

CLAIMS

1. An anti-C-KIT 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 GYTFTDYIMN (SEQ ID NO: 13), HCDR2 of MGRIYPGSGNTYYAQKFQG (SEQ ID NO: 14) and HCDR3 of GVYYYYDY (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQGIRTNLA (SEQ ID NO: 16), LCDR2 of AASSLQS (SEQ ID NO: 24) and LCDR3 of
10 QQYNSYPRT (SEQ ID NO: 12);
 - (b) the VH region amino acid sequence comprises HCDR1 of GYTFTDYIMN (SEQ ID NO: 13), HCDR2 of MGRIYPGSGNTYYAQKFQG (SEQ ID NO: 14) and HCDR3 of GVYYYYDY (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQGIRTNLA (SEQ ID NO: 16), LCDR2 of AASSLQS (SEQ ID NO: 24) and LCDR3 of
15 QQYANYPRT (SEQ ID NO: 25);
 - (c) the VH region amino acid sequence comprises HCDR1 of GYTFTDYIMN (SEQ ID NO: 13), HCDR2 of MGRIYPGSGNTYYAQKFQG (SEQ ID NO: 14) and HCDR3 of GVYYYYDY (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQGIRTNLA (SEQ ID NO: 16), LCDR2 of SASSLQS (SEQ ID NO: 17) and LCDR3 of
20 QQYANYPRT (SEQ ID NO: 25);
 - (d) the VH region amino acid sequence comprises HCDR1 of GYTFTDYIMN (SEQ ID NO: 13), HCDR2 of MGRIYPGSGNTYYAQKFQG (SEQ ID NO: 14) and HCDR3 of GVYYYYDY (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQGIRTNLA (SEQ ID NO: 16), LCDR2 of SASSLQS (SEQ ID NO: 17) and LCDR3 of
25 QQYNSYPRT (SEQ ID NO: 12);
 - (e) the VH region amino acid sequence comprises HCDR1 of GYTFTDYIMN (SEQ ID NO: 13), HCDR2 of MGRIYPGSGNTYYAQKFQG (SEQ ID NO: 14) and HCDR3 of GVYYLDY (SEQ ID NO: 18); and the VL region amino acid sequence comprises LCDR1 of RASQGIRTNVA (SEQ ID NO: 19), LCDR2 of SASYRQS (SEQ ID NO: 20) and LCDR3 of
30 QQYNSYPRT (SEQ ID NO: 12);
 - (f) the VH region amino acid sequence comprises HCDR1 of GYTFTDYIMN (SEQ ID NO: 13), HCDR2 of MGRIYPGSGNTYYAQKFQG (SEQ ID NO: 14) and HCDR3 of GVYYFDE (SEQ ID NO: 21); and the VL region amino acid sequence comprises LCDR1 of RASQGVRTNLA (SEQ ID NO: 22), LCDR2 of AASSRQS (SEQ ID NO: 23) and LCDR3 of
35 QQYNSYPRT (SEQ ID NO: 12); or
 - (g) the VH region amino acid sequence comprises HCDR1 of GYTFTDFYMN (SEQ ID NO: 180), HCDR2 of MGRIYPASGNTYYAQKFQG (SEQ ID NO: 26) and HCDR3 of

GVWYYDY (SEQ ID NO: 27); and the VL region amino acid sequence comprises LCDR1 of RASQGIRTNLA (SEQ ID NO: 16), LCDR2 of AASSLQS (SEQ ID NO: 24) and LCDR3 of QQYANYPRT (SEQ ID NO: 25).

- 5 2. The antibody or antigen-binding portion of claim 1, wherein
 - (a) the VH region amino acid sequence comprises SEQ ID NO:185 and the VL region amino acid sequence comprises SEQ ID NO:186;
 - (b) the VH region amino acid sequence comprises SEQ ID NO:187 and the VL region amino acid sequence comprises SEQ ID NO:188;
 - 10 (c) the VH region amino acid sequence comprises SEQ ID NO:189 and the VL region amino acid sequence comprises SEQ ID NO:190;
 - (d) the VH region amino acid sequence comprises SEQ ID NO:191 and the VL region amino acid sequence comprises SEQ ID NO:192;
 - (e) the VH region amino acid sequence comprises SEQ ID NO:193 and the VL region amino acid sequence comprises SEQ ID NO:194; or
 - 15 (f) the VH region amino acid sequence comprises SEQ ID NO:195 and the VL region amino acid sequence comprises SEQ ID NO:196.

- 20 3. An anti-C-KIT 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-T-F-T-X₁-X₂-Y-X₃-N, wherein X₁ is D or a conservative substitution of D, X₂ is Y or a conservative substitution of Y and X₃ is M or a conservative substitution of M (SEQ ID NO: 1);
 - 25 (b) the HCDR2 comprises X₁-X₂-R-I-Y-P-X₃-X₄-G-N-T-Y-Y-A-Q-K-F-Q-G, wherein X₁ is M or a conservative substitution of M, X₂ is G or a conservative substitution of G, X₃ is G or a conservative substitution of G and X₄ is S or a conservative substitution of S (SEQ ID NO: 2);
 - (c) the HCDR3 comprises G-V-X₁-X₂-X₃-X₄-X₅, wherein X₁ is Y or any other amino acid, X₂ is Y or any other amino acid, X₃ is F or any other amino acid, X₄ is D or any other amino acid and X₅ is Y or any other amino acid (SEQ ID NO: 3);
 - 30 (d) the LCDR1 comprises R-A-S-Q-G-X₁-X₂-X₃-X₄-L-A, wherein X₁ is I or a conservative substitution of I, X₂ is R or a conservative substitution of R, X₃ is T or any other amino acid and X₄ is N or any other amino acid (SEQ ID NO: 7);
 - 35 (e) the LCDR2 comprises X₁-A-S-X₂-X₃-X₄-S, wherein X₁ is A or any other amino acid, X₂ is S or any other amino acid, X₃ is L or any other amino acid and X₄ is Q or any other amino acid (SEQ ID NO: 8); and

(f) the LCDR3 comprises Q-Q-Y-X₁-X₂-Y-P-R-T, wherein X₁ is N or any other amino acid and X₂ is S or any other amino acid (SEQ ID NO: 9).

4. An anti-C-KIT antibody or an antigen-binding portion thereof, wherein the antibody
5 or antigen-binding portion cross-competes for binding to C-KIT 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 a deamidation site in the LCDR3; and/or
 - (c) comprises a human germline peptide sequence with high MHC class II binding
10 affinity in HCDR1 and/or LCDR2; and/or
 - (d) comprises a reduced number of immunogenic peptides compared to an anti-C-
KIT antibody comprising the variable domain sequences of antibody h37M; and/or
 - (e) exhibits reduced immunogenicity compared to an anti-C-KIT antibody
comprising the variable domain sequences of antibody h37M; and/or
15 (f) exhibits similar potency in receptor internalization to an anti-C-KIT antibody
comprising the variable domain sequences of antibody h37M and exhibits reduced potency
in C-KIT signalling blockade to an anti-C-KIT antibody comprising the variable domain
sequences of antibody h37M; and/or
 - (g) is immune effector null.
- 20
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
25 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
30 framework scaffold amino acid sequence into which the CDRs have been inserted.
8. The antibody or antigen-binding portion of claim 1 or 3, wherein the VH region
comprises an IGHV1-46 human germline scaffold amino acid sequence into which the
HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted.

35

9. The antibody or antigen-binding portion of any one of claims 1, 3 and 8, wherein the VL region comprises an IGKV1-16 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 IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S.
- 20 15. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region comprises SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201 or SEQ ID NO:202.
- 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.
- 35

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 C-KIT and the second antigen is not C-KIT.
- 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 C-KIT or (b) human C-KIT and cynomolgus C-KIT.
21. An immunoconjugate comprising the antibody or antigen-binding portion of any one
10 of claims 1-20 linked to a therapeutic agent.
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
15 enzymes, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.
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
20 acceptable carrier, diluent or excipient.
24. An isolated 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 23.
27. A method of producing an anti-C-KIT 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 34, wherein the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian
5 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.
- 10 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
15 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.
- 20 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.
- 25 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.