wherein the antibody is a monoclonal antibody, an antibody fragment, a human antibody, a humanized antibody, a chimeric antibody, or a full-length antibody.
 6. The antibody of claim 4 or 5, wherein:
 - a. 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;
 - b. the IgG1 Fc comprises a sequence selected from the group consisting of:
 - i. SEQ ID NO: 19;
 - ii. SEQ ID NO: 20, wherein X1 is V or A;
 - iii. 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;
 - iv. SEQ ID NO: 22, wherein X1 is V or A;
 - v. SEQ ID NO: 25, wherein X1 is V or A; X2 is M or L; and X3 is N or S;
 and

- vi. SEQ ID NO: 26, wherein X1 is K or R; X2 is D or E; and X3 is L or M;
or
 - c. 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.
7. The antibody of any one of claims 1-6, wherein the antibody binds SIRP α , SIRP β 1 and SIRP γ .
 8. The antibody of any one of claims 1-6, wherein the antibody binds SIRP α and SIRP γ and exhibits little or no binding to SIRP β 1.
 9. The antibody of any one of claims 1-6, wherein the antibody binds SIRP β 1 and SIRP γ and exhibits little or no binding to SIRP α .
 10. A pharmaceutical composition comprising any one of the antibodies of claims 1-9, and optionally a pharmaceutically acceptable carrier.
 11. A nucleic acid encoding for the antibody of any one of claims 1-9, optionally wherein:
 - a. 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;
 - b. 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;
 - c. 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; or
 - d. 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.

12. A vector comprising the nucleic acid of claim 11.
13. The antibody of any one of claims 1-9 or the pharmaceutical composition of claim 10, for use in therapy.
14. Use of the antibody of any one of claims 1-9 or the pharmaceutical composition of claim 10, in the manufacture of a medicament for treating a disease or condition in a subject in need thereof.
15. The use of claim 14, wherein the disease or condition is characterized by overactivation and/or hyperproliferation of lymphocytes, and the antibody induces depletion of lymphocytes, optionally wherein the lymphocytes are T cells, optionally 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.
16. The use of claim 14, wherein the disease or condition is characterized by overactivation and/or hyperproliferation of myeloid cells, and the antibody induces depletion of myeloid cells, optionally wherein the myeloid cells comprise monocytes, macrophages, dendritic cells, basophils, eosinophils, neutrophils, or mast cells, optionally wherein the myeloid cells comprise:
 - a. 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;
 - b. 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; or

- c. 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.
- 17.** The use of claim 14, wherein the disease or condition comprises a disease or disorder associated with both lymphocytes and myeloid cells, optionally wherein the disease or disorder comprises histiocytosis.
- 18.** The use of claim 14, wherein:
- a. 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, optionally wherein the malignancy-triggered HLH includes an HLH triggered by a hematological malignancy or solid tumor; or
 - b. the disease or disorder comprises a non-mendelian secondary HLH (secondary HLH, or sHLH) and wherein the secondary HLH
 - i. comprises an infection-associated HLH;
 - ii. is associated with a rheumatologic condition; or
 - iii. is associated with a kidney transplant or hematologic stem cell transplant.
- 19.** The use of claim 14, wherein the disease or condition:
- a. comprises cytokine release syndrome (CRS), optionally wherein the CRS is associated with iatrogenic immune activation, infection, T cell therapy, or T cell activating bispecific antibody therapy;
 - b. 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;

- c. comprises a granulomatous disease or condition, or a disease characterized by the presence of multinucleated giant cells, optionally 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);
 - d. comprises an autoimmune disorder or an inflammatory disorder, optionally wherein the autoimmune disorder comprises presentation of self antigens by antigen presenting dendritic cells in germinal centers of secondary lymphoid tissue of the subject;
 - e. is associated with pathological alloantibodies or autoantibodies; or
 - f. comprises a hematological malignancy.
- 20.** The use of any one of claims 14-19 wherein the subject is human.
- 21.** The use of any one of claims 14-20, wherein the antibody or pharmaceutical composition is to be administered intravenously or subcutaneously.