CLAIMS

What is claimed is:

1. An isolated antibody that binds an extracellular domain of a human SIRP-α polypeptide, wherein the antibody binds the extracellular domain of a human SIRP-α v1 polypeptide, the extracellular domain of a human SIRP-α v2 polypeptide, or both; and wherein the antibody comprises:

(A) a heavy chain variable (VH) domain comprising (i) an HVR-H1 sequence comprising the amino acid sequence of NFAMT (SEQ ID NO:175), NFAVT (SEQ ID NO:204), or NFALT (SEQ ID NO:305), (ii) an HVR-H2 sequence comprising the amino acid sequence of TIGSGDTYYADSVKG (SEQ ID NO:144), and (iii) an HVR-H3 sequence comprising the amino acid sequence of DSTVSWSGDFFDY (SEQ ID NO:145), and a light chain variable (VL) domain comprising (i) an HVR-L1 sequence comprising the amino acid sequence of RASQNVKNDLA (SEQ ID NO:146), (ii) an HVR-L2 sequence comprising the amino acid sequence of AARIRET (SEQ ID NO:147), and (iii) an HVR-L3 sequence comprising the amino acid sequence of QQYYDWPPFT (SEQ ID NO:148); or

(B) a heavy chain variable (VH) domain comprising (i) an HVR-H1 sequence comprising the amino acid sequence of IYAMS (SEQ ID NO:269), IYAVS (SEQ ID NO:213), or IYALS (SEQ ID NO:306), (ii) an HVR-H2 sequence comprising the amino acid sequence of TIGADDTYYADSVKG (SEQ ID NO:150), and (iii) an HVR-H3 sequence comprising the amino acid sequence of DSTVGWSGDFFDY (SEQ ID NO:151), and a light chain variable (VL) domain comprising (i) an HVR-L1 sequence comprising the amino acid sequence of RASQNVRSDIA (SEQ ID NO:152), (ii) an HVR-L2 sequence comprising the amino acid sequence of AASSRDT (SEQ ID NO:153), and (iii) an HVR-L3 sequence comprising the amino acid sequence of QQYYDWPPFT (SEQ ID NO:148).

2. The antibody of claim 1, wherein the antibody binds an extracellular domain of a human SIRP-α v1 polypeptide comprising the amino acid sequence of EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRGAGPGRELIYNQKEGHFPRV

TTVSDLTKRNNMDFSIRIGNITPADAGTYYCVKFRKGSPDDVEFKSGAGTELSVRAKPS (SEQ ID NO:5).

3. The antibody of claim 1, wherein the antibody binds an extracellular domain of a human SIRP-α v2 polypeptide comprising the amino acid sequence of EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQWFRGAGPARELIYNQKEGHFPRVT TVSESTKRENMDFSISISNITPADAGTYYCVKFRKGSPDTEFKSGAGTELSVRAKPS (SEQ ID NO:6).

4. The antibody of any one of claims 1-3, wherein the antibody binds an extracellular domain of a human SIRP-α v1 polypeptide comprising the amino acid sequence of EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRGAGPGRELIYNQKEGHFPRV TTVSDLTKRNNMDFSIRIGNITPADAGTYYCVKFRKGSPDDVEFKSGAGTELSVRAKPS (SEQ ID NO:5) and binds an extracellular domain of a human SIRP-α v2 polypeptide comprising the amino acid sequence of EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQWFRGAGPARELIYNQKEGHFPRVT TVSESTKRENMDFSISISNITPADAGTYYCVKFRKGSPDTEFKSGAGTELSVRAKPS (SEQ ID NO:6).

5. The antibody of any one of claims 1-4, wherein the antibody binds an extracellular domain of a monkey SIRP-α polypeptide.

6. The antibody of claim 5, wherein the monkey SIRP-α polypeptide is a cynomolgus SIRP-α polypeptide.

7. The antibody of claim 6, wherein the antibody binds an extracellular domain of a cynomolgus SIRP-α polypeptide comprising the amino acid sequence of SEQ ID NO:11.

8. The antibody of any one of claims 1-7, wherein the antibody binds an extracellular domain of a human SIRP-β polypeptide.

9. The antibody of any one of claims 1-8, wherein the antibody binds an extracellular domain of a human SIRP-γ polypeptide.

10. The antibody of any one of claims 8-9, wherein the antibody binds the extracellular domain of a human SIRP-β polypeptide comprising the amino acid sequence of SEQ ID NO:13.

11. The antibody of any one of claims 8-10, wherein the antibody binds the extracellular domain of a human SIRP-γ polypeptide comprising the amino acid sequence of SEQ ID NO:15.

12. The antibody of any one of claims 1-11, wherein the antibody modulates SIRP-α signaling in a cell expressing a human SIRP-α polypeptide.

13. The antibody of claim 12, wherein the cell is a leukocyte selected from the group consisting of a macrophage, a dendritic cell, a neutrophil, an eosinophil, and a myeloid-derived suppressor cell (MDSC).

14. The antibody of claim 13, wherein the antibody inhibits SIRP-α signaling in a macrophage expressing a human SIRP-α polypeptide.

15. The antibody of any one of claims 12-14 wherein the antibody enhances phagocytosis by a macrophage expressing a human SIRP-α polypeptide.

16. The antibody of any one of claims 1-15, wherein the antibody blocks binding between an extracellular domain of a human SIRP-α polypeptide and an IgSF domain of a human CD47 polypeptide.

17. The antibody of claim 1, wherein the VH domain comprises an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO:120, 335, 246, 258, or 327; and the VL domain comprises an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO:97 or 312.

18. The antibody of claim 17, wherein

(a) the VH domain comprises the amino acid sequence of SEQ ID NO:246, and the VL domain comprises the amino acid sequence of SEQ ID NO:97;

(b) the VH domain comprises the amino acid sequence of SEQ ID NO:258, and the VL domain comprises the amino acid sequence of SEQ ID NO:97;

(c) the VH domain comprises the amino acid sequence of SEQ ID NO:335, and the VL domain comprises the amino acid sequence of SEQ ID NO:97;

(d) the VH domain comprises the amino acid sequence of SEQ ID NO:327, and the VL domain comprises the amino acid sequence of SEQ ID NO:97;

(e) the VH domain comprises the amino acid sequence of SEQ ID NO:246, and the VL domain comprises the amino acid sequence of SEQ ID NO:312;

(f) the VH domain comprises the amino acid sequence of SEQ ID NO:258, and the VL domain comprises the amino acid sequence of SEQ ID NO:312;

(g) the VH domain comprises the amino acid sequence of SEQ ID NO:335, and the VL domain comprises the amino acid sequence of SEQ ID NO:312; or

(h) the VH domain comprises the amino acid sequence of SEQ ID NO:327, and the VL domain comprises the amino acid sequence of SEQ ID NO:312.

19. The antibody of claim 1, wherein the VH domain comprises an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO:341, 247, 259, or 328; and the VL domain comprises an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO:104 or 248.

20. The antibody of claim 19, wherein

(a) the VH domain comprises the amino acid sequence of SEQ ID NO:341, and the VL domain comprises the amino acid sequence of SEQ ID NO:104;

(b) the VH domain comprises the amino acid sequence of SEQ ID NO:247, and the VL domain comprises the amino acid sequence of SEQ ID NO:104;

(c) the VH domain comprises the amino acid sequence of SEQ ID NO:259, and the VL domain comprises the amino acid sequence of SEQ ID NO:104;

(d) the VH domain comprises the amino acid sequence of SEQ ID NO:328, and the VL domain comprises the amino acid sequence of SEQ ID NO:104;

(e) the VH domain comprises the amino acid sequence of SEQ ID NO:341, and the VL domain comprises the amino acid sequence of SEQ ID NO:248;

(f) the VH domain comprises the amino acid sequence of SEQ ID NO:247, and the VL domain comprises the amino acid sequence of SEQ ID NO:248;

(g) the VH domain comprises the amino acid sequence of SEQ ID NO:259, and the VL domain comprises the amino acid sequence of SEQ ID NO:248; or

(g) the VH domain comprises the amino acid sequence of SEQ ID NO:328, and the VL domain comprises the amino acid sequence of SEQ ID NO:248.

21. The antibody of claim 1, wherein the antibody binds to a human SIRP-α v1 polypeptide at one or more amino acid positions selected from the group consisting of I31, V33, Q52, K53, T67, R69, N70, and K96, according to SEQ ID NO:296.

22. The antibody of claim 21, wherein the antibody binds to the human SIRP-α v1 polypeptide at I31, V33, Q52, K53, T67, R69, N70, and K96, according to SEQ ID NO:296.

23. The antibody of claim 21 or claim 22, wherein the antibody further binds to the human SIRP-α v1 polypeptide at one or more amino acid positions selected from the group consisting of L30, P32, E54, T62, N71, M72, F74, and R95, according to SEQ ID NO:296.

24. The antibody of claim 23, wherein the antibody further binds to the human SIRP-α v1 polypeptide at L30, P32, E54, T62, N71, M72, F74, and R95, according to SEQ ID NO:296.

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

26. The antibody of any one of claims 1-24, wherein the antibody is a scFv-Fc~~, single domain antibody, single heavy chain antibody, or single light chain~~ antibody.

27. The antibody of any one of claims 1-24, wherein the antibody comprises a light chain constant region comprising the amino acid sequence of SEQ ID NO:325, 326, or 426.

28. The antibody of any one of claims 1-27, wherein the antibody comprises an Fc region.

29. The antibody of claim 28, wherein the antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:320-324.

30. The antibody of claim 28, wherein the Fc region is a human Fc region selected from the group consisting of an IgG1 Fc region, an IgG2 Fc region, and an IgG4 Fc region.

31. The antibody of claim 28, wherein the Fc region comprises a human IgG1 Fc region comprising one or more mutations selected from the group consisting of L234A, L235A, G237A, and N297A, according to EU numbering.

32. The antibody of claim 28, wherein the Fc region comprises a human IgG2 Fc region comprising one or more mutations selected from the group consisting of A330S, P331S and N297A, according to EU numbering.

33. The antibody of claim 28, wherein the Fc region comprises a human IgG4 Fc region comprising one or more mutations selected from the group consisting of S228P, E233P, F234V, L235A, L235E, delG236, and N297A, according to EU numbering.

34. The antibody of claim 1, wherein the antibody is an antibody fragment selected from the group consisting of a Fab, F(ab')2, Fab'-SH, Fv, and scFv fragment.

35. The antibody of any one of claims 1-34, wherein the antibody is conjugated to a cytotoxic agent or label.

36. The antibody of any one of claims 1-34, wherein the antibody is a bispecific antibody.

37. The antibody of claim 36, wherein the antibody comprises a first antigen binding domain that binds an extracellular domain of a human SIRP-α polypeptide and a second antigen binding domain that binds an antigen expressed by a cancer cell.

38. The antibody of claim 37, wherein the antigen expressed by the cancer cell is selected from the group consisting of CD19, CD20, CD22, CD30, CD33, CD38, CD52, CD56, CD70, CD74, CD79b, CD123, CD138, CS1/SLAMF7, Trop-2, 5T4, EphA4, BCMA, Mucin 1, Mucin 16, PD-L1, PTK7, STEAP1, Endothelin B Receptor, mesothelin, EGFRvIII, ENPP3, SLC44A4, GNMB, nectin 4, NaPi2b, LIV-1A, Guanylyl cyclase C, DLL3, EGFR, HER2, VEGF, VEGFR,

integrin αVβ3, integrin α5β1, MET, IGF1R, TRAILR1, TRAILR2, RANKL, FAP, Tenascin, Le^y, EpCAM, CEA, gpA33, PSMA, TAG72, a mucin, CAIX, EPHA3, folate receptor α, GD2, GD3, and an MHC/peptide complex comprising a peptide from NY-ESO-1/LAGE, SSX-2, a MAGE family protein, MAGE-A3, gp100/pmel17, Melan-A/MART-1, gp75/TRP1, tyrosinase, TRP2, CEA, PSA, TAG-72, immature laminin receptor, MOK/RAGE-1, WT-1, SAP-1, BING-4, EpCAM, MUC1, PRAME, survivin, BRCA1, BRCA2, CDK4, CML66, MART-2, p53, Ras, β-catenin, TGF-βRII, HPV E6, or HPV E7.

39. The antibody of any one of claims 1-38, wherein the antibody is a chicken, humanized, chimeric, or human antibody.

40. The antibody of any one of claims 1-39, wherein the antibody is generated by or derived from a chicken.

41. A polynucleotide encoding the antibody of any one of claims 1-40.

42. A vector comprising the polynucleotide of claim 41.

43. A host cell comprising the polynucleotide of claim 41 or the vector of claim 42.

44. A method of producing an antibody, the method comprising culturing the host cell of claim 43 such that the antibody is produced.

45. The method of claim 44, further comprising recovering the antibody from the host cell.

46. Use of an effective amount of the antibody of any one of claims 1-40 in the manufacture of a medicament for treating or delaying progression of cancer in an individual.

47. The use of claim 46, wherein the medicament is to be administered with an effective amount of a second antibody that binds an antigen expressed by the cancer.

48. The use of claim 47, wherein the antigen expressed by the cancer is selected from the group consisting of CD19, CD20, CD22, CD30, CD33, CD38, CD52, CD56, CD70, CD74, CD79b, CD123, CD138, CS1/SLAMF7, Trop-2, 5T4, EphA4, BCMA, Mucin 1, Mucin 16,

PTK7, STEAP1, Endothelin B Receptor, mesothelin, EGFRvIII, ENPP3, SLC44A4, GNMB, nectin 4, NaPi2b, LIV-1A, Guanylyl cyclase C, DLL3, EGFR, HER2, VEGF, VEGFR, integrin αVβ3, integrin α5β1, MET, IGF1R, TRAILR1, TRAILR2, RANKL, FAP, Tenascin, Le^y, EpCAM, CEA, gpA33, PSMA, TAG72, a mucin, CAIX, EPHA3, folate receptor α, GD2, GD3, and an MHC/peptide complex comprising a peptide from NY-ESO-1/LAGE, SSX-2, a MAGE family protein, MAGE-A3, gp100/pmel17, Melan-A/MART-1, gp75/TRP1, tyrosinase, TRP2, CEA, PSA, TAG-72, immature laminin receptor, MOK/RAGE-1, WT-1, SAP-1, BING-4, EpCAM, MUC1, PRAME, survivin, BRCA1, BRCA2, CDK4, CML66, MART-2, p53, Ras, β-catenin, TGF-βRII, HPV E6, or HPV E7.

49. The use of claim 46, wherein the medicament is to be administered with an effective amount of an immunotherapeutic agent.

50. The use of claim 49, wherein the immunotherapeutic agent comprises a second antibody.

51. The use of claim 50, wherein the second antibody binds to an antigen selected from the group consisting of PD-1, PD-L1, OX40, CTLA-4, CD137/4-1BB, TNFR2, B7-H3, FZD7, CD27, CCR4, CSF1R, CSF, TIM-3, LAG-3, VISTA, ICOS, CCR2, IDO, A2R, CD39, CD73, TIGIT, CD80, CD47, arginase, TDO, and PVRIG.

52. The use of claim 50, wherein the first antibody binds the extracellular domain of a human SIRP-α v1 polypeptide, the extracellular domain of a human SIRP-α v2 polypeptide, or the extracellular domains of both a human SIRP-α v1 polypeptide and a human SIRP-α v2 polypeptide with a dissociation constant (K_D) of less than 100nM, wherein the first antibody blocks binding between an extracellular domain of a human SIRP-α polypeptide and an IgSF domain of a human CD47 polypeptide, and wherein the second antibody binds to PD-1.

53. The use of claim 50, wherein the first antibody binds the extracellular domain of a human SIRP-α v1 polypeptide with a dissociation constant (K_D) of less than 100nM, wherein the first antibody blocks binding between an extracellular domain of a human SIRP-α polypeptide and an IgSF domain of a human CD47 polypeptide, and wherein the second antibody binds to PD-L1.

54. Use of an effective amount of the antibody of any one of claims 1-40 in the manufacture of a medicament for treating or delaying progression of an autoimmune disease or an inflammatory disease in an individual.

55. The use of claim 54, wherein the autoimmune disease or inflammatory disease is selected from the group consisting of multiple sclerosis, rheumatoid arthritis, a spondyloarthropathy, systemic lupus erythematosus, an antibody-mediated inflammatory or autoimmune disease, graft versus host disease, sepsis, diabetes, psoriasis, psoriatic arthritis, atherosclerosis, Sjogren's syndrome, progressive systemic sclerosis, scleroderma, acute coronary syndrome, ischemic reperfusion, Crohn's Disease, ulcerative colitis, endometriosis, glomerulonephritis, IgA nephropathy, polycystic kidney disease, myasthenia gravis, idiopathic pulmonary fibrosis, asthma, atopic dermatitis, acute respiratory distress syndrome (ARDS), vasculitis, and inflammatory autoimmune myositis.