

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 OF THE INVENTION

[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 one or more CDRs having an amino acid sequence that differs by not more than 3 amino acids as compared to a CDR amino acid sequence set forth in any of SEQ ID NOs: 2-4 and 6-8.

[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.

[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 use of an anti-SIRP α antibody disclosed herein in the manufacture of a medicament for detecting SIRP α expressing cells in an individual, wherein the antibody is detectably labeled, and wherein the medicament is to be administered to the individual, and

the SIRP α expressing cells are detected by 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 ~~invention~~ 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,

particularly including cancer antigens and/or antigens of chronic infection. The disclosure also provides compositions that include a subject anti-SIRP α antibody and an antibody that binds to a second antigen (e.g., a cancer cell marker, a marker of chronic infection, and the like).

[0007] Also provided are methods for determining the presence of SIRP α expressing cells, comprising exposing a patient sample suspected of containing SIRP α expressing cells to the anti-SIRP α antibody and determining binding of the antibody to the sample. For this use, the ~~present disclosure invention~~ provides a kit comprising the antibody and instructions for using the antibody.

[0008] The antibodies of the disclosure are efficacious in the treatment of disease. In some embodiments of method of treatment is provided, comprising contacting an individual with an effective dose of an antibody of the ~~present disclosure invention~~, wherein the effective dose provides for binding the antibody of the ~~present disclosure invention~~ to a phagocytic cell thereby increasing phagocytosis of target cells expressing CD47. Treatment may be systemic or localized, e.g. delivery by intratumoral injection, *etc.*

[0009] Embodiments of the disclosure include isolated antibodies and derivatives and fragments thereof that comprise at least one, usually at least 3 CDR sequences from a set, as provided herein, usually in combination with framework sequences from a human variable region. In some embodiments an antibody or derivative or fragment thereof comprises at least one light chain comprising a set of 3 light chain CDR sequences provided herein, situated in a variable region framework, which may be, without limitation, a human, canine, mouse, *etc.* variable region framework; and at least one heavy chain comprising the set of 3 heavy chain CDR sequence provided herein, situated in a variable region framework, which may be, without limitation, a human, canine, mouse, *etc.* variable region framework or other appropriate protein scaffold.

[0010] In other embodiments, the antibody comprises an amino acid sequence variant of one or more of the CDRs of the provided antibodies, which variant comprises one or more amino acid insertion(s) within or adjacent to a CDR residue and/or deletion(s) within or adjacent to a CDR residue and/or substitution(s) of CDR residue(s) (with substitution(s) being the preferred type of amino acid alteration for generating such variants). Such variants will normally having a binding affinity for human SIRP α of 10^{-5} M or better (e.g., 10^{-6} M or better, 10^{-8} M or better, *etc.*) and will bind to the same epitope as an antibody having the amino acid sequence of those set forth herein.

[0011] The disclosure further provides: isolated nucleic acids encoding the antibodies and variants thereof; a vector comprising that nucleic acid, optionally operably linked to control sequences recognized by a host cell transformed with the vector; a host cell comprising that vector; a process for producing the antibody comprising culturing the host cell so that the nucleic acid is expressed and, optionally, recovering the antibody from the host cell culture (e.g. from the host cell culture medium). The disclosure also provides a composition comprising one

17. The antibody of claim 16, wherein the antibody is a humanized monoclonal antibody.
18. The antibody of any of claims 1-17, wherein the antibody is a multispecific antibody that specifically binds to SIRP α and at least a second antigen.
19. The antibody of claim 18, wherein the second antigen is a marker of a CD47-expressing cell.
20. The antibody of claim 19, 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).
21. A polynucleotide encoding an antibody set forth in any of claims 1-20.
22. A cell that produces an antibody set forth in any of claims 1-20.
23. A pharmaceutical composition comprising an antibody set forth in any of claims 1-20.
24. The pharmaceutical composition of claim 23, further comprising a second antibody that specifically binds to a marker of a CD47-expressing cancer cell.
25. The pharmaceutical composition of claim 24, 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).
26. The pharmaceutical composition of claim 23, comprising a pharmaceutically acceptable excipient.
27. Use of a composition comprising an antibody set forth in any of claims 1-20 in the manufacture of a medicament for ~~A method of inducing phagocytosis in an individual, the method comprising:~~
~~—administering to an individual a composition comprising an antibody set forth in any of claims 1-20 in a dose effective to induce phagocytosis.~~
28. The ~~method~~ use according to claim 27, wherein the individual is human.

29. The ~~use method~~ according to claim 28, 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.

30. The ~~use method~~ according to claim 28 or claim 29, wherein the composition comprises a second antibody that specifically binds a marker of a CD47-expressing cell.

31. The ~~use method~~ according to claim 30, wherein the second antibody specifically binds a cancer cell marker.

32. The ~~use method~~ according to claim 31, 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).

33. 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 1-20, and determining the presence or absence of antibody bound to the biological sample or tissue.

34. ~~Use of an anti-SIRP α antibody set forth in any of claims 1-20 in the manufacture of a medicament for~~ A method of detecting SIRP α expressing cells in an individual, wherein the antibody is detectably labeled, and wherein the medicament is to be administered to the individual, comprising:

~~administering to the individual an anti-SIRP α antibody set forth in any of claims 1-20, wherein the antibody is detectably labeled; and~~

~~detecting the SIRP α expressing cells are detected by the presence or absence of the label in the individual.~~

35. The ~~method use~~ according to claim 34, wherein the detectable label is a radioisotope label.

36. The ~~use method~~ according to claim 35, wherein the detecting step comprises detecting the presence or absence of the label with positron emission tomography (PET).

37. The ~~use method~~ according to any of claims 34 to 36, wherein the individual has or is suspected of having cancer, inflammation, an inflammatory disease, and/or a chronic infection.