

phagocytosis of the cancer cell and/or the infected cell. Thus, anti-CD47 agents can be used to treat and/or protect against a wide variety of conditions/disorders. In fact, anti-CD47 and anti-SIRP α blocking antibodies significantly increase phagocytosis of cancer cells *in vitro* and *in vivo*. They have been shown to be effective at treating mice engrafted with a wide range of human cancers, from leukemias to solid tumors. However, in some cases an initial high dose of an anti-CD47 agent can cause a dose-dependent loss of red blood cells (RBCs) in mice and non-human primate (NHP) models by binding to CD47 on the surface of the RBCs. The severity of this anemia can preclude the use of higher doses that are required to achieve sustained serum concentrations associated with therapeutic efficacy.

[0004] The present disclosure provides anti-SIRP α antibodies that block the interaction of CD47 on one cell (e.g., a cancer cell, an infected cell, etc.) with SIRP α on another cell (e.g., a phagocytic cell), and facilitate the phagocytosis of the CD47-expressing cell. Also disclosed are antibodies that are bispecific for SIRP α and a second antigen (e.g., a tumor antigen). These bi-specific macrophage enhancing (BiME) antibodies exhibit enhanced properties.

SUMMARY

[0005] Compositions and methods are provided relating to anti-SIRP α antibodies.

[0005a] In one aspect of the present disclosure, there is provided an antibody that specifically binds to human SIRP α , and comprises:

(i) a heavy chain having three CDRs, wherein CDR-H1 has the amino acid sequence set forth in SEQ ID NO: 2, CDR-H2 has the amino acid sequence set forth in SEQ ID NO: 3, and CDR-H3 has the amino acid sequence set forth in SEQ ID NO: 4; and

(ii) a light chain having three CDRs, wherein CDR-L1 has the amino acid sequence set forth in SEQ ID NO: 6, CDR-L2 has the amino acid sequence set forth in SEQ ID NO: 7, and CDR-L3 has the amino acid sequence set forth in SEQ ID NO: 8.

[0005b] In another aspect of the present disclosure, there is provided a polynucleotide encoding an antibody disclosed herein.

[0005c] In a further aspect of the present disclosure, there is provided a cell that produces an antibody disclosed herein.

[0005d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising an antibody disclosed herein.

[0005e] In a further aspect of the present disclosure, there is provided a use of a composition comprising an antibody disclosed herein in the manufacture of a medicament for inducing phagocytosis in an individual, wherein the individual has a condition or disease selected from: cancer, a solid tumor, leukemia, a lymphoma, a chronic infection, an inflammatory disease, multiple sclerosis, and arthritis.

[0005f] In another aspect of the present disclosure, there is provided a method of detecting the presence of SIRP α in a biological sample or tissue, the method comprising: contacting the biological sample or tissue with the antibody disclosed herein, and determining the presence or absence of antibody bound to the biological sample or tissue.

[0005g] In a further aspect of the present disclosure, there is provided a method of detecting SIRP α expressing cells in an individual, comprising:
administering to the individual an anti-SIRP α antibody disclosed herein, wherein the antibody is detectably labeled; and
detecting the presence or absence of the label in the individual.

[0005h] The antibodies of the disclosure bind to human SIRP α and can block the interaction of CD47 expressed on a target cell of interest with SIRP α expressed on a phagocytic cell. The subject antibodies find use in various therapeutic methods. In some cases, an anti-SIRP α antibody of the present disclosure can bind SIRP α , but does not stimulate SIRP α signaling in the cell expressing the SIRP α . Embodiments of the disclosure include isolated antibodies and derivatives and fragments thereof, pharmaceutical formulations comprising one or more of the subject anti-SIRP α antibodies; and cell lines that produce these anti-SIRP α antibodies. Also provided are amino acid sequences of exemplary antibodies. Antibodies of interest include the provided anti-SIRP α antibodies, and variants thereof. The anti-SIRP α antibodies of the disclosure find particular utility as reagents for the treatment of diseases associated with CD47 in humans (e.g., cancer, chronic infection, etc.)

[0006] Various forms of the antibodies are provided herein. For example, an anti-SIRP α antibody may be a full length chimeric or humanized antibody, e.g. having a human immunoglobulin constant region of any isotype or modification, e.g. IgG1, IgG2, IgG3, IgG4, IgA, *etc.*; or an antibody fragment, e.g. a F(ab')₂ fragment, and F(ab) fragment, *etc.* Fragments comprising CDR regions are also of interest. Exemplary forms also include single-chain Fv species (scFv) having one heavy- and one light-chain variable domain that are covalently linked by a flexible peptide linker. Furthermore, the antibody may be labeled with a detectable label, immobilized on a solid phase and/or conjugated with a heterologous compound. The antibody may also be provided as a bispecific or multispecific antibody reactive with a second antigen,

THAT WHICH IS CLAIMED IS:

1. An antibody that specifically binds to human SIRP α , and comprises:
 - (i) a heavy chain having three CDRs, wherein CDR-H1 has the amino acid sequence set forth in SEQ ID NO: 2, CDR-H2 has the amino acid sequence set forth in SEQ ID NO: 3, and CDR-H3 has the amino acid sequence set forth in SEQ ID NO: 4; and
 - (ii) a light chain having three CDRs, wherein CDR-L1 has the amino acid sequence set forth in SEQ ID NO: 6, CDR-L2 has the amino acid sequence set forth in SEQ ID NO: 7, and CDR-L3 has the amino acid sequence set forth in SEQ ID NO: 8.

2. The antibody of claim 1, comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 9-10.

3. The antibody of claim 1, wherein the heavy chain comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 1, 11, 13, 15, and 17.

4. The antibody of claim 1, wherein the light chain comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 5, 12, 14, 16, and 18.

5. The antibody of claim 1, wherein:

(a) the heavy chain comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 1, 11, 13, 15, and 17; and

(b) the light chain comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 5, 12, 14, 16, and 18.

6. The antibody of claim 1, wherein:

(a) the heavy chain comprises the amino acid sequence of SEQ ID NO: 1, and the light chain comprises the amino acid sequence of SEQ ID NO: 5;

(b) the heavy chain comprises the amino acid sequence of SEQ ID NO: 11, and the light chain comprises the amino acid sequence of SEQ ID NO: 12;

(c) the heavy chain comprises the amino acid sequence of SEQ ID NO: 13, and the light chain comprises the amino acid sequence of SEQ ID NO: 14;

(d) the heavy chain comprises the amino acid sequence of SEQ ID NO: 15, and the light chain comprises the amino acid sequence of SEQ ID NO: 16; or

(e) the heavy chain comprises the amino acid sequence of SEQ ID NO: 17, and the light chain comprises the amino acid sequence of SEQ ID NO: 18.

7. The antibody of any of claims 1-6, wherein the antibody does not activate SIRPα upon binding.

8. The antibody of any of claims 1-7, wherein the antibody is a chimeric or humanized antibody.

9. The antibody of claim 8, wherein the antibody is a humanized monoclonal antibody.

10. The antibody of any of claims 1-9, wherein the antibody is a multispecific antibody that specifically binds to SIRP α and at least a second antigen.

11. The antibody of claim 10, wherein the second antigen is a marker of a CD47-expressing cell.

12. The antibody of claim 11, wherein the second antigen is selected from: CD19, CD20, CD22, CD24, CD25, CD30, CD33, CD38, CD44, CD52, CD56, CD70, CD96, CD97, CD99, CD123, CD279 (PD-1), EGFR, HER2, CD117, C-Met, PTHR2, and HAVCR2 (TIM3).

13. A polynucleotide encoding an antibody set forth in any of claims 1-12.

14. A cell that produces an antibody set forth in any of claims 1-12.

15. A pharmaceutical composition comprising an antibody set forth in any of claims 1-12.

16. The pharmaceutical composition of claim 15, further comprising a second antibody that specifically binds to a marker of a CD47-expressing cancer cell.

17. The pharmaceutical composition of claim 16, wherein the second antibody specifically binds to one or more markers selected from the group consisting of: CD19, CD20, CD22, CD24, CD25, CD30, CD33, CD38, CD44, CD52, CD56, CD70, CD96, CD97, CD99, CD123, CD279 (PD-1), EGFR, HER2, CD117, C-Met, PTHR2, and HAVCR2 (TIM3).

18. The pharmaceutical composition of claim 15, comprising a pharmaceutically acceptable excipient.

19. Use of a composition comprising an antibody set forth in any of claims 1-12 in the manufacture of a medicament for inducing phagocytosis in an individual, wherein the individual has a condition or disease selected from: cancer, a solid tumor, leukemia, a lymphoma, a chronic infection, an inflammatory disease, multiple sclerosis, and arthritis.

20. The use according to claim 19, wherein the individual is human.

21. The use according to claim 20, wherein the composition comprises a second antibody that specifically binds a marker of a CD47-expressing cell.

22. The use according to claim 21, wherein the second antibody specifically binds a cancer cell marker.

23. The use according to claim 22, wherein the cancer cell marker is selected from: CD19, CD20, CD22, CD24, CD25, CD30, CD33, CD38, CD44, CD52, CD56, CD70, CD96, CD97, CD99, CD123, CD279 (PD-1), EGFR, HER2, CD117, C-Met, PTHR2, and HAVCR2 (TIM3).

24. A method of detecting the presence of SIRP α in a biological sample or tissue, the method comprising: contacting the biological sample or tissue with the antibody set forth in any of claims 1-12, and determining the presence or absence of antibody bound to the biological sample or tissue.

25. A method of detecting SIRP α expressing cells in an individual, comprising: administering to the individual an anti-SIRP α antibody set forth in any of claims 1-12, wherein the antibody is detectably labeled; and detecting the presence or absence of the label in the individual.

26. The method according to claim 25, wherein the detectable label is a radioisotope label.

27. The method according to claim 25, wherein the detecting step comprises detecting the presence or absence of the label with positron emission tomography (PET).

28. The method according to any of claims 25 to 27, wherein the individual has or is suspected of having cancer, inflammation, an inflammatory disease, and/or a chronic infection.