

CLAIMS

1. An anti-CSF1R 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 GYTFSSYYMI (SEQ ID NO: 31), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO: 32) and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASNRAT (SEQ ID NO:38) and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);
 - (b) the VH region amino acid sequence comprises HCDR1 of GYTFSSNYMI (SEQ ID NO:50), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO: 32), HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASDRAT (SEQ ID NO:60) and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);
 - (c) the VH region amino acid sequence comprises HCDR1 of GYTFSSAYMI (SEQ ID NO:57), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32) and HCDR3 of EGPYFSNLYVMDY (HCDR3; SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO:37), LCDR2 of AASDRAT (SEQ ID NO:60) and LCDR3 of QLSNEDLLT (SEQ ID NO:39); or
 - (d) the VH region amino acid sequence comprises HCDR1 of GYTFTSYMYI (SEQ ID NO:41), HCDR2 of MGDINPYNGGTTYAQKFQG (SEQ ID NO:42) and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO:33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLA (SEQ ID NO:40), LCDR2 of AASNLAT (SEQ ID NO:43) and LCDR3 of QLSNEDLLT (SEQ ID NO:39).
2. The antibody or antigen-binding portion of claim 1, wherein
 - (a) the VH region amino acid sequence comprises SEQ ID NO:352 and the VL region amino acid sequence comprises SEQ ID NO:351;
 - (b) the VH region amino acid sequence comprises SEQ ID NO:354 and the VL region amino acid sequence comprises SEQ ID NO:353;
 - (c) the VH region amino acid sequence comprises SEQ ID NO:356 and the VL region amino acid sequence comprises SEQ ID NO:355; or
 - (d) the VH region amino acid sequence comprises SEQ ID NO:358 and the VL region amino acid sequence comprises SEQ ID NO:357.

3. — An anti-CSF1R 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 GYTFSSYYMI (SEQ ID NO: 31), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYQGENYLA (SEQ ID NO: 34), LCDR2 of DASNRAT (SEQ ID NO: 35), and LCDR3 of QLSNQDLLT (SEQ ID NO: 36);

(b) the VH region amino acid sequence comprises HCDR1 of GYTFSSYYMI (SEQ ID NO: 31), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);

(c) the VH region amino acid sequence comprises HCDR1 of GYTFSSYYMI (SEQ ID NO: 31), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLA (SEQ ID NO:40), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNQDLLT (SEQ ID NO: 36);

(d) the VH region amino acid sequence comprises HCDR1 of GYTFTSYYYMI (SEQ ID NO:41), HCDR2 of MGDINPYNGGTTYAQKFQG (SEQ ID NO: 42), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLA (SEQ ID NO:40), LCDR2 of AASNLAT (SEQ ID NO:43), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);

(e) the VH region amino acid sequence comprises HCDR1 of GYTFTSYYYMI (SEQ ID NO:41), HCDR2 of MGDINPYNGGANFAQKFQG (SEQ ID NO:44), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);

(f) the VH region amino acid sequence comprises HCDR1 of GYTFTSYYYMI (SEQ ID NO:41), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);

(g) the VH region amino acid sequence comprises HCDR1 of GYTFSSYYMI (SEQ ID NO: 31), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVEYQGDNYLN (SEQ ID NO:45), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);

~~(h) the VH region amino acid sequence comprises HCDR1 of GYTFTSYII (SEQ ID NO:46), HCDR2 of MGDINPYNGGATYAQKFQG (SEQ ID NO:47), and HCDR3 of EPPYFSNLYVMDY (SEQ ID NO:48); and the VL region amino acid sequence comprises LCDR1 of RASQSVEYEGDNYLN (SEQ ID NO:49), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNQDLLT (SEQ ID NO: 36);~~

~~(i) the VH region amino acid sequence comprises HCDR1 of GYTFSSNYMI (SEQ ID NO:50), HCDR2 of MGDINPYNGGATYNQKFQG (SEQ ID NO:51), and HCDR3 of EPPYFSNLYVMDY (SEQ ID NO:48); and the VL region amino acid sequence comprises LCDR1 of RASQSVEYEGENYLN (SEQ ID NO:52), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNQDLLT (SEQ ID NO: 36);~~

~~(j) the VH region amino acid sequence comprises HCDR1 of GYTFSSYYMI (SEQ ID NO: 31), HCDR2 of MGDINPYNGGTTYAQKFQG (SEQ ID NO: 42), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVEYQGENYLN (SEQ ID NO:53), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNQDLLT (SEQ ID NO: 36);~~

~~(k) the VH region amino acid sequence comprises HCDR1 of GYTFTSNYII (SEQ ID NO:54), HCDR2 of MGDINPYNGGTNYAQKFQG (SEQ ID NO:55), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVEYQGENYLN (SEQ ID NO:53), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSSDLLT (SEQ ID NO:56);~~

~~(l) the VH region amino acid sequence comprises HCDR1 of GYTFSSNYMI (SEQ ID NO:50), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);~~

~~(m) the VH region amino acid sequence comprises HCDR1 of GYTFSSAYMI (SEQ ID NO:57), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);~~

~~(n) the VH region amino acid sequence comprises HCDR1 of GYTFSSSYMI (SEQ ID NO:58), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);~~

~~(o) the VH region amino acid sequence comprises HCDR1 of GYTFSSHYMI (SEQ ID NO:59), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises~~

LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASNRAT (SEQ ID NO:38), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);

(p) the VH region amino acid sequence comprises HCDR1 of GYTFSSNYMI (SEQ ID NO:50), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASDRAT (SEQ ID NO:60), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);

(q) the VH region amino acid sequence comprises HCDR1 of GYTFSSAYMI (SEQ ID NO:57), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASDRAT (SEQ ID NO:60), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39);

(r) the VH region amino acid sequence comprises HCDR1 of GYTFSSSYMI (SEQ ID NO:58), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASDRAT (SEQ ID NO:60), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39); or

(s) the VH region amino acid sequence comprises HCDR1 of GYTFSSHYMI (SEQ ID NO:59), HCDR2 of MGDINPYNGGANYAQKFQG (SEQ ID NO:32), and HCDR3 of EGPYFSNLYVMDY (SEQ ID NO: 33); and the VL region amino acid sequence comprises LCDR1 of RASQSVSYEGENYLN (SEQ ID NO: 37), LCDR2 of AASDRAT (SEQ ID NO:60), and LCDR3 of QLSNEDLLT (SEQ ID NO: 39).

4. — An anti-CSF1R 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 the VH region amino acid sequence comprises SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; or SEQ ID NO:8; and the VL region amino acid sequence comprises SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11 or SEQ ID NO:12.

5. — The antibody or antigen-binding portion of claim 4, wherein

— (a) the VH region amino acid sequence comprises SEQ ID NO:1, and the VL region amino acid sequence comprises SEQ ID NO:9;

— (b) the VH region amino acid sequence comprises SEQ ID NO:1, and the VL region amino acid sequence comprises SEQ ID NO:10;

(c) the VH region amino acid sequence comprises SEQ ID NO:1, and the VL region amino acid sequence comprises SEQ ID NO:11;

~~(w) the VH region amino acid sequence comprises SEQ ID NO:6, and the VL region amino acid sequence comprises SEQ ID NO:11;~~

~~(x) the VH region amino acid sequence comprises SEQ ID NO:6, and the VL region amino acid sequence comprises SEQ ID NO:12;~~

~~(y) the VH region amino acid sequence comprises SEQ ID NO:7, and the VL region amino acid sequence comprises SEQ ID NO:9;~~

~~——(z) the VH region amino acid sequence comprises SEQ ID NO:7, and the VL region amino acid sequence comprises SEQ ID NO:10;~~

~~(aa) the VH region amino acid sequence comprises SEQ ID NO:7, and the VL region amino acid sequence comprises SEQ ID NO:11;~~

~~(bb) the VH region amino acid sequence comprises SEQ ID NO:7, and the VL region amino acid sequence comprises SEQ ID NO:12;~~

~~(cc) the VH region amino acid sequence comprises SEQ ID NO:8, and the VL region amino acid sequence comprises SEQ ID NO:9;~~

~~——(dd) the VH region amino acid sequence comprises SEQ ID NO:8, and the VL region amino acid sequence comprises SEQ ID NO:10;~~

~~(ee) the VH region amino acid sequence comprises SEQ ID NO:8, and the VL region amino acid sequence comprises SEQ ID NO:11; or~~

~~(ff) the VH region amino acid sequence comprises SEQ ID NO:8, and the VL region amino acid sequence comprises SEQ ID NO:12.~~

63. The antibody or antigen-binding portion of ~~any one of claims 1-5~~claim 1 or 2, wherein the antibody is -humanized or chimeric.

74. The antibody or antigen-binding portion of ~~any one of claims 1-6~~claim 1, 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.

85. The antibody or antigen-binding portion of ~~any one of claims 1-7~~claim 1, 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.

96. The antibody or antigen-binding portion of claim 1~~-or 3~~, wherein the VH region comprises an IGHV1-69*01 human germline scaffold amino acid sequence into which the HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted.

107. The antibody or antigen-binding portion of ~~any one of claims 1, 3, and 9~~claim 1 or 6, wherein the VL region comprises an IGKV3-11 human germline scaffold amino acid

sequence into which the LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted.

~~418~~. The antibody or antigen-binding portion of any one of claims 1-~~407~~, wherein the antibody comprises an immunoglobulin constant region.

~~429~~. The antibody or antigen-binding portion of claim ~~418~~, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.

~~4310~~. The antibody or antigen-binding portion of claim ~~429~~, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.

~~4411~~. The antibody or antigen-binding portion of claim ~~418~~, wherein the immunoglobulin constant region is immunologically inert.

~~4512~~. The antibody or antigen-binding portion of claim ~~418~~, 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 or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A, wherein numbering is according to the EU index as in Kabat.

~~4613~~. The antibody or antigen-binding portion of claim ~~418~~, wherein the immunoglobulin constant region comprises any one of SEQ ID NOS:359-364.

~~4714~~. The antigen-binding portion of any one of claims 1-~~4613~~, 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,

~~4815~~. The antibody or antigen-binding portion of any one of claims 1-~~4714~~, wherein the antibody is monoclonal.

~~4916~~. The antibody or antigen-binding portion of any one of claims 1-~~4815~~, wherein the antibody is a tetrameric antibody, a tetravalent antibody or a multispecific antibody.

~~2017~~. The antibody or antigen-binding portion of any one of claims 1-~~2016~~, wherein the antibody is a bispecific antibody that binds specifically to a first antigen and a second antigen, wherein the first antigen is CSF1R and the second antigen is not CSF1R.

2418. The antibody or antigen-binding portion of any one of claims 1-~~2017~~, wherein the antibody or antigen-binding portion binds specifically to (a) human CSF1R, (b) human CSF1R and cynomolgus CSF1R, or (c) human CSF1R, cynomolgus CSF1R, and rhesus CSF1R.

2219. An immunoconjugate comprising the antibody or antigen-binding portion of any one of claims 1-~~2418~~ linked to a therapeutic agent.

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.

2421. A pharmaceutical composition comprising the antibody or antigen-binding portion of any one of claims 1-~~2418~~ or the immunoconjugate of claim 1922 or 2023, and a pharmaceutically acceptable carrier, diluent or excipient.

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 amino acid sequence and the VL region amino acid sequences of the antibody or antigen-binding portion of any one of claims 1-~~2418~~.

2326. An expression vector comprising the nucleic acid molecule of claim 2522.

2427. A recombinant host cell comprising the nucleic acid molecule of claim 2522 or the expression vector of claim 2623.

2528. A method of producing an anti-CSF1R antibody or an antigen-binding portion thereof, the method comprising:

culturing a recombinant host cell comprising the expression vector of claim 2623 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.

~~29. Use of a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-21, 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.~~

2630. Use of a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-2418, 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 or prevention of cancer, an infectious disease, or an immune disease in a subject, wherein the medicament is to be administered to the subject.

2734. The use of claim 3026, wherein the cancer is 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.

2832. The use of claim 3026, wherein the infectious disease is viral, bacterial, fungal, or parasitic.

2933. The use of claim 3026, wherein the immune disease is pigmented villonodular synovitis.

3034. The antibody or antigen-binding portion of any one of claims 1-2418, 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 infectious disease, or an immune disease.

3135. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 3430, wherein the cancer is 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~~32. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim ~~34~~30, wherein the infectious disease is viral, bacterial, fungal, or parasitic.

~~37~~33. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim ~~34~~30, wherein the immune disease is pigmented villonodular synovitis.

~~38~~34. The antibody or antigen-binding portion of any one of claims 1-~~24~~18, the immunoconjugate of claim ~~22~~19 or ~~23~~20 or the pharmaceutical composition of claim ~~24~~21, for use as a medicament.