

CLAIMS

1. An anti-ERBB3 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 VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQEISTYLS (SEQ ID NO: 261), LCDR2 of AASTLQS (SEQ ID NO: 26) and LCDR3 of LQYDSSPLT (SEQ ID NO: 262);

(b) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO: 21), LCDR2 of AASSLDT (SEQ ID NO: 263) and LCDR3 of amino acids 89-97 of SEQ ID NO: 224;

(c) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO: 21), LCDR2 of AASSLDT (SEQ ID NO: 263) and LCDR3 of LQYDSTPYT (SEQ ID NO: 23);

(d) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO: 13), HCDR2 of VSTISDSGSYTYYPDSVKG (SEQ ID NO: 19) and HCDR3 of ELGDYDGFDF (SEQ ID NO: 20); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO: 21), LCDR2 of AASSLDS (SEQ ID NO: 22) and LCDR3 of LQYDSTPYT (SEQ ID NO: 23);

(e) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO: 21), LCDR2 of AASTLQS (SEQ ID NO: 26) and LCDR3 of LQYDSTPLT (SEQ ID NO: 18);

(f) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO: 13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO: 14) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQISSYLS (SEQ ID NO: 16), LCDR2 of AASSLQS (SEQ ID NO: 17) and LCDR3 of LQYDSTPLT (SEQ ID NO: 18);

(g) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO: 13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO: 14) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 27); and the VL region amino acid sequence comprises

LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18);

(h) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTTYADSVKG (SEQ ID NO:28) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); and the VL region amino acid sequence comprises LCDR1 of RASQSISGYLS (SEQ ID NO:30), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPYT (SEQ ID NO:23);

(i) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTTYADNVKG (SEQ ID NO:31) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); or

(j) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18).

2. The antibody or antigen-binding portion of claim 1, wherein

(a) the VH region amino acid sequence comprises SEQ ID NO:236 and the VL region amino acid sequence comprises SEQ ID NO:225;

(b) the VH region amino acid sequence comprises SEQ ID NO:235 and the VL region amino acid sequence comprises SEQ ID NO:224;

(c) the VH region amino acid sequence comprises SEQ ID NO:232 and the VL region amino acid sequence comprises SEQ ID NO:221;

(d) the VH region amino acid sequence comprises SEQ ID NO:253 and the VL region amino acid sequence comprises SEQ ID NO:254; or

(e) the VH region amino acid sequence comprises SEQ ID NO:255 and the VL region amino acid sequence comprises SEQ ID NO:256.

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 IGHV3-11 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 IGKV1-39 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 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 constant region comprises any one of SEQ ID NOS:239-245.
14. The 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.

15. The antibody or antigen-binding portion of any one of claims 1-14, wherein the antibody is monoclonal.
16. The antibody or antigen-binding portion of any one of claims 1-15, wherein the antibody 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 is a bispecific antibody that binds specifically to a first antigen and a second antigen, wherein the first antigen is ERBB3 and the second antigen is not ERBB3.
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 ERBB3 or (b) human ERBB3 and rhesus ERBB3.
19. An immunoconjugate comprising the antibody or antigen-binding portion of any one of claims 1-18 linked to a therapeutic agent.
20. The immunoconjugate of claim 19, 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.
21. A pharmaceutical composition comprising the antibody or antigen-binding portion of any one of claims 1-18 or the immunoconjugate of claim 19 or 20, and a pharmaceutically acceptable carrier, diluent or excipient.
22. A nucleic acid molecule encoding
(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 1-18.
23. An expression vector comprising the nucleic acid molecule of claim 22.
24. A recombinant host cell comprising the nucleic acid molecule of claim 22 or the expression vector of claim 23.

25. A method of producing an anti-ERBB3 antibody or an antigen-binding portion thereof, the method comprising:

culturing a recombinant host cell comprising the expression vector of claim 25 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.

26. Use of a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-18, the immunoconjugate of claim 19 or 20 or the pharmaceutical composition of claim 21 in the manufacture of a medicament for enhancing an immune response in a subject, wherein the medicament is to be administered to the subject.

27. Use of a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-18, the immunoconjugate of claim 19 or 20 or the pharmaceutical composition of claim 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.

28. The use of claim 27, 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.

29. The use of claim 27, 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.

30. The use of claim 27, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.

31. The use of claim 27, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

32. The antibody or antigen-binding portion of any one of claims 1-18, the immunoconjugate of claim 19 or 20 or the pharmaceutical composition of claim 21 for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease.

33. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 32, 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.

34. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 32, 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.

35. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 32, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.

36. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 32, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

37. The antibody or antigen-binding portion of any one of claims 1-18, the immunoconjugate of claim 19 or 20 or the pharmaceutical composition of claim 21, for use as a medicament.