

SIRPA ligands. In some embodiments, which may be combined with any of the preceding embodiments, the anti-SIRPA antibody decreases cellular levels of SIRPA and inhibits interaction between SIRPA and one or more SIRPA ligands. In some embodiments, which may be combined with any of the preceding embodiments, the anti-SIRPA antibody blocks binding of CD47 to human SIRPA.

[009a] In one aspect, there is provided an isolated anti-signal regulatory protein α (SIRPA) antibody, wherein the antibody selectively binds SIRPA and does not block binding of CD47 to SIRPA expressed on cells and further, wherein binding of the antibody to SIRPA decreases the level of SIRPA on the cell surface, wherein the SIRPA is human SIRPA.

[0010] In some embodiments, which may be combined with any of the preceding embodiments, the antibody selectively binds human SIRPA and does not substantially block binding of CD47 binding to human SIRPA expressed on cells and further, wherein binding to human SIRPA decreases the level of SIRPA on the cell surface. In some embodiments, the antibody binds to the D1 domain of SIRPA, *e.g.*, human SIRPA. In some embodiments, the antibody binds to the D2 domain of SIRPA *e.g.*, human SIRPA. In some embodiments, the antibody binds to the D3 domain of SIRPA, *e.g.*, human SIRPA. In some embodiments, such an anti-SIRPA antibody competes with an antibody comprising a V_H sequence comprising the amino acid sequence of SEQ ID NO:2 and a V_L sequence comprising the amino acid sequence of SEQ ID NO:3. In some embodiments, such an anti-SIRPA antibody comprises a V_H region comprising: a CDR3 comprising the amino acid sequence of SEQ ID NO:11, a CDR1 comprising the amino acid sequence of SEQ ID NO:9, or a CDR2 comprising the amino acid sequence of SEQ ID NO:10. In some embodiments, the anti-SIRPA antibody comprises a V_H region comprising: a) a CDR1 that comprises the amino acid sequence of SEQ ID NO:9, a CDR1 that comprises the amino acid sequence of SEQ ID NO:9 with no more than two amino acid substitutions, or a CDR1 having at least about 90% identity to the amino acid sequence of SEQ ID NO:9; (b) a CDR2 that comprises the amino acid sequence of SEQ ID NO:10 or a CDR2 that comprises the amino acid sequence of SEQ ID NO:10 with no more than two amino acid substitutions; or a CDR2 having at least about 90% identity to the amino acid sequence of SEQ ID NO:10; and (c) a CDR3 that comprises the amino acid sequence of SEQ ID NO:11, a CDR3 that comprises the amino acid sequence of SEQ ID NO:11 with no more than two amino acid substitutions; or a CDR3 having at least about 90% identity to the amino acid sequence of SEQ ID NO:11. In some embodiments, the anti-SIRPA comprises a V_H region comprising: a CDR1 comprising the amino acid sequence of SEQ ID NO:9 or a CDR1 comprising the amino acid sequence of SEQ ID NO:9 with no more than one amino acid substitution; a CDR2 comprising the amino acid sequence of SEQ ID NO:10 or a CDR2 comprising the amino acid sequence of SEQ ID NO:10 with no more than one amino acid substitution; and a CDR3 comprising the amino acid sequence of SEQ

[0017] In further embodiments, which may be combined with any of the preceding embodiments, the anti-SIRPA antibody is used in combination with one or more antibodies that specifically bind a disease-causing protein selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides, and any combination thereof; or with one or more antibodies that bind an immunomodulatory protein selected from the group consisting of: PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, LIGHT, BTLA, CD30, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR-5, CD2, CD5, CD39, CD73, TREM1, TREM2, CD33, Siglec-5, Siglec-7, Siglec-9, Siglec-11, phosphatidylserine, disease-causing nucleic acids, antisense GGCCCC (G2C4) repeat-expansion RNA, and any combination thereof.

[0017a] In another aspect, there is provided use of a therapeutically effective amount of the anti-SIRPA antibody described herein in the manufacture of a medicament for decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual with cancer.

[0018] In a further embodiment, the disclosure provides a method of decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an agent that binds or interacts with SIRPA, *e.g.*, an antibody of any of the embodiments described above.

[0018a] In another aspect, there is provided use of a therapeutically effective amount of the anti-SIRPA antibody described herein in the manufacture of a medicament for inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual with cancer.

[0019] In an additional embodiment, the disclosure provides a method of inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an agent, *e.g.*, an antibody of any of the embodiments described above, that decreases cellular levels of SIRPA, inhibits interaction between SIRPA

and one or more SIRPA ligands, or both. In some embodiments, the one or more immune cells are selected from the group consisting of dendritic cells, macrophages, neutrophils, NK cells, microglia, T cells, T helper cells, cytotoxic T cells, and any combination thereof.

[0019a] In another aspect, there is provided use of a therapeutically effective amount of an anti-SIRPA antibody described herein in the manufacture of a medicament for treating cancer in a patient that has a tumor that expresses CD47.

[0020] In another embodiment, the disclosure provides a method of treating cancer, the method comprising administering a therapeutically effective amount of an anti-SIRPA antibody of any of the embodiments described above to a patient that has a tumor the expresses CD47.

[0021] Disclosed is a method of treating cancer, the method comprising administering a therapeutically effective amount of an agent, *e.g.*, an anti-SIRPA antibody of any of the embodiments described above, that decreases the cellular levels of SIRPA. In some embodiments, the method further comprises administering a therapeutic agent that inhibits PD1, PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, CTLA4, PD-L2, B7-H3, B7-H4, HVEM, LIGHT, BTLA, CD30, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR-5, CD2, CD5, CD39, or CD73. In some embodiments, the therapeutic agent is an antibody that inhibits PD1, PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, CTLA4, PD-L2, B7-H3, B7-H4, HVEM, LIGHT, BTLA, CD30, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR-5, CD2, CD5, CD39, or CD73.

[0022] Disclosed is a method of treating cancer, the method comprising administering a therapeutically effective amount of an agent, *e.g.*, an anti-SIRPA antibody of any of the embodiments described above, that decreases the cellular levels of SIRPA. In some embodiments, the method further comprises administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or one or more standard or investigational anti-cancer therapies. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the anti-SIRPA antibody. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from the group consisting of an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti-B- and T-lymphocyte attenuator (BTLA) antibody, an anti-Killer inhibitory receptor (KIR) antibody, an anti-GAL9 antibody, an anti-TIM-1 antibody, an anti-TIM3 antibody, an anti-TIM-4 antibody, an anti-A2AR antibody, an anti-CD39 antibody, an anti-CD73 antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine

is selected from the group consisting of IFN- α 4, IFN- β , IL-1 β , TNF- α , IL-6, IL-8, CRP, IL-20 family members, LIF, IFN- γ , OSM, CNTF, GM-CSF, IL-11, IL-12, IL-15, IL-17, IL-18, IL-23, CXCL10, IL-33, MCP-1, MIP-1-beta, and any combination thereof.

[0023a] In another aspect, there is provided use of a therapeutically effective amount of an anti-SIRPA antibody described herein in the manufacture of a medicament for treating cancer in a patient that has cancer cells of a myeloid lineage that expresses SIRPA.

[0024] In a further embodiment, the disclosure provides a method of treating cancer, the method comprising administering a therapeutically effective amount of an anti-SIRPA antibody of any one of the preceding embodiments to a subject that has cancer cells of a myeloid lineage that expresses SIRPA.

[0024a] In another aspect, there is provided use of a therapeutically effective amount of the anti-SIRPA antibody described herein in the manufacture of a medicament for treating cancer.

[0024b] In another aspect, there is provided use of a therapeutically effective amount of an anti-SIRPA antibody described herein in the manufacture of a medicament for treating cancer in a subject that has cancer, wherein the cancer is selected from the group consisting of sarcoma, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, glioblastoma multiforme; renal clear cell carcinoma; adrenocortical carcinoma; bladder urothelial carcinoma; diffuse large B-cell lymphoma; lung adenocarcinoma; pancreatic adenocarcinoma, renal cell cancer, non-Hodgkin's lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, breast invasive carcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, diffuse large B-cell lymphoma, esophageal carcinoma, head and neck squamous cell carcinoma, kidney chromophobe, renal papillary cell carcinoma, lower grade glioma, hepatocellular carcinoma, lung squamous cell carcinoma, mesothelioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, pheochromocytoma and paraganglioma, prostate adenocarcinoma, rectal adenocarcinoma, cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumors, thyroid carcinoma, thymoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, and uveal melanoma.

[0025] In another embodiment, the disclosure provides a method of treating cancer, the method comprising administering a therapeutically effective amount of an anti-SIRPA antibody of any one of the preceding embodiments to a subject that has a cancer, wherein the cancer is selected from the group consisting of sarcoma, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, and fibrosarcoma; or wherein the cancer is selected from the group consisting of glioblastoma multiforme; renal clear cell carcinoma; adrenocortical carcinoma; bladder urothelial carcinoma; diffuse large B-cell lymphoma; lung adenocarcinoma; pancreatic adenocarcinoma, renal cell cancer, non-Hodgkin's lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, breast invasive carcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, diffuse large B-cell lymphoma, esophageal carcinoma, head and neck squamous cell carcinoma, kidney chromophobe, renal papillary cell carcinoma, lower grade glioma, hepatocellular carcinoma, lung squamous cell carcinoma, mesothelioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, pheochromocytoma and paraganglioma, prostate adenocarcinoma, rectal adenocarcinoma, cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumors, thyroid carcinoma, thymoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, and uveal melanoma. In some embodiments, the anti-SIRPA antibody is conjugated to a cytotoxic agent and/or induces ADCC.

[0026] In another aspect, there is provided a pharmaceutical composition comprising an anti-SIRPA antibody described herein and a physiologically acceptable carrier. In some embodiments, the disclosure provides an anti-

SIRPA antibody of any one of the preceding embodiments for use in the treatment of cancer; and/or for use in a method of preparing a medicament for the treatment of cancer.

[0026a] In another aspect, there is provided use of a therapeutically effective amount of the anti-SIRPA antibody described herein in the manufacture of a medicament for reducing risk, or treating a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, taupathy disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, stroke, frontotemporal dementia, spinal cord injury, Huntington's disease, infections, and cancer.

[0027] In a further embodiment, the disclosure provides a method of preventing, reducing risk, or treating a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, taupathy disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, stroke, frontotemporal dementia, spinal cord injury, Huntington's disease, infections, and cancer comprising administering to an individual in need thereof a therapeutically effective amount of an agent that decreases cellular levels of SIRPA, inhibits interaction between SIRPA and one or more SIRPA ligands, or both. In some embodiments, the disease, disorder, or injury is cancer and wherein the agent inhibits one or more SIRPA activities selected from the group consisting of: (a) promoting proliferation, maturation, migration, differentiation, and/or functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated suppressor neutrophils, tumor-associated suppressor NK cells, non-tumorigenic CD14+ myeloid cells, and regulatory T cells; (b) enhancing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, immunosuppressor NK cells, myeloid derived suppressor cells, tumor-associated macrophages, tumor-associated suppressor neutrophils, tumor-associated suppressor NK cells, and regulatory T cells into tumors; (c) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells and/or non-tumorigenic CD14+ myeloid cells in a tumor, in peripheral blood, or other lymphoid organ; (d) enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC) and/or non-tumorigenic CD14+ myeloid cells; (e) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; (f) increasing tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes; (g) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (h) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (i) decreasing infiltration of tumor-specific NK cells with tumor killing potential; (j) decreasing the tumor killing potential of NK cells; (k) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (l) increasing tumor volume; (m) increasing tumor growth rate; (n) increasing metastasis; (o) increasing rate of tumor

WHAT IS CLAIMED IS:

1. An isolated anti-signal regulatory protein α (SIRPA) antibody, wherein the antibody selectively binds SIRPA and does not block binding of CD47 to SIRPA expressed on cells and further, wherein binding of the antibody to SIRPA decreases the level of SIRPA on the cell surface, wherein the SIRPA is human SIRPA.
2. The anti-SIRPA antibody of claim 1, wherein the antibody binds to the D1 domain of SIRPA, the D2 domain of SIRPA, or the D3 domain of SIRPA.
3. The anti-SIRPA antibody of claim 1 or 2, wherein the antibody (a) competes with an antibody comprising a VH sequence comprising the amino acid sequence of SEQ ID NO:2 and a VL sequence comprising the amino acid sequence of SEQ ID NO:3.
4. The anti-SIRPA antibody of any one of claims 1 to 3, wherein the antibody comprises a VH region that comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:9, a CDR2 comprising the amino acid sequence of SEQ ID NO:10, and a CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region that comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:6, a CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a CDR3 comprising the amino acid sequence of SEQ ID NO:8.
5. The anti-SIRPA antibody of claim 4, wherein the antibody comprises a VH region comprising the amino acid sequence of hSB-3F9-H1 or hSB-3F9-H2 in Figure 14A; or comprises a VH region having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the amino acid sequence of hSB-3F9-H1 or hSB-3F9-H2 in Figure 14A.
6. The anti-SIRPA antibody of claim 4 or claim 5, wherein the VL region comprises the amino acid sequence of hSB-3F9-L1, hSB-3F9-L2, or hSB-3F9-L3 in Figure 14B; or comprises a VL region having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the amino acid sequence of hSB-3F9-L1, hSB-3F9-L2, or hSB-3F9-L3 in Figure 14B.
7. The anti-SIRPA antibody of any one of claims 1 to 3, wherein the antibody comprises a VH region that comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:15, a CDR2 comprising the amino acid sequence of SEQ ID NO:16, and a CDR3 comprising the amino acid sequence of SEQ ID NO:17; and a VL region that comprises a CDR1 comprising

the amino acid sequence of SEQ ID NO:12, a CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a CDR3 comprising the amino acid sequence of SEQ ID NO:14.

8. The anti-SIRPA antibody of claim 7, wherein the antibody comprises a VH region that comprises the amino acid sequence of hSB-9C2-H1, hSB-9C2-H2, hSB-9C2-H3, or hSB-9C2-H4 in Figure 14C; or comprises a VH region having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the amino acid sequence of hSB-9C2-H1, hSB-9C2-H2, hSB-9C2-H3, or hSB-9C2-H4 in Figure 14C.

9. The anti-SIRPA antibody of claim 7 or claim 8, wherein the VL region comprises the amino acid sequence of hSB-9C2-L1, hSB-9C2-L2, hSB-9C2-L3, or hSB-9C2-L4 in Figure 14D; or comprises a VL region having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the amino acid sequence of hSB-9C2-L1, hSB-9C2-L2, hSB-9C2-L3, or hSB-9C2-L4 in Figure 14D.

10. The isolated anti-SIRPA antibody of any one of claims 1 to 9, wherein the antibody comprises a VH region and a VL region comprising the six CDRs of a monoclonal antibody selected from the group consisting of 3F9 (which comprises VH and VL comprising SEQ ID Nos: 2 and 3), 9C2 (which comprises VH and VL comprising SEQ ID Nos: 4 and 5), 8A9 (which comprises VH and VL comprising SEQ ID Nos: 35 and 36), 8F4 (which comprises VH and VL comprising SEQ ID Nos: 37 and 39), 1E2 (which comprises VH and VL comprising SEQ ID Nos: 39 and 40), 7H9 (which comprises VH and VL comprising SEQ ID Nos: 41 and 42), and 4D8 (which comprises VH and VL comprising SEQ ID Nos: 43 and 44).

11. The anti-SIRPA antibody of any one of claims 1 to 10, wherein the antibody is a monoclonal antibody.

12. The anti-SIRPA antibody of any one of claims 1 to 11, wherein the antibody is a humanized antibody.

13. The anti-SIRPA antibody of any one of claims 1 to 12, wherein the antibody is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment.

14. The anti-SIRPA antibody of any one of claims 1 to 12, wherein the anti-SIRPA antibody has an IgG1, IgG2, IgG3, or IgG4 isotype.

15. The anti-SIRPA antibody of claim 14, wherein the antibody binds to an inhibitory Fc receptor.
16. The anti-SIRPa antibody of claim 15, wherein the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (Fc γ RIIB).
17. The anti-SIRPA antibody of claim 16, wherein:
 - (a) the anti-SIRPA antibody has a human IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: N297A, D265A, D270A, L234A, L235A, G237A, P238D, L328E, E233D, G237D, H268D, P271G, A330R, C226S, C229S, E233P, L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, N297Q, P238S, P238A, A327Q, A327G, P329A, K322A, T394D, and any combination thereof, wherein the numbering of the residues is according to EU numbering, or comprises an amino acid deletion in the Fc region at a position corresponding to glycine 236;
 - (b) the anti-SIRPA antibody has an IgG1 isotype and comprises an IgG2 isotype heavy chain constant domain 1(CH1) and hinge region, optionally wherein the IgG2 isotype CH1 and hinge region comprises the amino acid sequence of
 ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS
 WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT
 YTCNVDPHKPS NTKVDKTVERKCCVECPPCP (SEQ ID NO:34), and optionally wherein the antibody Fc region comprises a S267E amino acid substitution, a L328F amino acid substitution, or both, and/or a N297A or N297Q amino acid substitution, wherein the numbering of the residues is according to EU numbering;
 - (c) the anti-SIRPA antibody has an IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: P238S, V234A, G237A, H268A, H268Q, V309L, A330S, P331S, C214S, C232S, C233S, S267E, L328F, M252Y, S254T, T256E, H268E, N297A, N297Q, A330L, and any combination thereof, wherein the numbering of the residues is according to EU numbering;

- (d) the anti-SIRPA antibody has a human IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: L235A, G237A, S228P, L236E, S267E, E318A, L328F, M252Y, S254T, T256E, E233P, F234V, L234A/F234A, S228P, S241P, L248E, T394D, N297A, N297Q, L235E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or
 - (e) the anti-SIRPA antibody has a hybrid IgG2/4 isotype, and optionally wherein the antibody comprises an amino acid sequence comprising amino acids 118 to 260 of human IgG2 and amino acids 261 to 447 of human IgG4, wherein the numbering of the residues is according to EU numbering.
18. The anti-SIRPA antibody of claim 14, wherein:
- (a) the anti-SIRPA antibody has a human IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: N297A, N297Q, D270A, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering;
 - (b) the anti-SIRPA antibody has an IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: P238S, V234A, G237A, H268A, H268Q, H268E, V309L, N297A, N297Q, A330S, P331S, C232S, C233S, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or
 - (c) the anti-SIRPA antibody has an IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: E233P, F234V, L234A/F234A, L235A, G237A, E318A, S228P, L236E, S241P, L248E, T394D, M252Y, S254T, T256E, N297A, N297Q, and any combination thereof, wherein the numbering of the residues is according to EU numbering.
19. The anti-SIRPA antibody of claim 14, wherein:

- (a) the Fc region comprises one or more amino acid substitutions at a position selected from the group consisting of A330L, L234F; L235E, P331S, and any combination thereof, wherein the numbering of the residues is according to EU numbering;
- (b) the Fc region comprises one or more amino acid substitutions at a position selected from the group consisting of M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or
- (c) the Fc region comprises a S228P amino acid substitution according to EU numbering.

20. The anti-SIRPA antibody of claim 14, wherein the antibody has an IgG4 isotype, and wherein the anti-SIRPA antibody comprises an S228P amino acid substitution at residue position 228, an F234A amino acid substitution at residue position 234, and an L235A amino acid substitution at residue position 235, wherein the numbering of the residue position is according to EU numbering.

21. The anti-SIRPA antibody of any one of claims 1 to 12, wherein the anti-SIRPA antibody has a human IgG1 isotype and comprises substitution P331S; or substitutions L234A, L235A, and P331S; or substitutions S267E and L328F.

22. The anti-SIRPA antibody of any one of claims 1 to 21, wherein the antibody is a bispecific antibody.

23. The anti-SIRPA antibody of claim 22, wherein the bispecific antibody recognizes a first and a second antigen, wherein the first antigen is SIRPA and the second antigen is:

- (a) an antigen facilitating transport across the blood-brain-barrier;
- (b) an antigen facilitating transport across the blood-brain-barrier selected from the group consisting of transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopep peptide, and ANG1005;
- (c) a disease-causing agent selected from the group consisting of disease-causing peptides or proteins or, disease-causing nucleic acids, wherein the disease-causing

nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides; and

- (d) ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from the group consisting of PD1/PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, LIGHT, BTLA, CD30, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR-5, CD2, CD5, CD39, CD73, and phosphatidylserine; and a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells.

24. The anti-SIRPA antibody of any one of claims 1 to 23, wherein the anti-SIRPA antibody is conjugated to a detectable marker, a toxin, or a therapeutic agent.

25. The anti-SIRPA antibody of claim 24, wherein the anti-SIRPA antibody is conjugated to a toxin selected from the group consisting of ricin, ricin A chain, doxorubicin, daunorubicin, a maytansinoid, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin, diphtheria toxin, Pseudomonas exotoxin (PE) A, PE40, abrin, abrin A chain, modeccin A chain, alpha sarcin, gelonin, mitogellin, retstrictocin, phenomycin, enomycin, curicin, crotin, calicheamicin, Saponaria officinalis inhibitor, glucocorticoid, auristatin, auromycin, yttrium, bismuth, combrestatin, duocarmycins, dolastatin, cc1065, and a cisplatin.

26. Use of a therapeutically effective amount of the anti-SIRPA antibody of any one of claims 1 to 25 in the manufacture of a medicament for decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual with cancer.

27. Use of a therapeutically effective amount of the anti-SIRPA antibody of any one of claims 1 to 25 in the manufacture of a medicament for inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual with cancer.

28. The use of claim 27, wherein the one or more immune cells are selected from the group consisting of dendritic cells, macrophages, neutrophils, NK cells, microglia, T cells, T helper cells, cytotoxic T cells, and any combination thereof.

29. Use of a therapeutically effective amount of an anti-SIRPA antibody of any one of claims 1 to 25 in the manufacture of a medicament for treating cancer in a patient that has a tumor that expresses CD47.

30. Use of a therapeutically effective amount of the anti-SIRPA antibody of any one of claims 1 to 25 in the manufacture of a medicament for treating cancer.

31. Use of a therapeutically effective amount of an anti-SIRPA antibody of any one of claims 1 to 25 in the manufacture of a medicament for treating cancer in a patient that has cancer cells of a myeloid lineage that expresses SIRPA.

32. The use of any one of claims 29 to 31, wherein the medicament is to be administered with a therapeutic agent that inhibits PD1, PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, CTLA4, PD-L2, B7-H3, B7-H4, HVEM, LIGHT, BTLA, CD30, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR-5, CD2, CD5, CD39, or CD73.

33. The use of claim 32, wherein the therapeutic agent is an antibody that inhibits PD1, PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, CTLA4, PD-L2, B7-H3, B7-H4, HVEM, LIGHT, BTLA, CD30, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR-5, CD2, CD5, CD39, or CD73.

34. The use of any one of claims 29 to 31, wherein the medicament is to be administered to the individual with at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or one or more other anti-cancer therapies.

35. The use of claim 34, wherein the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from the group consisting of an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti- B- and T-lymphocyte attenuator (BTLA) antibody, an anti-Killer inhibitory receptor (KIR) antibody, an anti-GAL9 antibody, an anti-TIM-1 antibody, an anti-TIM3 antibody, an anti-TIM-4 antibody, an anti-A2AR antibody, an anti-CD39 antibody, an anti-CD73 antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, an anti-CD30 antibody, an anti-TNF α antibody, an anti-CD33 antibody, an anti-Siglec-5 antibody, an anti-Siglec-7 antibody, an anti-Siglec-9 antibody, an anti-Siglec-11 antibody, an antagonistic anti-TREM1 antibody, an antagonistic anti-TREM2 antibody, an anti-TIGIT antibody, an anti-VISTA antibody, an anti-CD2 antibody, an anti-CD5 antibody, and any combination thereof.

36. The use of claim 34, wherein the one or more other anti-cancer therapies are selected from the group consisting of radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib therapy, trastuzumab therapy, etanercept therapy, adoptive cell transfer (ACT) therapy, chimeric antigen receptor T cell transfer (CAR-T) therapy, vaccine therapy, and cytokine therapy.

37. The use of any one of claims 29 to 36, wherein the medicament is to be administered to the individual with at least one antibody that specifically binds to an inhibitory cytokine.

38. The use of claim 37, wherein the at least one antibody that specifically binds to an inhibitory cytokine is selected from the group consisting of an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof.

39. The use of any one of claims 29 to 38, wherein the medicament is to be administered to the individual with at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein.

40. The use of claim 39, wherein the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from the group consisting of an agonist anti-

CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonistic anti-TREM1 antibody, an agonistic anti-TREM2 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, an agonist anti-CD30 antibody, an agonist anti-BTLA antibody, an agonist anti-HVEM antibody, an agonist anti-CD2 antibody, an agonist anti-CD5 antibody, and any combination thereof.

41. The use of any one of claims 29 to 40, wherein the medicament is to be administered to the individual with at least one stimulatory cytokine, optionally IFN- α 4, IFN- β , IL-1 β , TNF- α , IL-6, IL-8, CRP, IL-20 family members, LIF, IFN- γ , OSM, CNTF, GM-CSF, IL-11, IL-12, IL-15, IL-17, IL-18, IL-23, CXCL10, IL-33, MCP-1, MIP-1-beta, and any combination thereof.

42. Use of a therapeutically effective amount of an anti-SIRPA antibody of any one of claims 1 to 25 in the manufacture of a medicament for treating cancer in a subject that has cancer, wherein the cancer is selected from the group consisting of sarcoma, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, glioblastoma multiforme; renal clear cell carcinoma; adrenocortical carcinoma; bladder urothelial carcinoma; diffuse large B-cell lymphoma; lung adenocarcinoma; pancreatic adenocarcinoma, renal cell cancer, non-Hodgkin's lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, breast invasive carcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, diffuse large B-cell lymphoma, esophageal carcinoma, head and neck squamous cell carcinoma, kidney chromophobe, renal papillary cell carcinoma, lower grade glioma, hepatocellular carcinoma, lung squamous cell carcinoma, mesothelioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, pheochromocytoma and paraganglioma, prostate adenocarcinoma, rectal adenocarcinoma, cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumors, thyroid carcinoma, thymoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, and uveal melanoma.

43. The use of claim 42, wherein the anti-SIRPa antibody is conjugated to a cytotoxic agent and/or induces ADCC.

44. A pharmaceutical composition comprising an anti-SIRPA antibody of any one of claims 1 to 25 and a physiologically acceptable carrier.

45. Use of a therapeutically effective amount of the anti-SIRPA antibody of any one of claims 1 to 25 in the manufacture of a medicament for reducing risk or treating a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, taupathy disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, stroke, frontotemporal dementia, spinal cord injury, Huntington's disease, infections, and cancer.

46. A polynucleotide comprising a nucleic acid sequence encoding a VH region and a VL region of an anti-SIRPA antibody of any one of claims 1 to 25.

47. An expression vector comprising the polynucleotide of claim 46.

48. A host cell comprising the polynucleotide of claim 46.

49. A host cell that expresses the anti-SIRPA antibody of any one of claims 1 to 25.

50. A host cell comprising the expression vector of claim 47.

51. A method of producing an anti-SIRPA antibody, the method comprising culturing a host cell of any one of claims 48 to 50 under conditions in which the antibody is expressed.

52. The method of claim 51, wherein the host cell is a mammalian host cell.