

CLAIMS

1. An anti-hVEGFR antibody or an antigen-binding fragment thereof, comprising heavy chain HCDR1, HCDR2 and HCDR3 and/or light chain LCDR1, LCDR2 and LCDR3 sequences, wherein:

the HCDR1 sequence comprises **SSWMN** (SEQ ID NO: 1), **DYYMS** (SEQ ID NO: 19), **X₁YGMS** (SEQ ID NO: 41), **X₄YWIM** (SEQ ID NO: 44);

the HCDR2 sequence comprises **RIFPGDGDYYNGKFQV** (SEQ ID NO: 2), **FIRNKANGYTTEYSASVKG** (SEQ ID NO: 20), **SISX₂GGSYTTYADSVX₁₉G** (SEQ ID NO: 42), **DIYPGX₅GSTNYNEKFKS** (SEQ ID NO: 45);

the HCDR3 sequence comprises **FLDTSGRYVDY** (SEQ ID NO: 3), **FDYYGSTYCFDY** (SEQ ID NO: 21), **EX₃DGNYDY** (SEQ ID NO: 43), **DSNPDY** (SEQ ID NO: 46);

the LCDR1 sequence comprises **KASQDVNTAVA** (SEQ ID NO: 4), **RASQSVSTSSSSFMH** (SEQ ID NO: 22), **RSSKSLLYKD GKTYLN** (SEQ ID NO: 28), **RASESVX₆NSGISFMX₇** (SEQ ID NO: 47);

the LCDR2 sequence comprises **SASYRYI** (SEQ ID NO: 5), **YASNLES** (SEQ ID NO: 23), **LMSTRAS** (SEQ ID NO: 29), **AASX₈QX₉S** (SEQ ID NO: 48);

the LCDR3 sequence comprises **QQHYRAPLT** (SEQ ID NO: 6), **QHTWEIPLT** (SEQ ID NO: 24), **QQLVEYPFT** (SEQ ID NO: 30), **QQSKEVPYT** (SEQ ID NO: 49);

wherein X₁ is I or M, X₂ is V or I, X₃ is L or M, X₄ is T or S, X₅ is T or S, X₆ is D or E, X₇ is T or H, X₈ is T or Y, X₉ is G or R, and X₁₉ is E or K.
2. The anti-hVEGFR antibody or an antigen-binding fragment thereof of claim 1, wherein the HCDR1 comprises an amino acid sequence of SEQ ID NO: 41, the HCDR2 comprises an amino acid sequence of SEQ ID NO: 42, the HCDR3 comprises an amino acid sequence of SEQ ID NO: 43, the LCDR1 comprises a sequence of SEQ ID NO: 28, the LCDR2 comprises a sequence of SEQ ID NO: 29, and the LCDR3 comprises a sequence of SEQ ID NO: 30.
3. The antibody or an antigen-binding fragment thereof of claim 1 or 2, wherein
 - a) the HCDR1 comprises the sequence of SEQ ID NO: 25, a HCDR2 comprises the sequence of SEQ ID NO: 26, the HCDR3 comprises the sequence of SEQ ID NO: 27; the LCDR1 comprises the sequence of SEQ ID NO: 28, the LCDR2 comprises the sequence of SEQ ID NO: 29, and the LCDR3 comprises the sequence of SEQ ID NO: 30; or

- b) the HCDR1 comprises the sequence of SEQ ID NO: 31, the HCDR2 comprises the sequence of SEQ ID NO: 32 or SEQ ID NO: 37, and the HCDR3 comprises the sequence of SEQ ID NO: 33, the LCDR1 comprises the sequence of SEQ ID NO: 28, the LCDR2 comprises the sequence of SEQ ID NO: 29, and the LCDR3 comprises the sequence of SEQ ID NO: 30; or
 - c) the HCDR1 comprises the sequence of SEQ ID NO: 34, the HCDR2 comprises the sequence of SEQ ID NO: 35 or SEQ ID NO: 37, and the HCDR3 comprises the sequence of SEQ ID NO: 36, the LCDR1 comprises the sequence of SEQ ID NO: 28, the LCDR2 comprises the sequence of SEQ ID NO: 29, and the LCDR3 comprises the sequence of SEQ ID NO: 30.
4. The anti-hVEGFR antibody or an antigen-binding fragment thereof of any one of claims 1-3, wherein the HCDR1 comprises an amino acid sequence of SEQ ID NO: 44, the HCDR2 comprises an amino acid sequence of SEQ ID NO: 45, the HCDR3 comprises an amino acid sequence of SEQ ID NO: 46, the LCDR1 comprises a sequence of SEQ ID NO: 47, the LCDR2 comprises a sequence of SEQ ID NO: 48, and the LCDR3 comprises a sequence of SEQ ID NO: 49.
5. The antibody or an antigen-binding fragment thereof of any one of claims 1-4, wherein
- a) the HCDR1 comprises the sequence of SEQ ID NO: 7, a HCDR2 comprises the sequence of SEQ ID NO: 8, the HCDR3 comprises the sequence of SEQ ID NO: 9; the LCDR1 comprises the sequence of SEQ ID NO: 10, the LCDR2 comprises the sequence of SEQ ID NO: 11, and the LCDR3 comprises the sequence of SEQ ID NO: 12; or
 - b) the HCDR1 comprises the sequence of SEQ ID NO: 13, the HCDR2 comprises the sequence of SEQ ID NO: 14, and the HCDR3 comprises the sequence of SEQ ID NO: 15, the LCDR1 comprises the sequence of SEQ ID NO: 16, the LCDR2 comprises the sequence of SEQ ID NO: 17, and the LCDR3 comprises the sequence of SEQ ID NO: 18.
6. The antibody or an antigen-binding fragment thereof of any one of claims 1-5, wherein
- a) the HCDR1 comprises the sequence of SEQ ID NO: 1, the HCDR2 comprises the sequence of SEQ ID NO: 2, and the HCDR3 comprises the sequence of SEQ ID NO: 3, the LCDR1 comprises the sequence of SEQ ID NO: 4, the LCDR2 comprises the sequence of SEQ ID NO: 5, and the LCDR3 comprises the sequence of SEQ ID NO: 6; or

- b) the HCDR1 comprises the sequence of SEQ ID NO: 19, the HCDR2 comprises the sequence of SEQ ID NO: 20, and the HCDR3 comprises the sequence of SEQ ID NO: 21, the LCDR1 comprises the sequence of SEQ ID NO: 22, the LCDR2 comprises the sequence of SEQ ID NO: 23, and the LCDR3 comprises the sequence of SEQ ID NO: 24.

7. The antibody or antigen-binding fragment thereof of any one of claims 1-6, wherein:

the HFR1 comprises a sequence selected from the group consisting of SEQ ID NOs: 64, 68 and 72,

the HFR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 65, 69 and 73,

the HFR3 comprises the sequence selected from the group consisting of SEQ ID NOs: 66, 70 and 74,

the HFR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 67, 71 and 75,

the LFR1 comprises the sequence selected from the group consisting of SEQ ID NOs: 76 and 80,

the LFR2 comprises a sequence selected from the group consisting of SEQ ID NO: 77 and 81,

the LFR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 78 and 82, and

the LFR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 79 and 83.

8. The antibody or an antigen-binding fragment thereof of any one of claims 1-7, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 98, and a homologous sequence thereof having at least 80% sequence identity yet retaining specific binding affinity to hVEGFR2; and wherein the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO:

61, SEQ ID NO: 63, SEQ ID NO: 96, SEQ ID NO: 97, and a homologous sequence thereof having at least 80% sequence identity yet retaining specific binding affinity to hVEGFR2.

9. The antibody or an antigen-binding fragment thereof of any one of claims 1-8, wherein:

- a) a heavy chain variable region comprising the sequence of SEQ ID NO: 50 and a light chain variable region comprising the sequence of SEQ ID NO: 51;
- b) the heavy chain variable region comprises a sequence of SEQ ID NO: 52 and the light chain variable region comprises a sequence of SEQ ID NO: 53;
- c) the heavy chain variable region comprises a sequence of SEQ ID NO: 54 and the light chain variable region comprises a sequence of SEQ ID NO: 55;
- d) the heavy chain variable region comprises a sequence of SEQ ID NO: 56 and the light chain variable region comprises a sequence of SEQ ID NO: 57;
- e) the heavy chain variable region comprises a sequence of SEQ ID NO: 58 and the light chain variable region comprises a sequence of SEQ ID NO: 59;
- f) the heavy chain variable region comprises a sequence of SEQ ID NO: 60 and the light chain variable region comprises a sequence of SEQ ID NO: 61;
- g) the heavy chain variable region comprises a sequence of SEQ ID NO: 62 and the light chain variable region comprises a sequence of SEQ ID NO: 63; or
- h) the heavy chain variable region comprises a sequence of SEQ ID NO: 93 or SEQ ID NO: 94 or SEQ ID NO: 98 and the light chain variable region comprises a sequence of SEQ ID NO: 96 or SEQ ID NO: 97.

10. The antibody or antigen-binding fragment thereof of any one of claims 1-9, further comprising an immunoglobulin constant region, or further comprising a constant region of human Ig, or further comprising a constant region of human IgG.

11. The antibody or antigen-binding fragment thereof of one of claims 1-10, wherein the constant region of human IgG1 is human IgG1 comprising SEQ ID NO: 38, or a homologous sequence

having at least 80% sequence identity thereof.

12. The antibody or an antigen-binding fragment thereof of any one of claims 1-11, which is humanized.

13. The antibody or antigen-binding fragment thereof of any one of claims 1-12, which is a diabody, a Fab, a Fab', a F(ab')₂, a Fd, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a (dsFv)₂, a bispecific dsFv (dsFv-dsFv'), a disulfide stabilized diabody (ds diabody), a single-chain antibody molecule (scFv), an scFv dimer (bivalent diabody), a multispecific antibody, a camelized single domain antibody, a nanobody, a domain antibody, or a bivalent domain antibody.

14. The antibody or antigen-binding fragment thereof of any one of claims 1-13, which is bispecific, capable of specifically binding to a first and a second epitope of hVEGFR2, or capable of specifically binding to hVEGFR2 and a second antigen.

15. The antibody or antigen-binding fragment thereof of any one of claims 1-14, wherein the second antigen is an immune related target or a tumor antigen, wherein the immune related target is selected from the group consisting of: PD-L1, PD-L2, PD-1, CLTA-4, TIM-3, LAG3, CD160, 2B4, TGF β , VISTA, BTLA, TIGIT, LAIR1, OX40, CD2, CD27, ICAM-1, NKG2C, SLAMF7, NKp80, CD160, B7-H3, LFA-1, 1COS, 4-1BB, GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, IL-2, IL-15, CD3, CD16 and CD83, and wherein the tumor antigen is selected from the group consisting of: claudin 18.2, CA-125, gangliosides G(D2), G(M2) and G(D3), CD20, CD52, CD33, Ep-CAM, CEA, bombesin-like peptides, PSA, HER2/neu, epidermal growth factor receptor (EGFR), erbB2, erbB3/HER3, erbB4, CD44v6, Ki-67, cancer-associated mucin, VEGF, VEGFRs (e.g., VEGFR3), estrogen receptors, Lewis-Y antigen, TGF β 1, IGF-1 receptor, EGF α , c-Kit receptor, transferrin receptor, IL-2R and CO17-1A.

16. The antibody or antigen-binding fragment thereof of any one of claims 1-15 linked to one or more conjugate moieties, wherein the conjugate moiety comprises a clearance-modifying agent, a chemotherapeutic agent, a toxin, a radioactive isotope, a lanthanide, a luminescent label, a fluorescent label, an enzyme-substrate label, a DNA-alkylators, a topoisomerase inhibitor, a tubulin-binders, or other anticancer drugs.

17. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-16, and one or more pharmaceutically acceptable carriers.
18. An isolated polynucleotide encoding the antibody or an antigen-binding fragment thereof of any one of claims 1-16.
19. A vector comprising the isolated polynucleotide of claim 18.
20. A host cell comprising the vector of claim 19.
21. A method of expressing the antibody or antigen-binding fragment thereof of any one of claims 1-16, comprising culturing a host cell comprising a vector comprising an isolated polynucleotide encoding the antibody or an antigen-binding fragment thereof of any one of claims 1-16 under the condition at which the vector is expressed.
22. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-16, in the manufacture of a medicament for treating, reducing the severity of and/or slowing the progression of a VEGFR2-related disease or condition in a subject.
23. The use of claim 22, wherein the VEGFR2-related disease or condition is a tumor or an angiogenic disease.
24. The use of claim 23, wherein the tumor produces VEGF (e.g., VEGF-A) and/or is sensitive to VEGF (e.g., VEGF-A) present in its microenvironment.
25. The use of claim 23, wherein the tumor is selected from the group consisting of breast carcinoma, lung carcinoma, colorectal carcinoma, pancreatic carcinoma, glioma and lymphoma, head and neck tumors, neuroendocrine tumors, colorectal tumors, prostate tumors, breast tumors, lung tumors, such as small cell and non-small cell lung tumors, pancreatic tumors, thyroid tumors, ovarian tumors, liver tumors, Kaposi's sarcoma, CNS neoplasms, neuroblastomas, capillary hemangioblastomas, meningiomas, cerebral metastases, melanoma, gastrointestinal and renal carcinomas and sarcomas (e.g., gastric cancer), rhabdomyosarcoma, glioblastoma, preferably glioblastoma multiforme, leiomyosarcoma, squamous cell carcinoma, basal cell carcinoma and skin cancers that can be treated by suppressing the growth of malignant keratinocytes, such as human malignant keratinocytes, , and wherein the angiogenic disease is selected from the group consisting of atherosclerosis, rheumatoid

arthritis (RA), neovascular glaucoma, proliferative retinopathy including proliferative diabetic retinopathy, macular degeneration, hemangiomas, angiofibromas, psoriasis, retinopathy of prematurity (e.g., retrolental fibroplastic), corneal graft rejection, insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, Chron's disease, autoimmune nephritis, primary biliary cirrhosis, acute pancreatitis, allograft rejection, allergic inflammation, contact dermatitis and delayed hypersensitivity reactions, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, cognition defects induced by neuronal inflammation, Osler-Weber syndrome, restinosis, and fungal, parasitic and viral infections, such as cytomegaloviral infections.

26. The use of any one of claims 22-25, wherein the subject is human.

27. A method of detecting presence or amount of VEGFR2 in a sample, comprising contacting the sample with the antibody or antigen-binding fragment thereof of any one of claims 1-16, and determining the presence or the amount of VEGFR2 in the sample.