

[0006] Regulated expression of SIRP α and CD47 establishes a homeostatic control mechanism to modulate phagocytic cell activity. For example, apoptotic cells downregulate expression of CD47 to facilitate engulfment by resident macrophages while live cells remain unharmed. Likewise, inflammatory stimuli, such as LPS, decrease SIRP α expression in macrophages and dendritic cells (DCs) to potentiate their activation during inflammation. However, dysregulation of SIRP α and CD47 expression contributes to immune-associated diseases, as seen in cancer. Several tumors significantly augment expression of CD47 relative to non-cancerous cells in order to evade immune surveillance mechanisms that normally eliminate malignant cells. Preclinical studies reveal that genetic knockdown of CD47 in syngeneic tumor models, such as B16F10 melanoma, is sufficient to inhibit tumor growth in immune-competent mice. Similar results have been observed with CD47-knocked down human cancer cell lines transplanted into immune-compromised mice. Alternatively, biologic agents that disrupt SIRP α —CD47 interaction, such as anti-CD47 antibodies, also enhance tumor clearance in mouse models. When combined with commercial anti-tumor antigen antibodies, such as trastuzumab or rituximab, anti-CD47 antibodies facilitate a synergistic increase in the anti-tumor response compared to standard monotherapy. Yet, given the ubiquitous expression of CD47, anti-CD47 antibodies risk severe toxicity burdens due to off-target effects limiting their therapeutic efficacy. Nevertheless, these studies establish a crucial role for the SIRP α -CD47 pathway in regulating myeloid cells with potential applications in cancer immunotherapy.

[0007] Anti-SIRPA antibodies have been previously described in, *e.g.*, International Patent Application Publication Nos: WO2018/057669, WO 2018/026600, WO 2017/178653, WO2017/068164, WO2016/063233, WO2016/205042, WO2015/138600, WO2013/0956352, WO2009/091547, WO2009/131453, and WO2009/046541.

[0008] Accordingly, there is a need for therapeutic anti-SIRPA antibodies to treat diseases, disorders, and conditions associated with undesired SIRPA activity.

[0009] All references cited herein, including patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[0010] The present disclosure is generally directed to compositions that include antibodies, *e.g.*, monoclonal, chimeric, humanized antibodies, antibody fragments, *etc.*, that specifically bind human SIRPA, and to methods of using such compositions.

[0011] Certain examples of the present disclosure are based, at least in part, on the identification of anti-SIRPA antibodies with improved and/or enhanced functional characteristics (*e.g.*, relative to an anti-SIRPA antibody with a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:5, including, for example, improved and/or enhanced capabilities of decreasing cell surface levels of SIRPA on cells, and/or have improved and/or enhanced binding kinetics, and/or have improved and/or enhanced KD, and/or have improved and/or enhanced EC50 values. In some examples, anti-SIRPA antibodies of the present disclosure have a KD for human SIRPA that is at least 2-fold, at least 3-fold, at least 4-fold, at

least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold lower than an anti-SIRPA antibody having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:5. In some examples, an anti-SIRPA antibody of the present disclosure has a KD for human SIRPA of less than 6 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, less than 1 nM, less than 0.9 nM, less than 0.8 nM, less than 0.7 nM, less than 0.6 nm, or less than 0.5 nM.

[0012] In some examples, anti-SIRPA antibodies of the present disclosure reduce cell surface expression levels of SIRPA *in vitro* with an EC50 that is at least about 20%, at least about 30%, at least about 40%, or at least about 50% lower than an anti-SIRPA antibody having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:5. Advantageously, an anti-SIRPA antibody of the present disclosure decreases cellular levels of SIRPA *in vitro* with a half-maximal effective concentration (EC50) that ranges from about 0.4 nM to about 0.5 nM. Advantageously, an anti-SIRPA antibody of the present disclosure has a dissociation constant (KD) for human SIRPA that ranges from about 0.6 nM to 0.7 nM.

[0013] In some examples, which may be combined with any of the examples herein, an anti-SIRPA antibody of the present disclosure binds human SIRPA v1. In some examples, which may be combined with any of the examples herein, an anti-SIRPA antibody of the present disclosure binds human SIRPA v2. In some examples, which may be combined with any of the examples herein, an anti-SIRPA antibody of the present disclosure binds human SIRPB (SIRPbeta) v3. In some examples, which may be combined with any of the examples herein, an anti-SIRPA antibody of the present disclosure does not bind human SIRPB v1. In some examples, which may be combined with any of the examples herein, an anti-SIRPA antibody of the present disclosure does not bind murine SIRPA. In some examples, which may be combined with any of the examples herein, an anti-SIRPA antibody of the present disclosure does not bind human SIRPγ. In some examples, which may be combined with any of the examples herein, an anti-SIRPA antibody of the present disclosure binds cynoSIRPA. In some examples, which may be combined with any of the examples herein, an anti-SIRPA antibody of the present disclosure does not bind cynoSIRPB1. In In some examples, which may be combined with any of the examples herein, an anti-SIRPA antibody of the present disclosure binds marmoset SIRPA.

[0014] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody binds human SIRPA, human SIRPA v1, human SIRPA v2, cyno SIRPA, marmoset SIRPA, and human SIRPβ3.

[0015] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:20; an HVR-H2 comprising

the amino acid sequence of SEQ ID NO:21; and an HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 22, 23, and 24.

[0016] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:9; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:10; and an HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 11, 12, 13, 14, 15, 16, 17, 18, and 19.

[0016a] In one aspect, the present disclosure refers to an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:20; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:21; an HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 22, 23, and 24; and the light chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:9; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:10; and an HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 11, 12, 13, 14, 15, 16, 17, 18, and 19.

[0017] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:20; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:21; an HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 22, 23, and 24; an HVR-L1 comprising the amino acid sequence of SEQ ID NO:9; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:10; and an HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 11, 12, 13, 14, 15, 16, 17, 18, and 19.

[0018] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence at least 90% or at least 95% or at least 99% identical to an amino acid sequence selected from SEQ ID NOs: 33, 34, and 35.

[0019] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence at least 90% or at least 95% or at least 99% identical to an amino acid sequence selected from SEQ ID NOs: 36, 37, 38, 39, 40, 41, 42, 43, and 44.

[0020] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one, two, three or four frame work regions selected from VH FR1 comprising the amino acid sequence of SEQ ID NO:25, VH FR2 comprising the amino acid sequence of SEQ ID NO:26, VH FR3 comprising the amino acid sequence of SEQ ID NO:27, and VH FR4 comprising the amino acid sequence of SEQ ID NO:28.

[0021] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises one, two, three or four frame work regions selected from VL FR1 comprising the amino acid sequence of SEQ ID NO:29, VL FR2 comprising the amino acid sequence of SEQ ID NO:30, VL FR3

comprising the amino acid sequence of SEQ ID NO:31, and VL FR4 comprising the amino acid sequence of SEQ ID NO:32.

[0022] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one, two, three or four frame work regions selected from VH FR1 comprising the amino acid sequence of SEQ ID NO:25, VH FR2 comprising the amino acid sequence of SEQ ID NO:26, VH FR3 comprising the amino acid sequence of SEQ ID NO:27, and VH FR4 comprising the amino acid sequence of SEQ ID NO:28; and wherein the light chain variable region comprises one, two, three or four frame work regions selected from VL FR1 comprising the amino acid sequence of SEQ ID NO:29, VL FR2 comprising the amino acid sequence of SEQ ID NO:30, VL FR3 comprising the amino acid sequence of SEQ ID NO:31, and VL FR4 comprising the amino acid sequence of SEQ ID NO:32.

[0023] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NOs:33, 34, and 35.

[0024] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NOs: 36, 37, 38, 39, 40, 41, 42, 43, and 44. **[0024a]** In another aspect, the present disclosure refers to an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NOs: 33, 34, and 35; or wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NOs: 36, 37, 38, 39, 40, 41, 42, 43, and 44.

[0025] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NOs:33, 34, and 35, and wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NOs: 36, 37, 38, 39, 40, 41, 42, 43, and 44. In one aspect, the present disclosure refers to an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NOs: 33, 34, and 35, and wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NOs: 36, 37, 38, 39, 40, 41, 42, 43, and 44.

[0026] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 8).

[0027] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 7).

[0027a] In yet another aspect, the present disclosure refers to an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 8); or wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 7).

[0028] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 8); and wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 7). In one aspect, the present disclosure refers to an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 8); and wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 7).

[0029] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Tables 7 and 8). In one aspect, the present disclosure refers to an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Tables 7 and 8).

[0030] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one, two, three, or four framework regions selected from VH FR1, VH FR2, VH FR3, and VH FR4, wherein: VH FR1 comprises the amino acid sequence of SEQ ID NO:25; VH FR2 comprises the amino acid sequence of SEQ ID NO:26; VH FR3 comprises the amino acid sequence of SEQ ID NO:27; and VH FR4 comprises the amino acid sequence of SEQ ID NO:28; and/or the light chain variable region comprises one, two, three, or four framework regions selected VL FR1, VL FR2, VL FR3, and VL FR4, wherein VL FR1 comprises the amino acid sequence of SEQ ID NO:29; VL FR2 comprises the amino acid sequence of SEQ ID NO:30; VL FR3 comprises the amino acid sequence of SEQ ID NO:31; and VL FR4 comprises the amino acid sequence of SEQ ID NO:32.

[0031] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:49 and the light chain comprises the amino acid sequence of SEQ ID NO:50.

[0032] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated anti-SIRPA antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:47 and the light chain comprises the amino acid sequence of SEQ ID NO:50.

[0033] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated anti-SIRPA antibody, wherein the antibody comprises a heavy chain and a

[0043] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA wherein the antibody is a humanized antibody.

[0044] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody is a Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.

[0045] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody is a multivalent antibody.

[0046] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

[0047] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA wherein the antibody is of the IgG class and as an IgG1, IgG2, IgG3, or IgG4 isotype.

[0048] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody binds to an inhibitory Fc receptor. In some examples, which may be combined with any of the examples herein, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγRIIB).

[0049] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody decreases cellular levels of FcγRIIB.

[0050] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody has a human or mouse IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at an amino acid residue 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.

[0051] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: C127S, L234A, L234F, L235A, L235E, S267E, K322A, L328F, A330S, P331S, E345R, E430G, S440Y, and any combination thereof, wherein the numbering of the amino acid residues is according to EU numbering.

[0052] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody decreases cell surface levels of SIRPA, decreases intracellular levels of SIRPA, decreases total cellular levels of SIRPA, or any combination thereof.

[0053] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody induces SIRPA degradation, induces SIRPA cleavage, induces SIRPA internalization, induces SIRPA shedding, induces downregulation of SIRPA expression, or any combination thereof.

[0054] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody reduces cell surface levels of SIRPA *in vitro*.

[0055] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody reduces cell surface levels of SIRPA *in vivo*.

[0056] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody down-regulates expression of SIRPA in human monocytes.

[0057] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody down-regulates expression of SIRPA in human macrophages.

[0058] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody down-regulates expression of SIRPA in human macrophages by about 70-95%.

[0059] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody has an affinity (KD) to human SIRPA of less than 6 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, or less than 1 nM.

[0060] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody has an affinity (KD) to human SIRPA of about 0.1 nM to 2 nM.

[0061] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody has an affinity to human SIRPA with a KD that is at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold lower than the affinity to human SIRPA of an anti-SIRPA antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:5.

[0062] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody reduces cell surface levels of SIRPA v1 *in vitro* with a half maximal effective concentration (EC50) of about 0.05 nM to 2 nM or about 0.4 nM about 0.5 nM as measured by flow cytometry.

[0063] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody reduces cell surface levels of SIRPA *in vitro* with a half maximal effective concentration (EC50) of about 0.05 to 0.20 nM for human SIRPA v1, of about 0.05 to 0.10 nM for human SIRPA v2, and/or of about 0.05 to 1 nM for cyno SIRPA as measured by flow cytometry.

[0064] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody binds to the D3 domain of human SIRPA v1 of SEQ ID NO:1.

[0065] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody binds to amino acid residues R282, Q284, and G337 of human SIRPA v1 of SEQ ID NO:1.

[0066] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody increases tumor cell phagocytosis in macrophages, increases tumor cell phagocytosis in M1 macrophages, increases tumor cell phagocytosis in M2 macrophages, down-regulates CD14 expression in macrophages, and/or any combination thereof.

[0067] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody enhances T cell proliferation.

[0068] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody blocks the interaction or binding of SIRPA with surfactant protein D (SP-D).

[0069] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody does not block the interaction or binding of SIRPA to CD47.

[0070] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody down-regulates cell surface expression of CD32A/B.

[0071] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody down-regulates cell surface expression of CD14.

[0072] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody enhances T cell proliferation without blocking the interaction of SIRPγ and CD47.

[0073] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody stimulates ROS production in monocytes and/or increases IL-8 expression in monocytes.

[0074] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody inhibits tumor growth *in vivo*.

[0075] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody reduces the number of CD14+ myeloid cells in peripheral blood and/or increases the number of CD14+ myeloid cells in a tumor.

[0076] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the antibody binds human SIRPA but does not substantially block binding of CD47 to SIRPA.

[0077] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the 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 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), and diphtheria toxin receptor;
- (c) a disease-causing agent selected from disease-causing peptides or proteins, disease-causing nucleic acids, wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from 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 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.

[0078] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody is conjugated to a peptide that facilitates transport across the blood-brain-barrier. In some examples, the peptide is selected from CRM197, a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopep peptide, and ANG1005.

[0079] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody is an opsonizing antibody.

[0080] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody is a conjugated antibody.

[0081] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody is conjugated to a detectable marker, a toxin, or a therapeutic agent.

[0082] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody is conjugated to a toxin selected from 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.

[0083] In some examples, which may be combined with any of the examples herein, the present disclosure provides an isolated antibody that binds to human SIRPA, wherein the anti-SIRPA antibody is used in combination with one or more antibodies that specifically bind a disease-causing protein selected from 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.

[0084] In some examples, which may be combined with any of the examples herein, the present disclosure provides a method of preventing, reducing risk, or treating cancer, wherein the method comprises administering to an individual in need thereof a therapeutically effective amount of an anti-SIRPA antibody of the present disclosure, thereby treating cancer. In some examples, which may be combined with any of the examples herein, the present disclosure provides a method of preventing, reducing risk, or treating an individual having a disease, disorder, or injury, wherein the disease, disorder, or injury is cancer, the method comprising administering to the individual a therapeutically effective amount of an anti-SIRPA antibody of the present disclosure, thereby preventing, reducing risk, or treating the individual.

[0084a] In yet another aspect, the present disclosure refers to use of an anti-SIRPA antibody as disclosed herein, in the manufacture of a medicament for treating cancer in an individual.

[0085] In some examples, which may be combined with any of the examples herein, the present disclosure provides a method of treating cancer, wherein the method comprises administering to an individual in need thereof a therapeutically effective amount of an anti-SIRPA antibody of the present disclosure, wherein the cancer is selected from sarcoma, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal pelvis cancer, leukemia, lung cancer, small cell lung cancer, melanoma, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, and fibrosarcoma, glioblastoma multiforme; renal clear cell carcinoma; adrenocortical carcinoma; bladder urothelial carcinoma, diffuse large B-cell lymphoma, lung adenocarcinoma; pancreatic adenocarcinoma, renal cell cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, indolent B cell lymphoma, aggressive B cell lymphoma, T cell lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, myelodysplastic syndromes, myeloproliferative neoplasms, 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.

[0086] In some examples, which may be combined with any of the examples herein, the present disclosure provides a method of treating cancer, wherein the method comprises administering to an individual in need thereof a therapeutically effective amount of an anti-SIRPA antibody of the present disclosure, 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 examples that may be combined with any of the examples

herein, 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.

[0087] In some examples, which may be combined with any of the examples herein, the present disclosure provides a method of treating cancer, wherein the method comprises administering to an individual in need thereof a therapeutically effective amount of an anti-SIRPA antibody of the present disclosure, the method comprising 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 examples, which may be combined with any of the examples herein, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the anti-SIRPA antibody. In some examples, which may be combined with any of the examples herein, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from 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.

[0088] In some examples, which may be combined with any of the examples herein, the one or more standard or investigational anti-cancer therapies are selected from 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.

[0089] In some examples, which may be combined with any of the examples herein, the present disclosure provides a method of treating cancer, wherein the method comprises administering to an individual in need thereof a therapeutically effective amount of an anti-SIRPA antibody of the present disclosure, wherein the method further comprises administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some examples, which may be combined with any of the examples herein, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the anti-SIRPA antibody. In some examples, which may be combined with any of the examples herein, the at least one antibody that specifically binds to an inhibitory cytokine is selected from an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof.

[0090] In some examples, which may be combined with any of the examples herein, the present disclosure provides a method of treating cancer, wherein the method comprises administering to an individual in need thereof a therapeutically effective amount of an anti-SIRPA antibody of the present disclosure, wherein the method further comprises administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In some examples, which may be combined with any of the examples herein, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the anti-SIRPA antibody. In some examples, which may be combined with any of the examples herein, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from 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.

[0091] In some examples, which may be combined with any of the examples herein, the present disclosure provides a method of treating cancer, wherein the method comprises administering to an individual in need thereof a therapeutically effective amount of an anti-SIRPA antibody of the present disclosure, the method further comprising administering to the individual at least one stimulatory cytokine. In some examples, the at least one stimulatory cytokine is selected from 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.

[0092] In some examples, the present disclosure provides an isolated nucleic acid comprising a nucleic acid sequence encoding an anti-SIRPA antibody of the present disclosure. In some examples, the present disclosure provides a vector comprising an isolated nucleic acid comprising a nucleic acid sequence encoding an anti-SIRPA antibody of the present disclosure. In some examples, the present disclosure provides an isolated host cell comprising a vector comprising an isolated nucleic acid comprising a nucleic acid sequence encoding an anti-SIRPA antibody of the present disclosure.

[0092a] In yet another aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleic acid sequence encoding the antibody as disclosed herein.

[0092b] In yet another aspect, the present disclosure refers to a vector comprising the nucleic acid as disclosed herein.

[0092c] In yet another aspect, the present disclosure refers to an isolated host cell comprising the nucleic acid or the vector as disclosed herein.

[0092d] In yet another aspect, the present disclosure refers to an isolated host cell that expresses the antibody as disclosed herein.

[0093] In some examples, the present disclosure provides a method of producing an antibody that binds to human SIRPA, wherein the method comprises culturing a host cell comprising a vector comprising an isolated nucleic acid comprising a nucleic acid sequence encoding an anti-SIRPA antibody of the present disclosure so that the antibody is produced. The present disclosure further provides for recovering the antibody produced by the cell.

[0093a] In yet another aspect, the present disclosure refers to a method of producing an antibody that binds to human SIRPA, comprising culturing the cell as disclosed herein so that the antibody is produced

[0094] In some examples, the present disclosure provides a pharmaceutical composition comprising an anti-SIRPA antibody of the present disclosure and a pharmaceutically acceptable carrier.

[0094a] In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

[0095] **FIG. 1** shows the amino acid sequence alignment of the extracellular domains of human SIRPA variant 1 and SIRPA proteins from various species. The percent identity recorded demonstrates high

CLAIMS

What is claimed is:

1. An isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:20; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:21; an HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 22, 23, and 24; and the light chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:9; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:10; and an HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 11, 12, 13, 14, 15, 16, 17, 18, and 19.
2. The antibody of claim 1, wherein the heavy chain variable region comprises one, two, three or four frame work regions selected from VH FR1 comprising the amino acid sequence of SEQ ID NO:25, VH FR2 comprising the amino acid sequence of SEQ ID NO:26, VH FR3 comprising the amino acid sequence of SEQ ID NO:27, and VH FR4 comprising the amino acid sequence of SEQ ID NO:28; or wherein the light chain variable region comprises one, two, three or four frame work regions selected from VL FR1 comprising the amino acid sequence of SEQ ID NO:29, VL FR2 comprising the amino acid sequence of SEQ ID NO:30, VL FR3 comprising the amino acid sequence of SEQ ID NO:31, and VL FR4 comprising the amino acid sequence of SEQ ID NO:32.
3. The antibody of claim 1, wherein the heavy chain variable region comprises one, two, three or four frame work regions selected from VH FR1 comprising the amino acid sequence of SEQ ID NO:25, VH FR2 comprising the amino acid sequence of SEQ ID NO:26, VH FR3 comprising the amino acid sequence of SEQ ID NO:27, and VH FR4 comprising the amino acid sequence of SEQ ID NO:28; and wherein the light chain variable region comprises one, two, three or four frame work regions selected from VL FR1 comprising the amino acid sequence of SEQ ID NO:29, VL FR2 comprising the amino acid sequence of SEQ ID NO:30, VL FR3 comprising the amino acid sequence of SEQ ID NO:31, and VL FR4 comprising the amino acid sequence of SEQ ID NO:32.
4. The antibody of claim 1 or 2, wherein the heavy chain variable region comprises an amino acid sequence at least 90% or at least 95% or at least 99% identical to an amino acid sequence selected from SEQ ID NOs: 33, 34, and 35; and/or wherein the light chain variable region comprises an amino acid sequence at least 90% or at least 95% or at least 99% identical to an amino acid sequence selected from SEQ ID NOs: 36, 37, 38, 39, 40, 41, 42, 43, and 44.
5. An isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an

amino acid sequence selected from SEQ ID NOs: 33, 34, and 35; or wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NOs: 36, 37, 38, 39, 40, 41, 42, 43, and 44.

6. An isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NOs: 33, 34, and 35, and wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NOs: 36, 37, 38, 39, 40, 41, 42, 43, and 44.

7. An isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 8); or wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 7).

8. An isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 8); and wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Table 7).

9. An isolated antibody that binds to human SIRPA, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody 3F9-1, 3F9-2, 3F9-3, 3F9-4, 3F9-5, 3F9-6, 3F9-7, 3F9-8, 3F9-9, 3F9-10, 3F9-11, 3F9-12, 3F9-13, 3F9-14, 3F9-15, 3F9-16, 3F9-17, 3F9-18, 3F9-19, 3F9-20, 3F9-21, 3F9-22, 3F9-23, 3F9-24, or 3F9-25 (as shown in Tables 7 and 8).

10. The antibody of any one of claims 7-9, wherein the heavy chain variable region comprises one, two, three, or four framework regions selected from VH FR1, VH FR2, VH FR3, and VH FR4, wherein: VH FR1 comprises the amino acid sequence of SEQ ID NO:25; VH FR2 comprises the amino acid

sequence of SEQ ID NO:26; VH FR3 comprises the amino acid sequence of SEQ ID NO:27; and VH FR4 comprises the amino acid sequence of SEQ ID NO:28; and/or the light chain variable region comprises one, two, three, or four framework regions selected VL FR1, VL FR2, VL FR3, and VL FR4, wherein VL FR1 comprises the amino acid sequence of SEQ ID NO:29; VL FR2 comprises the amino acid sequence of SEQ ID NO:30; VL FR3 comprises the amino acid sequence of SEQ ID NO:31; and VL FR4 comprises the amino acid sequence of SEQ ID NO:32.

11. The antibody of any one of claims 1-10, wherein the antibody is a monoclonal antibody.
12. The antibody of any one of claims 1-11, wherein the antibody is a humanized antibody.
13. The antibody of any one of claims 1-12, wherein the antibody is a Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.
14. The antibody of any one of claims 1-13, wherein the antibody is a multivalent antibody.
15. The antibody of any one of claims 1-14, wherein the antibody is of the IgG class, the IgM class, or the IgA class.
16. The antibody of claim 15, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.
17. The antibody of any one of claims 1-16, wherein the antibody binds to an inhibitory Fc receptor.
18. The antibody of claim 17, wherein the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγRIIB).
19. The antibody of claim 18, wherein the antibody decreases cellular levels of FcγRIIB.
20. The antibody of any one of claims 1-19, wherein the anti-SIRPA antibody has a human or mouse IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at an amino acid residue 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.

21. The antibody of any one of claims 1-20, wherein the antibody comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: C127S, L234A, L234F, L235A, L235E, S267E, K322A, L328F, A330S, P331S, E345R, E430G, S440Y, and any combination thereof, wherein the numbering of the amino acid residues is according to EU or Kabat numbering.

22. An isolated antibody that binds human SIRPA, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:53 and the light chain comprises the amino acid sequence of SEQ ID NO:50.

23. An isolated antibody that binds human SIRPA, wherein the antibody comprises a heavy chain and a light chain, wherein:

a. the heavy chain comprises the amino acid sequence of SEQ ID NO:47 and the light chain comprises the amino acid sequence of SEQ ID NO:50;

b. the heavy chain comprises the amino acid sequence of SEQ ID NO:48 and the light chain comprises the amino acid sequence of SEQ ID NO:50;

c. the heavy chain comprises the amino acid sequence of SEQ ID NO:49 and the light chain comprises the amino acid sequence of SEQ ID NO:50;

d. the heavy chain comprises the amino acid sequence of SEQ ID NO:54 and the light chain comprises the amino acid sequence of SEQ ID NO:50;

e. the heavy chain comprises the amino acid sequence of SEQ ID NO:51 and the light chain comprises the amino acid sequence of SEQ ID NO:50;

f. the heavy chain comprises the amino acid sequence of SEQ ID NO:52 and the light chain comprises the amino acid sequence of SEQ ID NO:50;

g. the heavy chain comprises the amino acid sequence of SEQ ID NO:55 and the light chain comprises the amino acid sequence of SEQ ID NO:50;

h. the heavy chain comprises the amino acid sequence of SEQ ID NO:56 and the light chain comprises the amino acid sequence of SEQ ID NO:50; or

i. the heavy chain comprises the amino acid sequence of SEQ ID NO:57 and the light chain comprises the amino acid sequence of SEQ ID NO:50.

24. The antibody of any one of claims 1-23, wherein the anti-SIRPA antibody decreases cell surface levels of SIRPA, decreases intracellular levels of SIRPA, decreases total cellular levels of SIRPA, or any combination thereof.
25. The antibody of any one of claims 1-24, wherein the anti-SIRPA antibody induces SIRPA degradation, induces SIRPA cleavage, induces SIRPA internalization, induces SIRPA shedding, downregulates SIRPA expression, or any combination thereof.
26. The antibody of any one of claims 1-25, wherein the antibody reduces cell surface levels of SIRPA *in vitro*.
27. The antibody of any one of claims 1-26, wherein the antibody reduces cell surface levels of SIRPA *in vivo*.
28. The antibody of any one of claims 1-27, wherein the antibody down-regulates expression of SIRPA in human monocytes.
29. The antibody of any one of claims 1-28, wherein the antibody down-regulates expression of SIRPA in human macrophages.
30. The antibody of claim 29, wherein the antibody down-regulates expression of SIRPA in human macrophages by about 70-95%.
31. The antibody of any one of claims 1-30, wherein the antibody has an affinity (K_D) to human SIRPA v1 of less than 6 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, or less than 1 nM.
32. The antibody of any one of claims 1-31, wherein the antibody has an affinity (K_D) to human SIRPA v1 of about 0.1 nM to 2 nM.
33. The antibody of any one of claims 1-32, wherein the antibody has an affinity to human SIRPA v1 with a K_D that is at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold lower than the affinity to human SIRPA of an anti-SIRPA antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:5.

34. The antibody of any one of claims 1-33, wherein the antibody reduces cell surface levels of SIRPA v1 *in vitro* with a half maximal effective concentration (EC50) of about 0.05 nM to 2 nM as measured by flow cytometry.
35. The antibody of any one of claims 1-34, wherein the antibody reduces cell surface levels of SIRPA *in vitro* with a half maximal effective concentration (EC50) of about 0.05 to 0.20 nM for human SIRPA v1, of about 0.05 to 0.10 nM for human SIRPA v2, and/or of about 0.05 to 1 nM for cyno SIRPA as measured by flow cytometry.
36. The antibody of any one of claims 1-35, wherein the antibody binds human SIRPA, human SIRPA v1, human SIRPA v2, cyno SIRPA, marmoset SIRPA, and human SIRPβ3.
37. The antibody of any one of claims 1-36, wherein the antibody binds to the D3 domain of human SIRPA v1 of SEQ ID NO:1.
38. The antibody of any one of claims 1-37, wherein the antibody binds to amino acid residues R282, Q284, and G337 of human SIRPA v1 of SEQ ID NO:1.
39. The antibody of any one of claims 1-38, wherein the anti-SIRPA antibody increases tumor cell phagocytosis in macrophages, increases tumor cell phagocytosis in M1 macrophages, increases tumor cell phagocytosis in M2 macrophages, down-regulates CD14 expression in macrophages, and/or any combination thereof.
40. The antibody of any one of claims 1-39, wherein the anti-SIRPA antibody enhances T cell proliferation.
41. The antibody of any one of claims 1-40, wherein the anti-SIRPA antibody enhances T cell proliferation without blocking the interaction of SIRPγ and CD47.
42. The antibody of any one of claims 1-41, wherein the anti-SIRPA antibody stimulates ROS production in monocytes and/or increases IL-8 expression in monocytes.
43. The antibody of any one of claims 1-42, wherein the anti-SIRPA antibody inhibits tumor growth *in vivo*.
44. The antibody of any one of claims 1-43, wherein the anti-SIRPA antibody reduces the number of CD14+ myeloid cells in peripheral blood and/or increases the number of CD14+ myeloid cells in a tumor.

45. The antibody of any one of claims 1-44, wherein the antibody binds human SIRPA but does not substantially block binding of CD47 to SIRPA.

46. The anti-SIRPA antibody of any one of claims 1-45, wherein the 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 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), and diphtheria toxin receptor;
- (c) a disease-causing agent selected from disease-causing peptides or proteins, disease-causing nucleic acids, wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from 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 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.

47. Use of an anti-SIRPA antibody of any one of claims 1-46, in the manufacture of a medicament for treating cancer in an individual.

48. The use of claim 47, wherein the cancer is selected from sarcoma, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal pelvis cancer, leukemia, lung cancer, small cell lung cancer, melanoma, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, and fibrosarcoma, glioblastoma multiforme; renal clear cell carcinoma; adrenocortical carcinoma; bladder urothelial carcinoma, diffuse large B-cell lymphoma, lung adenocarcinoma; pancreatic adenocarcinoma, renal cell cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, indolent B cell lymphoma, aggressive B cell lymphoma, T cell lymphoma, acute lymphoblastic leukemia (ALL),

acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, myelodysplastic syndromes, myeloproliferative neoplasms, 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.

49. The use of claim 47 or claim 48, wherein the individual is to be administered a therapeutic agent that inhibits or agonizes 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.

50. The use of any one of claims 47-49, wherein the individual is to be administered at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or one or more standard or investigational anti-cancer therapies.

51. The use of claim 50, wherein the individual is to be administered at least one antibody that specifically binds to an inhibitory checkpoint molecule in combination with the anti-SIRPA antibody.

52. The use of claim 50 or claim 51, wherein the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from 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.

53. The use of claim 50, wherein the one or more standard or investigational anti-cancer therapies are selected from 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.

54. The use of any one of claims 47-53, wherein the individual is to be administered at least one antibody that specifically binds to an inhibitory cytokine.
55. The use of claim 54, wherein the at least one antibody that specifically binds to an inhibitory cytokine is selected from an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof.
56. The use of any one of claims 47-55, wherein the individual is to be administered at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein.
57. The use of claim 56, wherein the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from 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.
58. The use of any one of claims 47-57, wherein the individual is to be administered at least one stimulatory cytokine.
59. The use of claim 58, wherein the at least one stimulatory cytokine is selected from 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.
60. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of claims 1-46.
61. A vector comprising the nucleic acid of claim 60.
62. An isolated host cell comprising the nucleic acid of claim 60 or the vector of claim 61.
63. An isolated host cell that expresses the antibody of any one of claims 1-46.
64. A method of producing an antibody that binds to human SIRPA, comprising culturing the cell of claim 62 or claim 63 so that the antibody is produced.
65. The method of claim 64, further comprising recovering the antibody produced by the cell.
66. A pharmaceutical composition comprising the antibody of any one of claims 1-46 and a pharmaceutically acceptable carrier.