

CLAIMS

1. An anti-CD47 antibody or an antigen-binding portion thereof, wherein the antibody
or antigen-binding portion comprises a heavy chain variable (VH) region and a light chain
variable (VL) region, 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 RSSQSLLHSNANTYLG (SEQ ID NO:55), LCDR2 of KGSNRFS (SEQ ID NO:52) and
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 RSSQSLLHSNGNTYLG (SEQ ID NO:51), LCDR2 of KGSNRFS (SEQ ID NO:52) and
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 RSSQSLLHSNAYNYLG (SEQ ID NO:56), LCDR2 of KGSNRFS (SEQ ID NO:52) and
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 RSSQSLLHSNAYNYLG (SEQ ID NO:56), LCDR2 of KGSNRFS (SEQ ID NO:52) and
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 RSSQSLLHSNANTYLG (SEQ ID NO:55), LCDR2 of KGSNRFS (SEQ ID NO:52) and
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 RSSQSLLHSNGNTYLG (SEQ ID NO:51), LCDR2 of KGSNRFS (SEQ ID NO:52) and
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 GGVRAMDY (SEQ ID NO:62); and the VL region amino acid sequence comprises LCDR1 of RSSQSLLHSNGNTYLG (SEQ ID NO:51), LCDR2 of KGSNRFS (SEQ ID NO:52) and LCDR3 of MQASQVPYT (SEQ ID NO:63);~~

~~(h) the VH region amino acid sequence comprises HCDR1 of GYSFTNYNIH (SEQ ID NO:57), HCDR2 of MGTIYPGDSDTRYNPKEFQG (SEQ ID NO:58) and HCDR3 of GGYRAEDY (SEQ ID NO:59); and the VL region amino acid sequence comprises LCDR1 of RSSQSLLHSNGNTYLG (SEQ ID NO:51), LCDR2 of KGSNRFS (SEQ ID NO:52) and LCDR3 of MQGSHVPY (SEQ ID NO:60); or~~

~~(i) the VH amino acid sequence comprises HCDR1 of GYSFTNYNIH (SEQ ID NO:57), HCDR2 of MGTIYPGDSDTSYNPKFQG (SEQ ID NO:94) and HCDR3 of GGYRAEDY (SEQ ID NO:59); and the VL amino acid sequence comprises LCDR1 of RSSQSLLHSNGNTYLG (SEQ ID NO:51), LCDR2 of KGSNRFS (SEQ ID NO:52) and LCDR3 of MQGSHVPYT (SEQ ID NO:97).~~

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; or

(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. The antibody or antigen-binding portion of claim 1 or 2, wherein the antibody is humanized or chimeric.
4. The antibody or antigen-binding portion of any one of claims 1-3, wherein the VH region, the VL region, or both the VH and the VL region comprise one or more human framework region amino acid sequences.
5. The antibody or antigen-binding portion of any one of claims 1-4, 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.
6. The antibody or antigen-binding portion of claim 1, 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.
7. The antibody or antigen-binding portion of claim 1 or 6, wherein 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.
8. The antibody or antigen-binding portion of any one of claims 1-7, wherein the antibody or antigen-binding portion comprises an immunoglobulin constant region.
9. The antibody or antigen-binding portion of claim 8, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.
10. The antibody or antigen-binding portion of claim 9, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.
11. The antibody or antigen-binding portion of claim 8, wherein the immunoglobulin constant region is immunologically inert.
12. The antibody or antigen-binding portion of claim 8, 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, wherein numbering is according to the EU index as in Kabat.

13. The antibody or antigen-binding portion of claim 8, wherein the immunoglobulin
5 constant region comprises any one of SEQ ID NOS:17-23.

14. The antibody or antigen-binding portion of any one of claims 1-13, wherein the
antibody or antigen-binding portion is an Fab, an Fab', an F(ab')₂, an Fv, an scFv, a
maxibody, a minibody, a diabody, a triabody, a tetrabody, or a bis-scFv.
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15. The antibody or antigen-binding portion of any one of claims 1-14, wherein the
antibody or antigen-binding portion is monoclonal.

16. The antibody or antigen-binding portion of any one of claims 1-15, wherein the
15 antibody or antigen-binding portion is ~~a tetrameric antibody, a tetravalent antibody or a multispecific antibody.~~

17. The antibody or antigen-binding portion of any one of claims 1-16, wherein the
antibody or antigen-binding portion is a bispecific antibody or antigen-binding portion that
20 binds specifically to a first antigen and a second antigen, wherein the first antigen is CD47
and the second antigen is not CD47.

18. The antibody or antigen-binding portion of any one of claims 1-17, wherein the
antibody or antigen-binding portion binds specifically to (a) human CD47 or (b) human
25 CD47 and cynomolgus CD47.

~~19. A single-chain Fv (scFv) comprising a heavy chain variable (VH) region and a light
chain variable (VL) region, wherein
—— (a) the VH amino acid sequence comprises the HCDR1 of GYSFTNYNIH (SEQ ID
30 NO:57), the HCDR2 of MGTIYPGSDTSYNPKFQG (SEQ ID NO:94) and the HCDR3 of
GGYRAEDY (SEQ ID NO:59); and
—— (b) the VL amino acid sequence comprises the LCDR1 of RSSQSLHNSNGNTYLG
(SEQ ID NO:51), the LCDR2 of KGSNRFS (SEQ ID NO:52) and the LCDR3 of
MQGSHVPYT (SEQ ID NO:97).~~

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~~20. The scFv of claim 19, further comprising an immunoglobulin constant region or a portion of an immunoglobulin constant region.~~

~~21. The scFv of claim 20, wherein the immunoglobulin constant region comprises any one of SEQ ID NOS:17-23.~~

~~2219.~~ An immunoconjugate comprising the antibody or antigen-binding portion of any one of claims 1-18 ~~or the scFv of any one of claims 19-21~~ linked to a therapeutic agent.

10 ~~2320.~~ The immunoconjugate of claim ~~2219~~, wherein the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, a cytostatic enzyme, a cytolytic enzyme, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.

15 ~~2421.~~ A pharmaceutical composition comprising the antibody or antigen-binding portion of any one of claims 1-18, ~~the scFv of any one of claims 19-21~~ or the immunoconjugate of claim ~~2219~~ or ~~2320~~, and a pharmaceutically acceptable carrier, diluent or excipient.

20 ~~2522.~~ A nucleic acid molecule encoding
~~(a) the VH region amino acid sequence;~~
~~—— (b) the VL region amino acid sequence; or~~
~~—— (c) both the VH region and the VL region amino acid sequences~~
of the antibody or antigen-binding portion of any one of claims 1-18 ~~or the scFv of any one of claims 19-21.~~

25 ~~2623.~~ An expression vector comprising the nucleic acid molecule of claim ~~2522~~.

~~2724.~~ A recombinant host cell comprising the nucleic acid molecule of claim ~~2522~~ or the expression vector of claim ~~2623~~.

30 ~~2825.~~ A method of producing an anti-CD47 antibody or an antigen-binding portion thereof, the method comprising:

culturing ~~a the~~ recombinant host cell ~~comprising the expression vector~~ of claim ~~2624~~ under conditions whereby the nucleic acid molecule is expressed, thereby producing the
35 antibody or antigen-binding portion; and
isolating the antibody or antigen-binding portion from the host cell or culture.

~~29. Use of a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-18, the scFv of any one of claims 19-21, the immunoconjugate of claim 22 or 23 or the pharmaceutical composition of claim 24 in the manufacture of a medicament for enhancing an immune response in a subject, wherein the medicament is to be administered to the subject.~~

~~3026. Use of a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-18, the scFv of any one of claims 19-21, the immunoconjugate of claim 22-19 or 23-20 or the pharmaceutical composition of claim 24-21 in the manufacture of a medicament for the treatment of cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease in a subject, wherein the medicament is to be administered to the subject.~~

~~3127. The use of claim 3026, 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.~~

~~32. The use of claim 30, 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.~~

~~33. The use of claim 30, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.~~

~~34. The use of claim 30, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.~~

~~3528. The antibody or antigen-binding portion of any one of claims 1-18, the scFv of any one of claims 19-21, the immunoconjugate of claim 22-19 or 23-20 or the pharmaceutical~~

composition of claim ~~24-21~~ for use in the treatment of cancer, ~~an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease.~~

5 ~~36-29.~~ The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim ~~35-28~~, 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.

15 ~~37.—The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 35, 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.~~

20 ~~38.—The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 35, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.~~

25 ~~39.—The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 35, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.~~

30 ~~40-30.~~ The antibody or antigen-binding portion of any one of claims 1-18, ~~the scFv of any one of claims 19-21,~~ the immunoconjugate of claim ~~22-19~~ or ~~23-20~~ or the pharmaceutical composition of claim ~~24-21~~, for use as a medicament.