

CLAIMS

It is claimed:

1. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:
 - (1) SEQ ID NOs:177, 46, 47, 178, 112, and 179, respectively;
 - (2) SEQ ID NOs:51, 52, 53, 117, 118, and 119, respectively;
 - (3) SEQ ID NOs:54, 55, 56, 120, 121, and 122, respectively;
 - 10 (4) SEQ ID NOs:57, 58, 59, 123, 124, and 125, respectively;
 - (5) SEQ ID NOs:60, 61, 62, 126, 127, and 128, respectively;
 - (6) SEQ ID NOs:180, 181, 182, 129, 130, and 131, respectively;
 - (7) SEQ ID NOs:72, 73, 74, 138, 139, and 140, respectively;
 - (8) SEQ ID NOs:78, 79, 80, 144, 145, and 146, respectively;
 - 15 (9) SEQ ID NOs:81, 82, 83, 147, 148, and 149, respectively;
 - (10) SEQ ID NOs:84, 85, 86, 150, 151, and 152, respectively;
 - (11) SEQ ID NOs:87, 88, 89, 153, 154, and 155, respectively;
 - (12) SEQ ID NOs:90, 91, 92, 156, 157, and 158, respectively;
 - (13) SEQ ID NOs:93, 94, 95, 159, 160, and 161, respectively;
 - 20 (14) SEQ ID NOs:96, 97, 98, 162, 163, and 164, respectively;
 - (15) SEQ ID NOs:99, 100, 101, 165, 166, and 167, respectively;
 - (16) SEQ ID NOs:102, 103, 104, 168, 169, and 170, respectively;
 - (17) SEQ ID NOs:105, 106, 107, 171, 172, and 173, respectively;
 - (18) SEQ ID NOs:108, 109, 110, 174, 175, and 176, respectively; or
 - 25 (19) SEQ ID NOs:201, 202, 203, 204, 205, and 206, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds CD47, preferably human CD47.
2. The isolated monoclonal antibody or antigen-binding fragment of claim 1, comprising a heavy chain variable region having a polypeptide sequence at least 95%
 - 30 identical to SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, or 43, or a light chain variable region having a polypeptide sequence at least 95%

identical to SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, or 44.

3. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1 or 2, comprising:

- 5 a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1, and a light chain variable region having the polypeptide sequence of SEQ ID NO:2;
- b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:3, and a light chain variable region having the polypeptide sequence of
10 SEQ ID NO:4;
- c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:5, and a light chain variable region having the polypeptide sequence of SEQ ID NO:6;
- d. a heavy chain variable region having the polypeptide sequence of SEQ ID
15 NO:7, and a light chain variable region having the polypeptide sequence of SEQ ID NO:8;
- e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:9, and a light chain variable region having the polypeptide sequence of SEQ ID NO:10;
- 20 f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:11, and a light chain variable region having the polypeptide sequence of SEQ ID NO:12;
- g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:13, and a light chain variable region having the polypeptide sequence of
25 SEQ ID NO:14;
- h. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;
- 30 i. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:17, and a light chain variable region having the polypeptide sequence of SEQ ID NO:18;

- j. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:19, and a light chain variable region having the polypeptide sequence of SEQ ID NO:20;
- 5 k. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:21, and a light chain variable region having the polypeptide sequence of SEQ ID NO:22;
- l. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:23, and a light chain variable region having the polypeptide sequence of SEQ ID NO:24;
- 10 m. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:25, and a light chain variable region having the polypeptide sequence of SEQ ID NO:26;
- n. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:27, and a light chain variable region having the polypeptide sequence of SEQ ID NO:28;
- 15 o. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;
- p. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:31, and a light chain variable region having the polypeptide sequence of SEQ ID NO:32;
- 20 q. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:33, and a light chain variable region having the polypeptide sequence of SEQ ID NO:34;
- 25 r. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:35, and a light chain variable region having the polypeptide sequence of SEQ ID NO:36;
- s. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:37, and a light chain variable region having the polypeptide sequence of SEQ ID NO:38;
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- t. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:39, and a light chain variable region having the polypeptide sequence of SEQ ID NO:40;
 - u. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:41, and a light chain variable region having the polypeptide sequence of SEQ ID NO:42; or
 - v. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44.
4. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 3, wherein the antibody or antigen-binding fragment thereof inhibits the interaction of CD47 and thrombospondin-1 (TSP-1) and/or that of CD47 and SIRP α .
5. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 4, wherein the antibody or antigen-binding fragment thereof is chimeric.
6. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 5, wherein the antibody or antigen-binding fragment thereof is human or humanized.
7. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 6, wherein the antibody or antigen-binding fragment thereof comprises:
- a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:183, and a light chain variable region having the polypeptide sequence of SEQ ID NO:191;
 - b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:183, and a light chain variable region having the polypeptide sequence of SEQ ID NO:192;
 - c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:183, and a light chain variable region having the polypeptide sequence of SEQ ID NO:193;
 - d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;

- e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:192;
- 5 f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:193;
- g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:185, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;
- 10 h. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:185, and a light chain variable region having the polypeptide sequence of SEQ ID NO:191;
- i. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:185, and a light chain variable region having the polypeptide sequence of SEQ ID NO:193;
- 15 j. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:185, and a light chain variable region having the polypeptide sequence of SEQ ID NO:198;
- k. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:187, and a light chain variable region having the polypeptide sequence of SEQ ID NO:194;
- 20 l. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:188, and a light chain variable region having the polypeptide sequence of SEQ ID NO:194;
- 25 m. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:188, and a light chain variable region having the polypeptide sequence of SEQ ID NO:196; or
- n. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:188, and a light chain variable region having the polypeptide sequence of SEQ ID NO:197
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- o. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:199, and a light chain variable region having the polypeptide sequence of SEQ ID NO:200.
8. The isolated monoclonal antibody or antigen-binding fragment of any one of
5 claims 1 to 7, wherein the antibody or antigen-binding fragment thereof is capable of blocking binding of CD47 to thrombospondin-1 (TSP1) and/or to signal regulatory protein alpha (SIRP α).
9. The isolated monoclonal antibody or antigen-binding fragment of any one of
10 claims 1 to 7, wherein the antibody or antigen-binding fragment thereof is capable of inducing macrophage-mediated phagocytosis of cancer cells.
10. The isolated monoclonal antibody or antigen-binding fragment of any one of claims 1 to 7, wherein the antibody or antigen-binding fragment thereof is capable of binding cancer cells with minimal to undetectable binding to red blood cells.
11. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding
15 fragment thereof of any of claims 1 to 10.
12. A vector comprising the isolated nucleic acid of claim 11.
13. A host cell comprising the vector of claim 12.
14. A pharmaceutical composition, comprising the isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 10 and a pharmaceutically
20 acceptable carrier.
15. A method of blocking binding of CD47 to thrombospondin-1 (TSP1) in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 14.
16. A method of blocking binding of CD47 to signal regulatory protein α (SIRP α) in
25 a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 14.
17. A method of treating cancer in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 14.
18. A method of treating an inflammatory disease in a subject in need thereof,
30 comprising administering to the subject the pharmaceutical composition of claim 14.

19. A method of treating an infectious disease in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 14.
20. A method of treating atherosclerosis in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 14.
- 5 21. A method of treating a cardiovascular disease in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 14.
22. A method of treating a metabolic disease in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 14.
23. A method of treating a radiation-induced injury in a subject in need thereof,
10 comprising administering to the subject the pharmaceutical composition of claim 14.
24. A method of treating an autoimmune disease in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 14.
25. A method of determining a level of CD47 in a subject, the method comprising:
a. obtaining a sample from the subject;
15 b. contacting the sample with an antibody or antigen-binding fragment thereof of any one of claims 1 to 10;
c. determining a level of CD47 in the subject.
26. The method of claim 25, wherein the sample is a tissue sample
27. The method of claim 26, wherein the tissue sample is a cancer tissue sample.
- 20 28. The method of claim 25, wherein the sample is a blood sample.
29. A method of producing the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 10, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof under conditions to produce the monoclonal antibody or antigen-binding fragment thereof, and
25 recovering the antibody or antigen-binding fragment thereof from the cell or culture.
30. A method of producing a pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 10, comprising combining the monoclonal antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

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