

Claims

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;
- (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;
- (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;
- (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
- (19) SEQ ID NOs:201, 202, 203, 204, 205, and 206, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds CD47.

2. The isolated monoclonal antibody or antigen-binding fragment of claim 1, comprising:
- (a) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:1, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:2;

- (b) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:3, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:4;
- (c) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:5, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:6;
- (d) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:7, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:8;
- (e) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:9, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:10;
- (f) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:11, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:12;
- (g) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:13, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:14;
- (h) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:15, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:16;
- (i) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:17, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:18;
- (j) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:19, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:20;
- (k) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:21, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:22;

- (l) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:23, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:24;
- (m) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:25, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:26;
- (n) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:27, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:28;
- (o) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:29, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:30;
- (p) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:31, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:32;
- (q) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:33, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:34;
- (r) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:35, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:36;
- (s) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:37, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:38;
- (t) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:39, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:40;
- (u) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:41, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:42; or

- (v) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:43, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:44;
- (w) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:183, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:191;
- (x) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:183, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:192;
- (y) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:183, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:193;
- (z) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:184, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:190;
- (aa) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:184, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:192;
- (bb) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:184, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:193;
- (cc) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:185, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:190;
- (dd) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:185, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:191;
- (ee) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:185, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:193;

- (ff) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:185, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:198;
- (gg) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:187, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:194;
- (hh) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:188, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:194;
- (ii) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:188, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:196;
- (jj) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:188, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:197; or
- (kk) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:199, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:200.
3. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1 or 2, comprising:
- 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 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 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;

- 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 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;
- 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;
- 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;
- 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;
- 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;
- 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;
- 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;
- 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;
- 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;
- w. 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;
- x. 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;
- y. 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;
- z. 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;
- aa. 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;
- bb. 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;
- cc. 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;
- dd. 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;
- ee. 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;

- ff. 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;
 - gg. 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;
 - hh. 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;
 - ii. 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;
 - jj. 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; or
 - kk. 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.
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 is chimeric and/or human or humanized.
 5. The isolated monoclonal antibody or antigen-binding fragment of any one of claims 1-4, wherein the antibody or antigen-binding fragment thereof is capable of blocking binding of CD47 to signal regulatory protein alpha (SIRP α), inducing macrophage-mediated phagocytosis of cancer cells, and/or binding cancer cells with minimal to undetectable binding to red blood cells.
 6. A bispecific antibody comprising the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-5.
 7. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof of any of claims 1-5.
 8. A vector comprising the isolated nucleic acid of claim 7.
 9. A host cell comprising the vector of claim 8.

10. A pharmaceutical composition, comprising the isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-5 and a pharmaceutically acceptable carrier.
11. A pharmaceutical composition of claim 10 for use in the treatment of cancer in a subject in need thereof, wherein the pharmaceutical composition is to be administered to the subject.
12. A method of determining a level of CD47 in a subject, the method comprising:
 - a. obtaining a sample from the subject;
 - b. contacting the sample with an antibody or antigen-binding fragment thereof of any one of claims 1-5;
 - c. determining a level of CD47 in the subject.
13. The method of claim 12, wherein the sample is a tissue sample or a blood sample.
14. A method of producing the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-5, 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 recovering the antibody or antigen-binding fragment thereof from the cell or culture.
15. A method of producing a pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-5, comprising combining the monoclonal antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.
16. The monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-5, wherein the monoclonal antibody or antigen-binding fragment thereof specifically binds human CD47.
17. The method of claim 13, wherein the tissue sample is a cancer tissue sample.
18. Use of a pharmaceutical composition of claim 10 in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the pharmaceutical composition is to be administered to the subject.