

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 LQYDSTPYT (SEQ ID NO: 23);
 - (c) 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), [Clone 15G11]; or
 - (d) 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); [Clone 16B09]
 - (e) 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 RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) 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: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);
 - (g) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYIYYADSVKG (SEQ ID NO:28) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); and the VL region amino acid sequence comprises

LCDR1 of RASQSIGYLS (SEQ ID NO:30), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPYT (SEQ ID NO:23);

- (h) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYADNVKG (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

- (i) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYADSVKG (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:232 and the VL region amino acid sequence comprises SEQ ID NO:221;

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

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

3. 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 HCDR1 comprises the amino acid sequence G-F-T-F-S-D-Y-X₁-M-S, wherein X₁ is G or any other amino acid (SEQ ID NO:1);

- (b) the HCDR2 comprises V-S-T-I-S-D-X₁-G-X₂-X₃-X₄-Y-Y-X₅-D-X₆-V-K-G, wherein X₁ is G or any other amino acid, X₂ is T or a conservative substitution of T, X₃ is Y or any other amino acid, X₄ is T or any other amino acid, X₅ is P or any other amino acid, and X₆ is N or a conservative substitution of N (SEQ ID NO:2);

- (c) the HCDR3 comprises X₁-X₂-G-D-X₃-D-G-X₄-D-X₅, wherein X₁ is E or any other amino acid, X₂ is W or any other amino acid, X₃ is Y or any other amino acid, X₄ is F or any other amino acid, and X₅ is Y or any other amino acid (SEQ ID NO:3);

(d) the LCDR1 comprises R-A-S-Q-X₁-I-S-X₂-Y-L-X₃, wherein X₁ is E or any other amino acid, X₂ is G or a conservative substitution of G, and X₃ is S or a conservative substitution of S (SEQ ID NO:7);

- (e) the LCDR2 comprises X₁-A-S-X₂-L-X₃-S, wherein X₁ is A or any other amino acid, X₂ is T or a conservative substitution of N, and X₃ is or D any other amino acid (SEQ ID NO:8); and
- 5 (f) the LCDR3 comprises X₁-Q-X₂-X₃-S-X₄-X₅-X₆-T, wherein X₁ is L or any other amino acid, X₂ is Y or any other amino acid, X₃ is D or any other amino acid, X₄ is Y or any other amino acid, X₅ is P or any other amino acid, and X₆ is Y or any other amino acid (SEQ ID NO:9).
- 10 4. An anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody or antigen-binding portion cross-competes for binding to ERBB3 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 isomerization site in the LCDR2; and/or
- 15 (c) does not comprise a 'DG' isomerization site in the HCDR2; and/or
- (d) does not comprise an oxidation site at position 2 in the HCDR3; and/or
- (e) exhibits a reduced number of predicted foreign human T cell receptor binding peptides in its v-domains in comparison to h24C05; and/or
- (f) contains no predicted foreign human T cell receptor binding peptides in its v-
- 20 domains.
5. The antibody or antigen-binding portion of any one of claims 1-4, wherein the antibody is human, humanized or chimeric.
- 25 6. The antibody or antigen-binding portion of any one of claims 1-5, 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.
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.
- 30 8. The antibody or antigen-binding portion of claim 1 or 3, 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.
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9. The antibody or antigen-binding portion of any one of claims 1, 3 and 8, 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.
- 5 10. The antibody or antigen-binding portion of any one of claims 1-9, wherein the antibody comprises an immunoglobulin constant region.
11. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.
- 10 12. The antibody or antigen-binding portion of claim 11, wherein the immunoglobulin 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.
- 15 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.
- 20 15. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region comprises any one of SEQ ID NOS:239-245.
- 25 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.
- 30 17. The antibody or antigen-binding portion of any one of claims 1-16, wherein the antibody is monoclonal.
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.
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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 antigen, wherein the first antigen is ERBB3 and the second antigen is not ERBB3.
- 5 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 ERBB3 or (b) human ERBB3 and rhesus ERBB3.
- 10 21. An immunoconjugate comprising the antibody or antigen-binding portion of any one of claims 1-20 linked to a therapeutic agent.
- 15 22. The immunoconjugate of claim 21, 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.
- 20 23. A pharmaceutical composition comprising the antibody or antigen-binding portion of any one of claims 1-20 or the immunoconjugate of claim 21 or 22, and a pharmaceutically acceptable carrier, diluent or excipient.
24. A nucleic acid molecule encoding
(a) the VH region amino acid sequence;
(b) the VL region amino acid sequence; or
25 (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.
25. An expression vector comprising the nucleic acid molecule of claim 24.
- 30 26. A recombinant host cell comprising the nucleic acid molecule of claim 24 or the expression vector of claim 25.
27. A method of producing an anti-ERBB3 antibody or an antigen-binding portion thereof, the method comprising:
35 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.

28. 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 immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23.
29. 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 immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23.
30. The method of claim 29, 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.
31. The method of claim 29, 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.
32. The method of claim 29, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.
33. The method of claim 29, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.
34. The antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23 for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease.
35. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 24, 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.

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

37. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 34, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.

38. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 34, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

39. The antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23, for use as a medicament.