

CLAIMS

1. An anti-CD47 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region,
5 wherein
 - (a) the VH region amino acid sequence comprises HCDR1 of GYTFTNYAMH (SEQ ID NO:48), HCDR2 of MGTIYPGNDDTKYNQKFQG (SEQ ID NO:49) and HCDR3 of GGFRAMDY (SEQ ID NO:50); and the VL region amino acid sequence comprises LCDR1 of RSSQSLHSNANTYLG (SEQ ID NO:55), LCDR2 of KGSNRFS (SEQ ID NO:52) and
10 LCDR3 of FQASHVPYT (SEQ ID NO:53);
 - (b) the VH region amino acid sequence comprises HCDR1 of GYTFTNYAMH (SEQ ID NO:48), HCDR2 of MGTIYPGNDDTKYNQKFQG (SEQ ID NO:49) and HCDR3 of GGFRAMDY (SEQ ID NO:50); and the VL region amino acid sequence comprises LCDR1 of RSSQSLHSGNTYLG (SEQ ID NO:51), LCDR2 of KGSNRFS (SEQ ID NO:52) and
15 LCDR3 of FQASHVPYT (SEQ ID NO:53);
 - (c) the VH region amino acid sequence comprises HCDR1 of GYTFTNYAMH (SEQ ID NO:48), HCDR2 of MGTIYPGNDDTKYNQKFQG (SEQ ID NO:49) and HCDR3 of GGFRAMDY (SEQ ID NO:50); and the VL region amino acid sequence comprises LCDR1 of RSSQSLHSNAYNYLG (SEQ ID NO:56), LCDR2 of KGSNRFS (SEQ ID NO:52) and
20 LCDR3 of FQASHVPYT (SEQ ID NO:53);
 - (d) the VH region amino acid sequence comprises HCDR1 of GYTFTNYAMH (SEQ ID NO:48), HCDR2 of MGTIYPGNDDTKYNQKFQG (SEQ ID NO:49) and HCDR3 of GGFRAMDY (SEQ ID NO:50); and the VL region amino acid sequence comprises LCDR1 of RSSQSLHSNAYNYLG (SEQ ID NO:56), LCDR2 of KGSNRFS (SEQ ID NO:52) and
25 LCDR3 of FQASQVPYT (SEQ ID NO:54);
 - (e) the VH region amino acid sequence comprises HCDR1 of GYTFTNYAMH (SEQ ID NO:48), HCDR2 of MGTIYPGNDDTKYNQKFQG (SEQ ID NO:49) and HCDR3 of GGFRAMDY (SEQ ID NO:50); and the VL region amino acid sequence comprises LCDR1 of RSSQSLHSNANTYLG (SEQ ID NO:55), LCDR2 of KGSNRFS (SEQ ID NO:52) and
30 LCDR3 of FQASQVPYT (SEQ ID NO:54);
 - (f) the VH region amino acid sequence comprises HCDR1 of GYTFTNYAMH (SEQ ID NO:48), HCDR2 of MGTIYPGNDDTKYNQKFQG (SEQ ID NO:49) and HCDR3 of GGFRAMDY (SEQ ID NO:50); and the VL region amino acid sequence comprises LCDR1 of RSSQSLHSGNTYLG (SEQ ID NO:51), LCDR2 of KGSNRFS (SEQ ID NO:52) and
35 LCDR3 of FQASQVPYT (SEQ ID NO:54);
 - (g) the VH region amino acid sequence comprises HCDR1 of GYSFTNYNIH (SEQ ID NO:57), HCDR2 of MGTIYPGNSDTSYNPSFQG (SEQ ID NO: 61) and HCDR3 of

GGVVRAMDY (SEQ ID NO:62); and the VL region amino acid sequence comprises LCDR1 of RSSQSLHLSNGNTYLG (SEQ ID NO:51), LCDR2 of KGSNRFS (SEQ ID NO:52) and LCDR3 of MQASQVPYT (SEQ ID NO:63); or

- (h) the VH region amino acid sequence comprises HCDR1 of GYSFTNYNIH (SEQ ID NO:57), HCDR2 of MGTIYPGDS DTRYNPKFQG (SEQ ID NO:58) and HCDR3 of GGYRAEDY (SEQ ID NO:59); and the VL region amino acid sequence comprises LCDR1 of RSSQSLHLSNGNTYLG (SEQ ID NO:51), LCDR2 of KGSNRFS (SEQ ID NO:52) and LCDR3 of MQGSHVPY (SEQ ID NO:60).
2. The antibody or antigen-binding portion of claim 1, wherein
- (a) the VH region amino acid sequence comprises SEQ ID NO:1 and the VL region amino acid sequence comprises SEQ ID NO:2;
- (b) the VH region amino acid sequence comprises SEQ ID NO:3 and the VL region amino acid sequence comprises SEQ ID NO:4;
- (c) the VH region amino acid sequence comprises SEQ ID NO:5 and the VL region amino acid sequence comprises SEQ ID NO:6;
- (d) the VH region amino acid sequence comprises SEQ ID NO:7 and the VL region amino acid sequence comprises SEQ ID NO:8;
- (e) the VH region amino acid sequence comprises SEQ ID NO:9 and the VL region amino acid sequence comprises SEQ ID NO:10;
- (f) the VH region amino acid sequence comprises SEQ ID NO:11 and the VL region amino acid sequence comprises SEQ ID NO:12;
- (g) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:14; or
- (h) the VH region amino acid sequence comprises SEQ ID NO:15 and the VL region amino acid sequence comprises SEQ ID NO:16.

3. An anti-CD47 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein
- (a) the HCDR1 comprises the amino acid sequence G-Y- X₁-F-T-X₂-Y-X₃-X₄-X₅, wherein X₁ is S or a conservative substitution of S, X₂ is N or a conservative substitution of N, X₃ is N or any other amino acid, X₄ is M or a conservative substitution of M and X₅ is H or any other amino acid (SEQ ID NO:42);
- (b) the HCDR2 comprises the amino acid sequence X₁-X₂-X₃-I-Y-P-G-X₄-X₅-X₆-T-X₇-Y-X₈-X₉-X₁₀-F-Q-G, wherein X₁ is M or a conservative substitution of M, X₂ is G or a conservative substitution of G, X₃ is T or any other amino acid, X₄ is N or a conservative

substitution of N, X₅ is D or any other amino acid, X₆ is D or any other amino acid, X₇ is S or any other amino acid, X₈ is N or any other amino acid, X₉ is Q or any other amino acid and X₁₀ is K or any other amino acid (SEQ ID NO:43);

- (c) the HCDR3 comprises the amino acid sequence X₁-G-X₂-R-X₃-X₄-D-Y, wherein
 5 X₁ is G or any other amino acid, X₂ is Y or any other amino acid, X₃ is A or any other amino acid and X₄ is M or any other amino acid (SEQ ID NO:44);

- (d) the LCDR1 comprises the amino acid sequence R-S-S-Q-S-X₁-X₂-X₃-S-X₄-X₅-X₆-X₇-Y-L-X₈, wherein X₁ is I or a conservative substitution of I, X₂ is V or a conservative substitution of V, X₃ is Y or a conservative substitution of Y, X₄ is N or any other amino
 10 acid, X₅ is G or any other amino acid, X₆ is N or any other amino acid, X₇ is T or any other amino acid and X₈ is G or any other amino acid (SEQ ID NO:45);

(e) the LCDR2 comprises the amino acid sequence K-X₁-S-N-R-X₂-S, wherein X₁ is V or any other amino acid and X₂ is F or any other amino acid (SEQ ID NO:46); and

- (f) the LCDR3 comprises the amino acid sequence X₁-Q-X₂-X₃-X₄-X₅-P-Y-X₆,
 15 wherein X₁ is F or any other amino acid, X₂ is G or any other amino acid, X₃ is S or any other amino acid, X₄ is H or any other amino acid, X₅ is V or any other amino acid, X₆ is T or any other amino acid (SEQ ID NO:47).

4. An anti-CD47 antibody or an antigen-binding portion thereof, wherein the antibody or
 20 antigen-binding portion cross-competes for binding to CD47 with the antibody or antigen-binding portion of any one of claims 1-3; and

- (a) comprises fully germline human framework amino acid sequences; and/or
 (b) does not comprise an 'NG' deamidation site in the LCDR1; and/or
 (c) does not comprise an 'NT' deamidation site in the LCDR1; and/or
 25 (d) comprises a human germline peptide sequence with high MHC class II binding affinity in HCDR1 and/or HCDR2; and/or
 (e) does not comprise a human T cell epitope sequence in the LCDR1; and/or
 (f) does not comprise a human T cell epitope sequence in the HCDR1 or in the HCDR1/Framework 2 region of the VH domain.

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5. The antibody or antigen-binding portion of any one of claims 1-4, wherein the antibody is human, humanized or chimeric.

6. The antibody or antigen-binding portion of any one of claims 1-5, wherein the VH
 35 region, the VL region, or both the VH and the VL region comprise one or more human framework region amino acid sequences.

7. The antibody or antigen-binding portion of any one of claims 1-6, wherein the VH region, the VL region, or both the VH and the VL region comprise a human variable region framework scaffold amino acid sequence into which the CDRs have been inserted.
- 5 8. The antibody or antigen-binding portion of claim 1 or 3, wherein the VH region comprises an IGHV5-51 or IGHV1-3 human germline scaffold amino acid sequence into which the HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted.
9. The antibody or antigen-binding portion of any one of claims 1, 3 and 8, wherein
10 the VL region comprises an IGKV2-28 human germline scaffold amino acid sequence into which the LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted.
10. The antibody or antigen-binding portion of any one of claims 1-9, wherein the antibody comprises an immunoglobulin constant region.
- 15 11. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.
12. The antibody or antigen-binding portion of claim 11, wherein the immunoglobulin
20 constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.
13. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is immunologically inert.
- 25 14. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A or a wild-type human IgG2 constant region.
- 30 15. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region comprises any one of SEQ ID NOS:17-23.
- 35 16. The antigen-binding portion of any one of claims 1-15, wherein the antibody or antigen-binding portion is an Fab, an Fab', an F(ab')₂, an Fd, an Fv, an scFv, a single domain antibody (dAb), a maxibody, a minibody, an intrabody, a diabody, a triabody, a tetrabody, a v-NAR or a bis-scFv.

17. The antibody or antigen-binding portion of any one of claims 1-16, wherein the antibody is monoclonal.
- 5 18. The antibody or antigen-binding portion of any one of claims 1-17, wherein the antibody is a tetrameric antibody, a tetravalent antibody or a multispecific antibody.
19. The antibody or antigen-binding portion of any one of claims 1-18, wherein the antibody is a bispecific antibody that binds specifically to a first antigen and a second
10 antigen, wherein the first antigen is CD47 and the second antigen is not CD47.
20. The antibody or antigen-binding portion of any one of claims 1-19, wherein the antibody or antigen-binding portion binds specifically to (a) human CD47 or (b) human CD47 and cynomolgus CD47.
- 15 21. A single-chain Fv (scFv) comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein
- (a) the HCDR1 comprises G-Y-T-F-T-X₁-Y-X₂-X₃-X₄, wherein X₁ is N or a conservative substitution of N, X₂ is N or any other amino acid, X₃ is M or a conservative
20 substitution of M and X₄ is H or any other amino acid (SEQ ID NO:104);
- (b) the HCDR2 comprises M-G-X₁-I-Y-P-G-X₂-X₃-X₄-T-X₅-Y-X₆-X₇-X₈-F-Q-G, wherein X₁ is T or any other amino acid, X₂ is N or a conservative substitution of N, X₃ is D or any other amino acid, X₄ is D or any other amino acid, X₅ is S or any other amino acid, X₆ is N or any other amino acid, X₇ is Q or any other amino acid and X₈ is K or any other
25 amino acid (SEQ ID NO: 105);
- (c) the HCDR3 comprises ; X₁-G-X₂-R-X₃-X₄-D-Y, wherein X₁ is G or any other amino acid, X₂ is Y or any other amino acid, X₃ is A or any other amino acid and X₄ is M or any other amino acid (SEQ ID NO:44)
- (d) the LCDR1 comprises R-S-S-Q-S-X₁-X₂-X₃-S-X₄-X₅-X₆-X₇-Y-L-X₈, wherein X₁ is
30 I or a conservative substitution of I, X₂ is V or a conservative substitution of V, X₃ is Y or a conservative substitution of Y, X₄ is N or any other amino acid, X₅ is G or any other amino acid, X₆ is N or any other amino acid, X₇ is T or any other amino acid and X₈ is G or any other amino acid (SEQ ID NO:45);
- (e) the LCDR2 comprises K-X₁-S-N-R-X₂-S, wherein X₁ is V or any other amino
35 acid and X₂ is F or any other amino acid (SEQ ID NO:46); and
- (f) the LCDR3 comprises X₁-Q-X₂-X₃-X₄-X₅-P-Y-X₆, wherein X₁ is F or any other amino acid, X₂ is G or any other amino acid, X₃ is S or any other amino acid, X₄ is H or any

other amino acid, X₅ is V or any other amino acid, X₆ is T or any other amino acid (SEQ ID NO:47); and

wherein the VH region comprises an IGHV5-51 human germline scaffold amino acid sequence into which the HCDR1, HCDR2 and HCDR3 amino acid sequences have
5 been inserted.

22. The scFv of claim 21, wherein

(a) the VH amino acid sequence comprises the HCDR1 of GYSFTNYNIH (SEQ ID NO:57), the HCDR2 of MGTIYPGDSDTSYNPKFQG (SEQ ID NO:94) and the HCDR3 of
10 GGYRAEDY (SEQ ID NO:59); and

(b) the VH amino acid sequence comprises the LCDR1 of RSSQSLLHSNGNTYLG (SEQ ID NO:51), the LCDR2 of KGSNRFS (SEQ ID NO:52) and the LCDR3 of MQGSHVPYT (SEQ ID NO:97).

23. The scFv of claim 21 or 22, further comprising an immunoglobulin constant region or a portion of an immunoglobulin constant region.

24. The scFv of claim 23, wherein the immunoglobulin constant region comprises any one of SEQ ID NOS:17-23.
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25. An immunoconjugate comprising the antibody or antigen-binding portion of any one of claims 1-20 or the scFv of any one of claims 21-24 linked to a therapeutic agent.

26. The immunoconjugate of claim 25, wherein the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, an anti-angiogenic agent, an antiproliferative agent, a pro-apoptotic agent, a cytostatic enzyme, a cytolytic enzymes, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.
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27. A pharmaceutical composition comprising the antibody or antigen-binding portion of any one of claims 1-20, the scFv of any one of claims 21-24 or the immunoconjugate of claim 25 or 26, and a pharmaceutically acceptable carrier, diluent or excipient.
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28. A nucleic acid molecule encoding
35 (a) the VH region amino acid sequence;
(b) the VL region amino acid sequence; or
(c) both the VH and the VL region amino acid sequences

of the antibody or antigen-binding portion of any one of claims 1-20 or the scFv of any one of claims 21-24.

29. An expression vector comprising the nucleic acid molecule of claim 28.

30. A recombinant host cell comprising the nucleic acid molecule of claim 28 or the expression vector of claim 29.

31. A method of producing an anti-CD47 antibody or an antigen-binding portion thereof, the method comprising:

culturing a recombinant host cell comprising the expression vector of claim 29 under conditions whereby the nucleic acid molecule is expressed, thereby producing the antibody or antigen-binding portion; and

isolating the antibody or antigen-binding portion from the host cell or culture.

32. A method for enhancing an immune response in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-20, the scFv of any one of claims 21-24, the immunoconjugate of claim 25 or 26 or the pharmaceutical composition of claim 27.

33. A method of treating cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-20, the scFv of any one of claims 21-24, the immunoconjugate of claim 25 or 26 or the pharmaceutical composition of claim 27.

34. The method of claim 33, wherein the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues.

35. The method of claim 33, wherein the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto's thyroiditis or ankylosing spondylitis.
- 5 36. The method of claim 33, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.
37. The method of claim 33, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.
- 10 38. The antibody or antigen-binding portion of any one of claims 1-20, the scFv of any one of claims 21-24, the immunoconjugate of claim 25 or 26 or the pharmaceutical composition of claim 27 for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease.
- 15 39. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 38, wherein the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues.
- 20 40. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 38, wherein the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto's thyroiditis or ankylosing spondylitis.
- 25 41. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 38, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.
- 30 42. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 38, wherein the fibrotic disease is
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myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

43. The antibody or antigen-binding portion of any one of claims 1-20, the scFv of any
5 one of claims 21-24, the immunoconjugate of claim 25 or 26 or the pharmaceutical
composition of claim 27, for use as a medicament.