

treatment of several types of cancer, inflammatory disease, autoimmune disease, respiratory disease, infectious disease, or fibrosis.

SUMMARY

[0008] The present disclosure addresses the above need by providing agents, in particular antibodies or antigen-binding fragments thereof, which bind (e.g., specifically) to SIRP α , in particular human SIRP α . In one example of the disclosure, the antibodies or antigen-binding fragments thereof, block the interaction between SIRP α and CD47. In another example of the disclosure, the antibodies or antigen-binding fragments thereof, block CD47-mediated SIRP α signaling.

[0009] The antibodies or antigen-binding fragments thereof of the disclosure are useful, for example, for the treatment and/or prevention of diseases or disorders that can be alleviated by modulating the interaction between SIRP α and CD47, in particular by blocking CD47-mediated SIRP α signaling. In one example of the disclosure, the antibodies or antigen-binding fragments thereof, are useful, for example for the treatment of cancer, inflammatory disease, autoimmune disease, respiratory disease, infectious disease or fibrosis, preferably cancer.

[0010] The disclosure provides an anti-SIRP α antibody or antigen-binding fragments thereof, having one or more of the properties described herein below.

[0011] In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof binds specifically to SIRP α , in particular human SIRP α or cynomolgus monkey SIRP α , more particularly human SIRP α . In one example, the anti-SIRP α antibody or antigen-binding fragment thereof binds to the V1 and/or V2 alleles of human SIRP α . In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof does not bind (e.g., there is no detectable binding or the anti-SIRP α antibody or antigen-binding fragment thereof binds with a K_D of 1 μ M or greater) to SIRP γ , in particular cynomolgus monkey SIRP γ or human SIRP γ , more particularly human SIRP γ . In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof, does not bind (e.g., there is no detectable binding or the anti-SIRP α antibody or antigen-binding fragment thereof binds with a K_D of 1 μ M or greater) to rabbit, mouse, rat, or dog SIRP α .

[0012] In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof blocks the binding of CD47 to SIRP α , in particular human SIRP α or cynomolgus monkey

SIRP α , more particularly human SIRP α . In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof blocks the binding of CD47 to human SIRP α -V1 and SIRP α -V2. In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof blocks CD47-mediated SIRP α signaling. In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof enhances phagocytosis by macrophages and/or dendritic cells. In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof enhances antibody dependent cellular phagocytosis (ADCP), in combination with a tumor targeting agent, in particular a tumor targeting antibody. In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof enhances phagocytosis of tumor cells by macrophages and/or dendritic cells. In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof blocks inhibition of T-cell proliferation. In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof has favorable pharmacokinetic properties. In one example of the disclosure, an anti-SIRP α antibody or antigen-binding fragment thereof has favorable biophysical properties, for example yield, quality, stability or solubility.

[0013] In one example of the disclosure, an anti-SIRP α antibody or an antigen-binding fragment thereof comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 33 (H-CDR1); the amino acid sequence of SEQ ID NO: 34 (H-CDR2); and the amino acid sequence of SEQ ID NO: 35 (H-CDR3), and
a light chain variable region comprising the amino acid sequence of SEQ ID NO: 36 or SEQ ID NO: 37 (L-CDR1); the amino acid sequence of SEQ ID NO: 38 (L-CDR2); and the amino acid sequence of SEQ ID NO: 39 (L-CDR3),
or
- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 223 (H-CDR1); the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO: 224 (H-CDR2); and the amino acid sequence of SEQ ID NO: 6 (H-CDR3); and
a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 or SEQ ID NO: 225 (L-CDR1); the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 or SEQ ID NO: 226 (L-CDR2); and the amino acid sequence of SEQ ID NO: 12 or SEQ ID NO: 227 (L-CDR3),
or

- c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 52 (H-CDR1); the amino acid sequence of SEQ ID NO: 53 (H-CDR2); and the amino acid sequence of SEQ ID NO: 54 (H-CDR3); and
a light chain variable region comprising the amino acid sequence of SEQ ID NO: 55 (L-CDR1); the amino acid sequence of SEQ ID NO: 56 (L-CDR2); and the amino acid sequence of SEQ ID NO: 57 (L-CDR3),
or
- d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 33 (H-CDR1); the amino acid sequence of SEQ ID NO: 70 (H-CDR2); and the amino acid sequence of SEQ ID NO: 71 (H-CDR3); and
a light chain variable region comprising the amino acid sequence of SEQ ID NO: 36 (L-CDR1); the amino acid sequence of SEQ ID NO: 72 (L-CDR2); and the amino acid sequence of SEQ ID NO: 39 (L-CDR3),
or
- e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 262 (H-CDR1); the amino acid sequence of SEQ ID NO: 87 (H-CDR2); and the amino acid sequence of SEQ ID NO: 88 (H-CDR3); and
a light chain variable region comprising the amino acid sequence of SEQ ID NO: 36 (L-CDR1); the amino acid sequence of SEQ ID NO: 72 (L-CDR2); and the amino acid sequence of SEQ ID NO: 89 (L-CDR3).

[0014] In one example of the disclosure, an anti-SIRP α antibody or an antigen-binding fragment thereof comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 33 (H-CDR1); the amino acid sequence of SEQ ID NO: 34 (H-CDR2); the amino acid sequence of SEQ ID NO: 35 (H-CDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 233, wherein amino acids X1= D or G and X2 = L or A (L-CDR1); the amino acid sequence of SEQ ID NO: 38, (L-CDR2); the amino acid sequence of SEQ ID NO: 39 (L-CDR3), or
- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 228(H-CDR1), wherein amino acids X1 = N or D; the amino acid sequence of SEQ ID NO: 229, wherein X1=Y or D, X2=N or T, X3=N or Q, and X4=S or P (H-CDR2); the amino acid sequence of SEQ ID NO: 6 (H-CDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 230, wherein X1=K or R, X2= N or T, X3=G or A and X4=N, A

or T (L-CDR1); the amino acid sequence of SEQ ID NO:231, wherein X1=L, Q or G and X2=N or S (L-CDR2); the amino acid sequence of SEQ ID NO:232, wherein X1=M or G (L-CDR3).

[0015] In one example of the disclosure, an anti-SIRP α antibody or an antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 100, 110, 111, 112, 113, 114, 115, 116, or 117; and a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 105, 125, or 126.

[0016] In a further example, an anti-SIRP α antibody or an antigen-binding fragment thereof of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 104, 118, 119, 120, 121, 122, 123, 124 or 221; and a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 109, 127, 128, 129, 130 or 222.

[0017] In one example of the disclosure, an anti-SIRP α antibody or an antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 100, 101, 102, 103, or 104; and a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 105, 106, 107, 108, or 109.

[0018] In one example of the disclosure, an anti-SIRP α antibody or an antigen-binding fragment thereof comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 100; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 105; or
- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 110; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125; or
- c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 111; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125; or
- d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 112; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125; or
- e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 113; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125; or
- f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 114; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125; or
- g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 115; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125; or
- h) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 116; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125; or

- i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 117; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125; or
- j) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 111; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126; or
- k) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 112; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126; or
- l) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 113; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126; or
- m) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 114; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126; or
- n) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 115; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126; or
- o) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 116; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126; or
- p) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 117; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126.

[0019] In one example of the disclosure, an anti-SIRP α antibody or an antigen-binding fragment thereof comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 104; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 109; or
- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127; or
- c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 128; or
- d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127; or
- e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129; or
- f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 120; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127; or
- g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 120; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129; or
- h) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 121; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127; or

- i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 122; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127; or
- j) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or
- k) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 121; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129; or
- l) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 122; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129; or
- m) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or
- n) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 123; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127; or
- o) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 120; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or
- p) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 123; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129; or
- q) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 121; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or
- r) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 122; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or
- s) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 124; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129; or
- t) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 124; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127; or
- u) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 123; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or
- v) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 124; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or
- w) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 221; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 222.

[0020] In one example of the disclosure, an anti-SIRP α antibody or an antigen-binding fragment thereof comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 100; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 105; or

- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 101; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 106; or
- c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 102; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 107; or
- d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 103; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 108; or
- e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 104; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 109.

[0021] In one example of the disclosure, an anti-SIRP α antibody comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NO: 131, 138, 139, 140, 141, 142, 143, 144, 145, 146, 148, 149, 150, 151 or 152; and a light chain comprising the amino acid sequence of any one of SEQ ID NO: 174, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195 or 218.

[0022] In a further example, an anti-SIRP α antibody of the disclosure comprises:

- a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 131; and a light chain comprising the amino acid sequence of SEQ ID NO: 174; or
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 138; and a light chain comprising the amino acid sequence of SEQ ID NO: 121; or
- c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 139; and a light chain comprising the amino acid sequence of SEQ ID NO: 182; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 140; and a light chain comprising the amino acid sequence of SEQ ID NO: 183; or
- e) a heavy chain comprising the amino acid sequence of SEQ ID NO: 141; and a light chain comprising the amino acid sequence of SEQ ID NO: 184; or
- f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 142; and a light chain comprising the amino acid sequence of SEQ ID NO: 185; or
- g) a heavy chain comprising the amino acid sequence of SEQ ID NO: 143; and a light chain comprising the amino acid sequence of SEQ ID NO: 186; or
- h) a heavy chain comprising the amino acid sequence of SEQ ID NO: 144; and a light chain comprising the amino acid sequence of SEQ ID NO: 187; or
- i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 145; and a light chain comprising the amino acid sequence of SEQ ID NO: 188; or

- j) a heavy chain comprising the amino acid sequence of SEQ ID NO: 146; and a light chain comprising the amino acid sequence of SEQ ID NO: 189; or
- k) a heavy chain comprising the amino acid sequence of SEQ ID NO: 147; and a light chain comprising the amino acid sequence of SEQ ID NO: 190; or
- l) a heavy chain comprising the amino acid sequence of SEQ ID NO: 148; and a light chain comprising the amino acid sequence of SEQ ID NO: 191; or
- m) a heavy chain comprising the amino acid sequence of SEQ ID NO: 149; and a light chain comprising the amino acid sequence of SEQ ID NO: 192; or
- n) a heavy chain comprising the amino acid sequence of SEQ ID NO: 150; and a light chain comprising the amino acid sequence of SEQ ID NO: 193; or
- o) a heavy chain comprising the amino acid sequence of SEQ ID NO: 151; and a light chain comprising the amino acid sequence of SEQ ID NO: 194; or
- p) a heavy chain comprising the amino acid sequence of SEQ ID NO: 152; and a light chain comprising the amino acid sequence of SEQ ID NO: 195; or
- q) a heavy chain comprising the amino acid sequence of SEQ ID NO: 217; and a light chain comprising the amino acid sequence of SEQ ID NO: 218.

[0023] In one example of the disclosure, an anti-SIRP α antibody comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NO: 135, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173 or 219; and a light chain comprising the amino acid sequence of any one of SEQ ID NO: 178, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216 or 220.

[0024] In one example of the disclosure, an anti-SIRP α antibody comprises:

- a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 135; and a light chain comprising the amino acid sequence of SEQ ID NO: 178; or
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 153; and a light chain comprising the amino acid sequence of SEQ ID NO: 196; or
- c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 154; and a light chain comprising the amino acid sequence of SEQ ID NO: 197; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 155; and a light chain comprising the amino acid sequence of SEQ ID NO: 198; or
- e) a heavy chain comprising the amino acid sequence of SEQ ID NO: 156; and a light chain comprising the amino acid sequence of SEQ ID NO: 199; or

w) a heavy chain comprising the amino acid sequence of SEQ ID NO: 219; and a light chain comprising the amino acid sequence of SEQ ID NO: 220.

[0025] In one example of the disclosure, an anti-SIRP α antibody comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NO: 131, 133, 134, 137 or 135; and a light chain comprising the amino acid sequence of any one of SEQ ID NO: 174, 176, 177, 180, or 178.

[0026] In one example of the disclosure, an anti-SIRP α antibody comprises:

- a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 131; and a light chain comprising the amino acid sequence of SEQ ID NO: 174; or
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 133; and a light chain comprising the amino acid sequence of SEQ ID NO: 176; or
- c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 134; and a light chain comprising the amino acid sequence of SEQ ID NO: 177; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 137; and a light chain comprising the amino acid sequence of SEQ ID NO: 180; or
- e) a heavy chain comprising the amino acid sequence of SEQ ID NO: 135; and a light chain comprising the amino acid sequence of SEQ ID NO: 178.

[0027] In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof, is a human antibody or antigen-binding fragment thereof. In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof, is a monoclonal antibody. In one example of the disclosure, the anti-SIRP α antibody is a full-length antibody. In one example of the disclosure, the anti-SIRP α antibody or fragment thereof, is a human monoclonal antibody, for example a full-length human monoclonal antibody.

[0028] In a one example of the disclosure, the anti-SIRP α antibody, or an antigen-binding fragment thereof, comprises a heavy chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 100, 110, 111, 112, 113, 114, 115, 116, or 117 and a light chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 105, 125, or 126. In a further example of the disclosure, the antibody or antigen-binding fragment thereof that comprises a heavy chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 100, 110, 111, 112, 113, 114, 115, 116, or 117 and a light chain variable region having at least 90%, at least 95%, at least 98%, or

at least 99% identity to the amino acid sequences of SEQ ID NO: 105, 125, or 126 specifically binds to SIRP α . In a one example of the disclosure, the anti-SIRP α antibody, or an antigen-binding fragment thereof, comprises a heavy chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 104, 118, 119, 120, 121, 122, 123, 124, or 221 and a light chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 109, 127, 128, 129, 130, or 222. In a further example of the disclosure, the antibody or antigen-binding fragment thereof that comprises a heavy chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 104, 118, 119, 120, 121, 122, 123, 124, or 221 and a light chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 109, 127, 128, 129, 130, or 222 specifically binds to SIRP α . In one example of the disclosure, the anti-SIRP α antibody, or an antigen-binding fragment thereof, comprises a heavy chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 101, 102 or 103 and a light chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 106, 107, 108. In a further example of the disclosure, the antibody or antigen-binding fragment thereof that comprises a heavy chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 101, 102 or 103 and a light chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 106, 107, 108 specifically binds to SIRP α .

[0029] In one example of the disclosure, the anti-SIRP α antibody, or an antigen-binding fragment thereof, comprises a heavy chain constant region from an antibody selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgM, IgA and IgE, for example human IgG1, IgG2, IgG3, IgG4, IgM, IgA or IgE, more particularly, human IgG1, IgG2, IgG3, IgG4.

[0030] In one example of the disclosure, the anti-SIRP α antibody or an antigen-binding fragment thereof comprises a heavy chain constant region, wherein the heavy chain constant region is of an IgG4 with a S241P substitution. In one example of the disclosure, the anti-SIRP α antibody or an antigen-binding fragment thereof comprises a heavy chain lacking a C-terminal lysine residue.

[0031] In one example of the disclosure, the anti-SIRP α antibody or an antigen-binding fragment thereof comprises a heavy chain constant region wherein the heavy chain constant region is of an IgG1 with L234A and L235A substitutions.

[0032] In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof comprises a light chain constant region selected from the group consisting of a kappa and a lambda light chain.

[0033] In one example of the disclosure, the anti-SIRP α antibody or antigen-binding fragment thereof, is optionally administered in combination with an additional therapeutic agent. The additional therapeutic agent may be a chemotherapeutic agent, an anti-PD-1 or PD-L1 antibody, an anti-CTLA4 antibody, a T-cell engager, a CD137-agonist-anti-FAP bispecific antibody, a tumor-targeting antibody, a VEGF-ANG2 bispecific antibody, a STING agonist, a MDM2 antagonist, or radiation therapy.

[0034] In one example, the anti-SIRP α antibody or an antigen-binding fragment thereof is administered in combination with an anti-PD-1 antibody, for example, nivolumab, pembrolizumab, pidilizumab, ezabenlimab, or atezolizumab. In a further example, the anti-SIRP α antibody or an antigen-binding fragment thereof is administered in combination with an anti-PD-L1 antibody including, for example, avelumab or durvalumab.

[0035] In one example, the anti-SIRP α antibody or antigen-binding fragment thereof is administered in combination with a tumor targeting antibody, for example an antibody that targets HER2 (e.g., trastuzumab), EGFR (e.g., cetuximab, panitumumab), CD20 (e.g., rituximab, ofatumumab), or CD52 (e.g., alemtuzumab).

[0036] In one example, the anti-SIRP α antibody or antigen-binding fragment thereof is administered in combination with two therapeutic agents. In a further example, the anti-SIRP α antibody or antigen-binding fragment thereof is administered in combination with an anti-PD-1 antibody (e.g., nivolumab, pembrolizumab, pidilizumab, ezabenlimab, or atezolizumab), or an anti-PD-L1 antibody (e.g., avelumab or durvalumab) and a tumor targeting antibody, for example and antibody that targets HER2 (e.g., trastuzumab), EGFR (e.g., tetuximab, panitumumab), CD20 (e.g., rituximab, ofatumumab), or CD52 (e.g., alemtuzumab).

[0037] In one example of the disclosure, the antibody or antigen-binding fragment thereof recognizes a specific linear or conformational "SIRP α epitope" on a SIRP α protein comprising the amino acid sequence set forth in any one of SEQ ID NOs: 240-252. In one example of the disclosure, the antibody or antigen-binding fragment thereof recognizes a specific linear or conformational "SIRP α epitope" on a SIRP α protein comprising the amino acid sequence set forth in any one of SEQ ID NOs: 253-260 and 264, in particular any one or more of SEQ ID NOS: 256 and 257. In one example of the disclosure the antibody or antigen-binding fragment thereof binds to a SIRP α

epitope comprising the amino acids: LEU 60, ILE 61, VAL 63, GLY 64, PRO 65, GLN 82, LYS 83, GLU 84, THR 97, LYS 98, ARG 99, GLU 100, LYS 126, GLY 127, SER 128, PRO 129 and ASP 130 as set forth in SEQ ID NO: 266. In one example of the disclosure the antibody or antigen-binding fragment thereof binds to a SIRP α epitope comprising the amino acids LEU 60, ILE 61, VAL 63, GLY 64, PRO 65, GLN 82, LYS 83, GLU 84, THR 97, LYS 98, ARG 99, ASN 100, LYS 126, GLY 127, SER 128, PRO 129 and ASP 130 as set forth in SEQ ID NO: 265. In another example of the disclosure, the antibody or antigen-binding fragment thereof binds to the SIRP α epitope comprising the amino acid ASP130. In another example, the antibody or antigen-binding fragment thereof binds to a SIRP α epitope comprising any one or more of SEQ ID NO: 253, SEQ ID NO: 254, SEQ ID NO: 255, SEQ ID NO: 264, and SEQ ID NO: 256, in particular SEQ ID NO: 256.

[0038] In one example of the disclosure the antibody or antigen-binding fragment thereof binds to the SIRP α epitope comprising the amino acids ARG 70, GLY 71, ALA 72, GLY 73, PRO 74, ALA 75, ARG 76, GLU 77, ALA 114, ALA 116, GLY 117, THR 118, TYR 120, THR 131, GLU 132, PHE 133, SER 135 and GLU 140 as set forth in SEQ ID NO: 266. In one example of the disclosure the antibody or antigen-binding fragment thereof binds to a SIRP α epitope comprising the amino acids ARG 70, GLY 71, ALA 72, GLY 73, PRO 74, GLY 75, ARG 76, GLU 77, ALA 114, ALA 116, GLY 117, THR 118, TYR 120, VAL 132, GLU 133, PHE 134, SER 136 and GLU 141 as set forth in SEQ ID NO: 265. In another example of the disclosure, the antibody or antigen-binding fragment thereof binds to the SIRP α epitope comprising the amino acid ALA72. In another example, the antibody or antigen-binding fragment thereof binds to a SIRP α epitope comprising any one or more of SEQ ID NO: 257, SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, in particular SEQ ID NO: 257. In another example of the disclosure, the antibody or antigen-binding fragment thereof blocks binding of any of Antibody A-E to SIRP α .

[0039] In another example, the antibody or antigen-binding fragment thereof exhibits comparable binding to (e.g., less than a 10-fold difference in affinity for) the modified SIRP α V1 polypeptide sequence of SEQ ID NO: 269 or 270, compared to its binding to the SIRP α V1 polypeptide of SEQ ID NO: 268, which optionally is measured at room temperature. Preferably the antibody or antigen-binding fragment thereof is antibody A, A4, A10, or an antigen-binding fragment thereof.

[0040] In another example, the antibody or antigen-binding fragment thereof exhibits reduced binding affinity for (e.g., at least a 10-fold reduction in affinity for) the modified SIRP α V1 polypeptide sequence of SEQ ID NO: 271 or 272, compared to its binding to the SIRP α V1

polypeptide of SEQ ID NO: 268, which optionally is measured at room temperature. Preferably the antibody or antigen-binding fragment thereof is antibody A, A4, A10, or an antigen-binding fragment thereof.

[0041] In another example, the antibody or antigen-binding fragment thereof exhibits comparable binding to (e.g., less than a 10-fold difference in affinity for) the modified SIRP α V2 polypeptide sequence of SEQ ID NO: 274 or 275, compared to its binding to the SIRP α V2 polypeptide of SEQ ID NO: 273, which optionally is measured at room temperature. Preferably the antibody or antigen-binding fragment thereof is antibody A, A4, A10, or an antigen-binding fragment thereof.

[0042] In another example, the antibody or antigen-binding fragment thereof exhibits reduced binding affinity for (e.g., at least a 10-fold reduction in affinity for) the modified SIRP β 1 polypeptide sequence of SEQ ID NO: 277, compared to its binding to the SIRP β 1 polypeptide of SEQ ID NO: 276, which optionally is measured at room temperature. Preferably the antibody or antigen-binding fragment thereof is antibody A, A4, A10, or an antigen-binding fragment thereof.

[0043] In another example, the antibody or antigen-binding fragment thereof exhibits binding to the modified polypeptide sequence of SEQ ID NO: 279, which optionally is measured at room temperature. Preferably the antibody or antigen-binding fragment thereof is antibody A, A4, A10, or an antigen-binding fragment thereof.

[0044] In another example, the antibody or antigen-binding fragment thereof exhibits binding to the modified polypeptide sequence of SEQ ID NO: 282 or 283, which optionally is measured at room temperature. Preferably the antibody or antigen-binding fragment thereof is antibody A, A4, A10, or an antigen-binding fragment thereof.

[0045] In one example, the anti-SIRP α antibody or antigen-binding fragment thereof exhibits comparable binding affinity for human SIRP α V1 and SIRP α V2, such as less than 10-fold difference (preferably less than 5-fold difference) in the binding affinity (K_D) for human SIRP α V1 and SIRP α V2, which optionally is measured at room temperature.

[0046] In one example, the present disclosure provides an anti-SIRP α antibody or antigen-binding fragment thereof that competes for binding to V1-SIRP α and/or V2-SIRP α , with an anti-SIRP α antibody or antigen-binding fragment thereof of the disclosure. In one example, the present disclosure provides an anti-SIRP α antibody or antigen-binding fragment thereof that competes for binding to V1-SIRP α and/or V2 SIRP α , with an antibody comprising a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 100, 110, 111, 112, 113, 114,

115, 116, or 117 and a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 105, 125, or 126; or an antibody comprising a heavy chain comprising the amino acid sequence of any one of SEQ ID NO: 131, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, or 217 and a light chain comprising the amino acid sequence of any one of SEQ ID NO: 174, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 218.

[0047] In one example, the present disclosure provides an anti-SIRP α antibody or antigen-binding fragment thereof that competes for binding to V1-SIRP α and/or V2-SIRP α , with an anti-SIRP α antibody or antigen-binding fragment thereof of the disclosure. In one example, the present disclosure provides an anti-SIRP α antibody or antigen-binding fragment thereof that competes for binding to V1-SIRP α and/or V2-SIRP α , with an antibody comprising a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 104, 118, 119, 120, 121, 122, 123, 124, or 221 and a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOS: 109, 127, 128, 129, 130, or 222; or an antibody comprising a heavy chain comprising the amino acid sequence of any one of SEQ ID NO: 135, 153, 154, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, or 219 and a light chain comprising the amino acid sequence of any one of SEQ ID NO: 178, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, or 220.

[0048] In one example, the disclosure provides a pharmaceutical composition comprising an anti-SIRP α antibody or antigen-binding fragment thereof as described above, and a pharmaceutically acceptable excipient, optionally in combination with one or more (e.g., one or two) additional therapeutic agents. In a further example, the additional therapeutic agent is a chemotherapeutic agent, an anti-PD-1 or PD-L1 antibody, an anti-CTLA4 antibody, a T cell engager, a CD137-agonist-anti-FAP bispecific antibody, a tumor-targeting antibody, a VEGF-ANG2 bispecific antibody, a STING agonist, or a MDM2 antagonist.

[0049] In one example, the disclosure provides an anti-SIRP α antibody or antigen-binding fragment thereof as described above for use as a medicament or in the preparation of a medicament.

[0050] In one example, the disclosure provides a method of treating a SIRP α pathway disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of the anti-SIRP α antibody or antigen-binding fragment thereof as described above. In one example, the disclosure provides an anti-SIRP α antibody or antigen-binding fragment thereof as described

above for use in treating a SIRP α pathway disorder. In one example, the disclosure provides the use of the anti- SIRP α antibody or antigen-binding fragment thereof as described above in manufacture of a medicament for treating a SIRP α pathway disorder.

[0051] In one example, the disclosure provides a method of modulating the interaction between SIRP α and CD47 in a subject (e.g., a human) comprising administering to the subject a composition comprising an anti-SIRP α antibody or the antigen-binding fragment as described above in an amount sufficient to block the CD47-mediated SIRP α signaling in the subject. In one example, the disclosure provides an anti-SIRP α antibody or the antigen-binding fragment as described above for use in modulating the interaction between SIRP α and CD47 in a subject. In one example, the disclosure provides the use of an anti-SIRP α antibody or the antigen-binding fragment as described above in the manufacture of a medicament for modulating the interaction between SIRP α and CD47 in a subject.

[0052] In one example, the disclosure provides a method of enhancing phagocytosis comprising administering to a subject a composition comprising an anti-SIRP α antibody or the antigen-binding fragment as described above in an amount sufficient to block the CD47-mediated SIRP α signaling. In one example, the disclosure provides an anti-SIRP α antibody or the antigen-binding fragment as described above for use in enhancing phagocytosis by macrophages and/or dendritic cells in a subject. In one example, the disclosure provides an anti-SIRP α antibody or the antigen-binding fragment as described above for use in enhancing phagocytosis of tumor cells by macrophages and/or dendritic cells in a subject. In one example, the present disclosure provides the use of an anti-SIRP α antibody or the antigen-binding fragment as described above in the manufacture of a medicament for a subject. In one example of the disclosure, the disclosure provides a method of enhancing antibody dependent cellular phagocytosis (ADCP), in combination with a tumor targeting agent, preferably a tumor targeting antibody, the method comprising administering to a subject a composition comprising an anti-SIRP α antibody or the antigen-binding fragment as described above in an amount sufficient to block the CD47-mediated SIRP α signaling in combination with a tumor targeting agent, preferably a tumor targeting antibody, more preferably a tumor targeting antibody that targets HER2 (e.g., trastuzumab), EGFR (e.g., cetuximab, panitumumab), CD20 (e.g., rituximab, ofatumumab) CD52 (e.g., alemtuzumab).

[0053] In one example, in a method above, in an anti-SIRP α antibody or antigen-binding fragment thereof for use above, or in the use of an anti-SIRP α antibody or antigen-binding

fragment thereof above, the disease is selected from the group consisting of cancer, inflammatory disease, autoimmune disease, respiratory disease, infectious disease or fibrosis.

[0054] In one example, in the method above, in the anti-SIRP α antibody or antigen-binding fragment thereof for use above, or in the use of the anti-SIRP α antibody or antigen-binding fragment thereof above, the antibody or antigen-binding fragment thereof is administered by a parenteral route, intravenous route, or subcutaneous route of administration.

[0055] In one example, the disclosure provides an isolated polynucleotide encoding a heavy chain variable region amino and/or a light chain variable region as described above.

[0056] In one example, the disclosure provides an isolated polynucleotide encoding a heavy chain and/or a light chain as described above.

[0057] In one example, the disclosure provides an isolated polynucleotide encoding a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 100, 101, 102, 103, 104, 105, 110, 111, 112, 113, 114, 115, 116, 117, 104, 118, 119, 120, 121, 122, 123, 124, or 221.

[0058] In one example, the disclosure provides an isolated polynucleotide encoding a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 105, 106, 107, 108, 109, 125, 126, 109, 127, 128, 129, 130, or 222.

[0059] In one example, the disclosure provides an isolated polynucleotide encoding a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 100, 101, 102, 103, 104, 105, 110, 111, 112, 113, 114, 115, 116, 117, 104, 118, 119, 120, 121, 122, 123, 124, or 221; and an isolated polynucleotide encoding a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 105, 106, 107, 108, 109, 125, 126, 109, 127, 128, 129, 130, or 222.

[0060] In one example, the disclosure provides an isolated polynucleotide encoding a heavy chain region comprising the amino acid sequence of any one of SEQ NO: 131,138,139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 217, 135,153, 154, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 219, 133, 134, 137, 132, or 136.

[0061] In one example, the disclosure provides an isolated polynucleotide encoding of a light chain region comprising the amino acid sequence of any one any one of SEQ NO: 174, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 218, 178, 196, 197, 198,

199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 220, 176, 177, 180, 175, or 179.

[0062] In one example, the disclosure provides an isolated polynucleotide encoding a heavy chain region comprising the amino acid sequence of any one of SEQ NO: 131,138,139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 217, 135,153, 154, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 219, 133, 134, 137, 132, or 136; and an isolated polynucleotide encoding of a light chain region comprising the amino acid sequence of any one any one of SEQ NO: 174, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 218, 178, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 220, 176, 177, 180, 175, or 179.

[0063] In one example, the disclosure provides an expression vector comprising a polynucleotide as described above.

[0064] In one example, the disclosure provides an expression vector comprising a polynucleotide encoding a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 100, 101, 102, 103, 104, 105, 110, 111, 112, 113, 114, 115, 116, 117, 104, 118, 119, 120, 121, 122, 123, 124, or 221.

[0065] In one example, the disclosure provides an expression vector comprising a polynucleotide encoding a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 105, 106, 107, 108, 109, 125, 126, 109, 127, 128, 129, 130, or 222.

[0066] In one example, the disclosure provides an expression vector comprising a polynucleotide encoding a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 100, 101, 102, 103, 104, 105, 110, 111, 112, 113, 114, 115, 116, 117, 104, 118, 119, 120, 121, 122, 123, 124, or 221; and a polynucleotide encoding a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 105, 106, 107, 108, 109, 125, 126, 109, 127, 128, 129, 130, or 222.

[0067] In one example, the disclosure provides an expression vector comprising a polynucleotide encoding a heavy chain region comprising the amino acid sequence of any one of SEQ NO: 131,138,139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 217, 135,153, 154, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 219, 133, 134, 137, 132, or 136.

[0068] In one example, the disclosure provides an expression vector comprising a polynucleotide encoding of a light chain region comprising the amino acid sequence of any one any one

of SEQ NO: 174, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 218, 178, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 220, 176, 177, 180, 175, or 179.

[0069] In one example, the disclosure provides an expression vector comprising a polynucleotide encoding a heavy chain region comprising the amino acid sequence of any one of SEQ NO: 131, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 217, 135, 153, 154, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 219, 133, 134, 137, 132, or 136; and a polynucleotide encoding of a light chain region comprising the amino acid sequence of any one any one of SEQ NO: 174, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 218, 178, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 220, 176, 177, 180, 175, or 179.

[0070] In one example, the disclosure provides a host cell comprising an expression vector as described above. In one example, the host cell is a mammalian cell.

[0071] In one example, the disclosure provides a method of manufacturing an antibody or antigen-binding fragment thereof comprising the steps of:

- culturing a host cell comprising an expression vector comprising an isolated polynucleotide encoding a heavy chain variable region as described above and an expression vector comprising polynucleotide encoding light chain variable region as described above under conditions that allow formation of an antibody or antigen-binding fragment thereof comprising both the heavy and light chain variable region, and
- recovering said antibody or antigen-binding fragment thereof.

[0072] In one example, the disclosure provides a method of manufacturing an antibody or antigen-binding fragment thereof comprising the steps of:

- culturing a host cell comprising an expression vector comprising an isolated polynucleotide encoding a heavy chain as described above and comprising a polynucleotide encoding light chain as described above under conditions that allow formation of an antibody or antigen-binding fragment thereof comprising both the heavy and light chain variable region; and
- recovering said antibody or antigen-binding fragment thereof.

[0073] In one example, a method above further comprises the step of purifying the antibody or antigen-binding fragment thereof. In one example, a method above further

comprises the step of formulating the antibody or antigen-binding fragment thereof into a pharmaceutical composition. Also provided herein are pharmaceutical formulations comprising an anti-SIRP α antibody or an antigen-binding fragment thereof as disclosed herein.

[0073a] In one aspect, the present disclosure relates to an anti-human SIRP α antibody or an antigen-binding fragment thereof comprising: a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 33 (H-CDR1); the amino acid sequence of SEQ ID NO: 34 (H-CDR2); and the amino acid sequence of SEQ ID NO: 35 (H-CDR3), and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 36 or SEQ ID NO: 37 (L-CDR1); the amino acid sequence of SEQ ID NO: 38 (L-CDR2); and the amino acid sequence of SEQ ID NO: 39 (L-CDR3), or b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 223 (H-CDR1); the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO: 224 (H-CDR2); and the amino acid sequence of SEQ ID NO: 6 (H-CDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 or SEQ ID NO: 225 (L-CDR1); the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 or SEQ ID NO: 226 (L-CDR2); and the amino acid sequence of SEQ ID NO: 12 or SEQ ID NO: 227 (L-CDR3).

[0073b] In another aspect, the present disclosure relates to the anti-SIRP α antibody or antigen-binding fragment thereof as disclosed herein for use as a medicament.

[0073c] In another aspect, the present disclosure relates to a pharmaceutical composition comprising an antibody or antigen-binding fragment as disclosed herein and a pharmaceutically acceptable carrier.

[0073d] In another aspect, the present disclosure relates to use of the anti-SIRP α antibody or antigen-binding fragment as disclosed herein, or a pharmaceutical composition as disclosed herein, in manufacture of a medicament for treating a disease, wherein the disease is selected from cancer, inflammatory disease, autoimmune disease, respiratory disease, infectious disease or fibrosis.

[0073e] In another aspect, the present disclosure relates to an isolated polynucleotide encoding a heavy chain variable region and/or a light chain variable region as disclosed herein.

[0073f] In another aspect, the present disclosure relates to a vector comprising a polynucleotide as disclosed herein, preferably an expression vector, more preferred a vector comprising the polynucleotide according to the invention in functional association with an expression control sequence.

[0073g] In another aspect, the present disclosure relates to a host cell comprising a polynucleotide as disclosed herein.

[0073h] In another aspect, the present disclosure relates to a method for the production of an anti-SIRP α antibody or antigen-binding fragment as disclosed herein, comprising the steps: (a) cultivating the host cell under conditions allowing the expression of the anti-SIRP α antibody or antigen-binding fragment; and (b) recovering the anti-SIRP α antibody or antigen-binding fragment.

[0073i] In another aspect, the present disclosure relates to a method of manufacturing an antibody comprising the steps of: a) culturing a host cell comprising an expression vector comprising an isolated polynucleotide encoding a heavy chain variable region as disclosed herein and comprising a polynucleotide encoding light chain variable region as disclosed herein under conditions that allow formation of an antibody; and b) recovering said antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

[0074] The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the disclosed compositions, methods, and kits there are shown in the drawings exemplary embodiments of methods and kits; however, these should not be limited to the specific embodiments disclosed.

[0075] Figures 1A-1C are series of graphs depicting the binding of antibodies to full-length human V1-SIRP α or V2-SIRP α expressed on CHO cells. Figure 1A. Antibody binding to parental CHO cells. Figure 1B. Antibody binding to CHO cells expressing full-length human SIRP α V1 (NP_542970.1). Figure 1C. Antibody binding to CHO cells expressing full-length human SIRP α V2-expressing CHO cells (CAA71403.1).

[0076] Figures 2A-2B are series of graphs depicting the binding of antibodies to endogenous human V1-SIRP α or V2-SIRP α expressed on human monocytic cell lines. Figure 2A. Antibody binding to U-937 human monocytic cell line. Figure 2B. Antibody binding to THP-1 human monocytic cell line.

[0077] Figures 3A-3D are series of graphs depicting the binding of antibodies to endogenous human V1-SIRP α and/or V2-SIRP α expressed on primary human monocytes. Antibody binding to primary human CD14⁺ monocytes from donors homozygous for V1-SIRP α allele (Figures 3A-3D). Solid, dashed, and dotted lines indicate antibody molecules engineered on hIgG1 (LALA), hIgG4P, hIgG1 (K322A) backbones, respectively.

[0078] Figures 4A-4D are series of graphs depicting the binding of antibodies to endogenous human V1-SIRP α and/or V2-SIRP α expressed on primary human monocytes. Antibody binding to primary human CD14⁺ monocytes from donors heterozygous for V1- and V2-SIRP α alleles (Figures 4A-4D). Solid, dashed, and dotted lines indicate antibody molecules engineered on hIgG1 (LALA), hIgG4P, hIgG1 (K322A) backbones, respectively.

[0079] Figures 5A-5D are series of graphs depicting the binding of antibodies to endogenous human V1-SIRP α and/or V2-SIRP α expressed on primary human monocytes.

What is claimed is:

1. An anti-human SIRP α antibody or an antigen-binding fragment thereof comprising:
 - a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 33 (H-CDR1); the amino acid sequence of SEQ ID NO: 34 (H-CDR2); and the amino acid sequence of SEQ ID NO: 35 (H-CDR3), and
a light chain variable region comprising the amino acid sequence of SEQ ID NO: 36 or SEQ ID NO: 37 (L-CDR1); the amino acid sequence of SEQ ID NO: 38 (L-CDR2); and the amino acid sequence of SEQ ID NO: 39 (L-CDR3),
or
 - b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 223 (H-CDR1); the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO: 224 (H-CDR2); and the amino acid sequence of SEQ ID NO: 6 (H-CDR3); and
a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 or SEQ ID NO: 225 (L-CDR1); the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 or SEQ ID NO: 226 (L-CDR2); and the amino acid sequence of SEQ ID NO: 12 or SEQ ID NO: 227 (L-CDR3).
2. The anti-SIRP α antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises:
 - a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 100; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 105;
or
 - b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 110; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
or
 - c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 111; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
or
 - d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 112; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
or

- e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 113;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
or
- f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 114;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
or
- g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 115;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
or
- h) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 116;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
or
- i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 117;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
or
- j) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 110;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126;
or
- k) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 111;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126;
or
- l) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 112;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126;
or
- m) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 113;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126;
or
- n) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 114;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126;
or
- o) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 115;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126;
or

- p) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 117;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 126.

3. The anti-SIRP α antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 104;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 109;
or
- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127;
or
- c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 128;
or
- d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127;
or
- e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129;
or
- f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 120;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127;
or
- g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 120;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129;
or
- h) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 121;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127;
or
- i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 122;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127;
or

- j) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130;
or
- k) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 121;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129;
or
- l) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 122;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129;
or
- m) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130;
or
- n) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 123;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127;
or
- o) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 120;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130;
or
- p) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 123;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129;
or
- q) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 121;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130;
or
- r) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 122;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130;
or
- s) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 124;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129;
or
- t) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 124;
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 127;
or

- u) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 123; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or
- v) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 124; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or
- w) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 221; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 222.

4. The anti-SIRP α antibody according to claim 1, wherein the antibody comprises

- a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 131; and a light chain comprising the amino acid sequence of SEQ ID NO: 174; or
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 138; and a light chain comprising the amino acid sequence of SEQ ID NO: 181; or
- c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 139; and a light chain comprising the amino acid sequence of SEQ ID NO: 182; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 140; and a light chain comprising the amino acid sequence of SEQ ID NO: 183; or
- e) a heavy chain comprising the amino acid sequence of SEQ ID NO: 141; and a light chain comprising the amino acid sequence of SEQ ID NO: 184; or
- f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 142; and a light chain comprising the amino acid sequence of SEQ ID NO: 185; or
- g) a heavy chain comprising the amino acid sequence of SEQ ID NO: 143; and a light chain comprising the amino acid sequence of SEQ ID NO: 186; or
- h) a heavy chain comprising the amino acid sequence of SEQ ID NO: 144; and a light chain comprising the amino acid sequence of SEQ ID NO: 187; or
- i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 145; and a light chain comprising the amino acid sequence of SEQ ID NO: 188; or
- j) a heavy chain comprising the amino acid sequence of SEQ ID NO: 146; and a light chain comprising the amino acid sequence of SEQ ID NO: 189; or
- k) a heavy chain comprising the amino acid sequence of SEQ ID NO: 147; and a light chain comprising the amino acid sequence of SEQ ID NO: 190; or
- l) a heavy chain comprising the amino acid sequence of SEQ ID NO: 148; and a light chain comprising the amino acid sequence of SEQ ID NO: 191; or

- m) a heavy chain comprising the amino acid sequence of SEQ ID NO: 149; and a light chain comprising the amino acid sequence of SEQ ID NO: 192; or
- n) a heavy chain comprising the amino acid sequence of SEQ ID NO: 150; and a light chain comprising the amino acid sequence of SEQ ID NO: 193; or
- o) a heavy chain comprising the amino acid sequence of SEQ ID NO: 151; and a light chain comprising the amino acid sequence of SEQ ID NO: 194; or
- p) a heavy chain comprising the amino acid sequence of SEQ ID NO: 152; and a light chain comprising the amino acid sequence of SEQ ID NO: 195; or
- q) a heavy chain comprising the amino acid sequence of SEQ ID NO: 217; and a light chain comprising the amino acid sequence of SEQ ID NO: 218.

5. The anti-SIRP α antibody according to claim 1, wherein the antibody comprises:

- a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 135; and a light chain comprising the amino acid sequence of SEQ ID NO: 178; or
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 153; and a light chain comprising the amino acid sequence of SEQ ID NO: 196; or
- c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 154; and a light chain comprising the amino acid sequence of SEQ ID NO: 197; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 155; and a light chain comprising the amino acid sequence of SEQ ID NO: 198; or
- e) a heavy chain comprising the amino acid sequence of SEQ ID NO: 156; and a light chain comprising the amino acid sequence of SEQ ID NO: 199; or
- f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 157; and a light chain comprising the amino acid sequence of SEQ ID NO: 200; or
- g) a heavy chain comprising the amino acid sequence of SEQ ID NO: 158; and a light chain comprising the amino acid sequence of SEQ ID NO: 201; or
- h) a heavy chain comprising the amino acid sequence of SEQ ID NO: 159; and a light chain comprising the amino acid sequence of SEQ ID NO: 202; or
- i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 160; and a light chain comprising the amino acid sequence of SEQ ID NO: 203; or
- j) a heavy chain comprising the amino acid sequence of SEQ ID NO: 161; and a light chain comprising the amino acid sequence of SEQ ID NO: 204; or
- k) a heavy chain comprising the amino acid sequence of SEQ ID NO: 162; and a light chain comprising the amino acid sequence of SEQ ID NO: 205; or

- l) a heavy chain comprising the amino acid sequence of SEQ ID NO: 163; and a light chain comprising the amino acid sequence of SEQ ID NO: 206; or
- m) a heavy chain comprising the amino acid sequence of SEQ ID NO: 164; and a light chain comprising the amino acid sequence of SEQ ID NO: 207; or
- n) a heavy chain comprising the amino acid sequence of SEQ ID NO: 165; and a light chain comprising the amino acid sequence of SEQ ID NO: 208; or
- o) a heavy chain comprising the amino acid sequence of SEQ ID NO: 166; and a light chain comprising the amino acid sequence of SEQ ID NO: 209; or
- p) heavy chain comprising the amino acid sequence of SEQ ID NO: 167; and a light chain comprising the amino acid sequence of SEQ ID NO: 210; or
- q) a heavy chain comprising the amino acid sequence of SEQ ID NO: 168; and a light chain comprising the amino acid sequence of SEQ ID NO: 211; or
- r) a heavy chain comprising the amino acid sequence of SEQ ID NO: 169; and a light chain comprising the amino acid sequence of SEQ ID NO: 212; or
- s) a heavy chain comprising the amino acid sequence of SEQ ID NO: 170; and a light chain comprising the amino acid sequence of SEQ ID NO: 213; or
- t) a heavy chain comprising the amino acid sequence of SEQ ID NO: 171; and a light chain comprising the amino acid sequence of SEQ ID NO: 214; or
- u) a heavy chain comprising the amino acid sequence of SEQ ID NO: 172; and a light chain comprising the amino acid sequence of SEQ ID NO: 215; or
- v) a heavy chain comprising the amino acid sequence of SEQ ID NO: 173; and a light chain comprising the amino acid sequence of SEQ ID NO: 216; or
- w) a heavy chain comprising the amino acid sequence of SEQ ID NO: 219; and a light chain comprising the amino acid sequence of SEQ ID NO: 220.

6. The anti-SIRP α antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody is a human antibody.

7. The anti-SIRP α antibody or antigen-binding fragment thereof according to any one of claims 1 to 6 for use as a medicament.

8. A pharmaceutical composition comprising an antibody or antigen-binding fragment according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

9. An anti-SIRP α antibody or antigen-binding fragment according to any one of claims 1 to 6, or a pharmaceutical composition of claim 8, for use in treating a disease, wherein the disease is selected from cancer, inflammatory disease, autoimmune disease, respiratory disease, infectious disease or fibrosis.

10. Use of the anti-SIRP α antibody or antigen-binding fragment according to any one of claims 1 to 6, or a pharmaceutical composition of claim 8, in manufacture of a medicament for treating a disease, wherein the disease is selected from cancer, inflammatory disease, autoimmune disease, respiratory disease, infectious disease or fibrosis.

11. The anti-SIRP α antibody or antigen-binding fragment according to claim 9, or the use of the anti-SIRP α antibody or antigen-binding fragment according to claim 10, wherein the disease is cancer.

12. An isolated polynucleotide encoding a heavy chain variable region and/or a light chain variable region according to any one of claims 2 or 3.

13. An isolated polynucleotide encoding a heavy chain and/or a light chain according to any one of claims 4 or 5.

14. A vector comprising a polynucleotide according to any one of claims 12 or 13, preferably an expression vector, more preferred a vector comprising the polynucleotide according to the invention in functional association with an expression control sequence.

15. A host cell comprising a polynucleotide according to any one of claims 12 or 13.

16. A method for the production of an anti-SIRP α antibody or antigen-binding fragment according to any one of claims 1 to 6, comprising the steps:

(a) cultivating the host cell under conditions allowing the expression of the anti-SIRP α antibody or antigen-binding fragment; and

(b) recovering the anti-SIRP α antibody or antigen-binding fragment.

17. A method of manufacturing an antibody comprising the steps of:

- a) culturing a host cell comprising an expression vector comprising an isolated polynucleotide encoding a heavy chain variable region according to any one of claims 2 or 3 and comprising a polynucleotide encoding light chain variable region according to any one of claims 2 or 3 under conditions that allow formation of an antibody; and
- b) recovering said antibody.

18. A method of manufacturing an antibody comprising the steps of:

- a) culturing a host cell comprising an expression vector comprising an isolated polynucleotide encoding a heavy chain according to claim 4 or 5 and a polynucleotide encoding a light chain according to claim 4 or 5 under conditions that allow formation of an antibody; and
- b) recovering said antibody.

19. The method of claim 17 or 18, further comprising the step of purifying said antibody.

20. The method of claim 17 or 18, further comprising the step of formulating said antibody into a pharmaceutical composition.