Claims

1. An isolated antibody, or antigen binding fragment thereof, that binds to vascular endothelial growth factor receptor 1 (VEGFR1) comprising:

a heavy chain variable region (VH) comprising a heavy chain complementarity determining region 1 (HCDR1), a heavy chain complementarity determining region 2 (HCDR2), a heavy chain complementarity determining region 3 (HCDR3) and

a light chain variable region (VL) comprising a light chain complementarity determining region 1 (LCDR1), a light chain complementarity determining region 2 (LCDR2), and a light chain complementarity determining region 3 (LCDR3),

wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of:(a) SEQ ID NOs: 25, 26, 27, 28, 29, 30, respectively;

SEQ ID NOs: 89, 90, 91, 92, 93, 94, respectively;

SEQ ID NOs: 113, 114, 115, 116, 117, 118, respectively; or

SEQ ID NOs: 137, 138, 139, 140, amino acid sequence FNS, and SEQ ID NO: 142, respectively;

(b) SEQ ID NOs: 7, 175, 9, 10, 11, 12, respectively;

SEQ ID NOs: 71, 176, 73, 74, 75, 76, respectively;

SEQ ID NOs: 95, 177, 97, 98, 99, 100, respectively; or

SEQ ID NOs: 119, 178, 121, 122, amino acid sequence LNS, and SEQ ID NO: 124, respectively;

(c) SEQ ID NOs: 7, 8, 9, 10, 11, 12, respectively;

SEQ ID NOs: 71, 72, 73, 74, 75, 76, respectively;

SEQ ID NOs: 95, 96, 97, 98, 99, 100, respectively; or

SEQ ID NOs: 119, 120, 121, 122, amino acid sequence LNS, and SEQ ID NO: 124, respectively;

(d) SEQ ID NOs: 13, 14, 15, 16, 17, 18, respectively;

SEQ ID NOs: 77, 78, 79, 80, 81, 82, respectively;

SEQ ID NOs: 101, 102, 103, 104, 105, 106, respectively; or

SEQ ID NOs: 125, 126, 127, 128, amino acid sequence FNF, and SEQ ID NO: 130, respectively; or

(e) SEQ ID NOs: 19, 20, 21, 22, 23, 24, respectively;
SEQ ID NOs: 83, 84, 85, 86, 87, 88, respectively;
SEQ ID NOs: 107, 108, 109, 110, 111, 112, respectively; or
SEQ ID NOs: 131, 132, 133, 134, amino acid sequence YD, and SEQ ID NO: 136, respectively.

2. The isolated antibody or antigen binding fragment thereof of claim 1, wherein

a. the antibody or antigen biding fragment thereof comprises:

i) a heavy chain variable domain (VH) comprising the amino acid sequence of SEQ ID NO: 39, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 39; and

ii) a light chain variable domain (VL) comprising the amino acid sequence of SEQ ID NO: 40, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 40;

b. the antibody or antigen biding fragment thereof comprises:

i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 31, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 31; and

ii) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 32;

c. the antibody or antigen biding fragment thereof comprises:

i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 33, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 33; and

ii) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 32;

d. the antibody or antigen biding fragment thereof comprises:

i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 34, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 34; and

ii) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 35, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 35;

e. the antibody or antigen biding fragment thereof comprises:

i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 36, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 36; and

ii) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 37, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical to the amino acid sequence of SEQ ID NO: 37; or

f. the antibody or antigen biding fragment thereof comprises:

i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99%identical to the amino acid sequence of SEQ ID NO: 38; and

ii) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 37, or having an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical, or is identical to the amino acid sequence of SEQ ID NO: 37.

3. The isolated antibody or antigen binding fragment thereof of claim 1 or claim 2, wherein:

a. the antibody or antigen biding fragment thereof comprises: i) a heavy chain (HC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 59; and ii) a light chain (LC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 60,

optionally wherein the antibody or antigen biding fragment thereof comprises the heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 59 and the light chain (LC) comprising the amino acid sequence of SEQ ID NO: 60;

b. the antibody or antigen biding fragment thereof comprises: i) a heavy chain (HC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 51; and ii) a light chain (LC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 52,

optionally wherein the antibody or antigen biding fragment thereof comprises the heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 51 and the light chain (LC) comprising the amino acid sequence of SEQ ID NO: 52;

c. the antibody or antigen biding fragment thereof comprises: i) a heavy chain (HC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 53; and ii) a light chain (LC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 52,

optionally wherein the antibody or antigen biding fragment thereof comprises the heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 53 and the light chain (LC) comprising the amino acid sequence of SEQ ID NO: 52;

d. the antibody or antigen biding fragment thereof comprises: i) a heavy chain (HC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 54; and ii) a light chain (LC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 55,

optionally wherein the antibody or antigen biding fragment thereof comprises the heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 54 and the light chain (LC) comprising the amino acid sequence of SEQ ID NO: 55;

e. the antibody or antigen biding fragment thereof comprises: i) a heavy chain (HC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 56; and ii) a light chain (LC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 57,

optionally wherein the antibody or antigen biding fragment thereof comprises the heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 56 and the light chain (LC) comprising the amino acid sequence of SEQ ID NO: 57; or

F. the antibody or antigen biding fragment thereof comprises: i) a heavy chain (HC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 58; and ii) a light chain (LC) comprising an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 57,

optionally wherein the antibody or antigen biding fragment thereof comprises the heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 58 and the light chain (LC) comprising the amino acid sequence of SEQ ID NO: 57.

4. An isolated antibody or antigen binding fragment thereof that binds to an epitope within the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 173, and wherein the antibody or antigen binding fragment prevents the binding of VEGFA to VEGFR1.

5. The isolated antibody or antigen binding fragment thereof of claim 4, wherein the antibody or antigen binding fragment binds to epitopes on VEGFR1 having the amino acid sequence FPLDTL (SEQ ID NO: 143) or EIGL (SEQ ID NO: 144) or binds to the epitopes having the amino acid sequences FPLDTL (SEQ ID NO: 143) and EIGL (SEQ ID NO: 144).

6. The isolated antibody or antigen binding fragment thereof of claim 4 or claim 5, wherein:

(a) the antibody or antigen binding fragment thereof binds to human, mouse, rat, and/or cynomolgus monkey VEGFR1

optionally wherein the antibody or antigen binding fragment thereof binds human VEGFR1,

such as wherein the antibody or antigen binding fragment thereof binds to human VEGFR1 and a VEGFR1 from at least one species selected from the group consisting of cynomolgus monkey, mouse, and rat,

for example wherein the antibody or antigen binding fragment thereof binds to human VEGFR1 and a VEGFR1 from at least two species selected from the group consisting of cynomolgus monkey, mouse, and rat,

further optionally wherein the antibody or antigen binding fragment thereof binds to human VEGFR1 and a VEGFR1 from cynomolgus monkey, mouse, and rat; and/or

(b) the antibody or antigen binding fragment thereof binds to a human VEGFR1, mouse VEGFR1, and cynomolgus monkey VEGFR1, with a KD of 6×10−8 M or less, particularly 1×10−8 M or less, more particularly 5×10−9 M or less, 1×10−9 M or less, 5×10−10 M or less, or 1×10−10 M or less, as determined by using surface plasmon resonance (SPR).

7. The isolated antigen binding fragment of any one of claims 1 to 6, wherein the antigen binding fragment is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb, a VHH or single chain antibody.

8. The isolated antibody or antigen binding fragment thereof of any one of claims 1 to 7, wherein the antibody or antigen binding fragment thereof is of an IgG1, an IgG2, an IgG3, or an IgG4 isotype.

9. The isolated antibody or antigen binding fragment thereof of claim 8, wherein

(i) the antibody or antigen binding fragment thereof is an IgG1 isotype;

(ii) the isolated antibody or antigen binding fragment comprises an Ig constant region or a fragment of the Ig constant region;

(iii) the Ig constant region or the fragment of the Ig constant region comprises at least one mutation that results in reduced binding of the antibody or antigen binding fragment thereof to a Fcγ receptor (FcγR);

(iv) the at least one mutation that results in reduced binding of the antibody or antigen binding fragment thereof to a FcγR is selected from the group consisting of F234A/L235A, L234A/L235A, L234A/L235A/D265S, V234A/G237A/ P238S/H268A/V309L/A330S/P331S, F234A/L235A, S228P/F234A/ L235A, N297A, V234A/G237A, K214T/E233P/ L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M, H268Q/V309L/A330S/P331S,

S267E/L328F, L234F/L235E/D265A, L234A/L235A/G237A/P238S/H268A/A330S/P331S, S228P/F234A/L235A/G237A/P238S and S228P/F234A/L235A/G236-deleted/G237A/P238S, wherein residue numbering is according to the EU index;

(v) the Ig constant region or the fragment of the constant region comprises the mutations of L234A_L235A_D265S;

(vi) the FcγR is FcγRI, FcγRIIA, FcγRIIB or FcγRIII, or any combination thereof;

(vii) the Ig constant region or the fragment of the Ig constant region further comprises at least one mutation that modulates a half-life of the antibody or antigen binding fragment thereof; and/or

(viii) the at least one mutation that modulates the half-life of the antibody or antigen binding fragment thereof is selected from the group consisting of H435A, P257I/N434H, D376V/N434H, M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R, wherein residue numbering is according to the EU index.

10. An immunoconjugate comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1 to 9 conjugated to a therapeutic agent or an imaging agent.

11. A pharmaceutical composition comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1 to 9 or the immunoconjugate of claim 10, and a pharmaceutically acceptable carrier.

12. An isolated polynucleotide encoding the isolated antibody or antigen binding fragment thereof of any one of claims 1 to 9.

13. The isolated polynucleotide of claim 12, wherein the isolated polynucleotide comprises a polynucleotide sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical or is identical to the polynucleotide sequence of SEQ ID NOs: 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70.

14. A vector comprising the polynucleotide of claim 12 or claim 13.

15. A host cell expressing the isolated antibody or antigen binding fragment thereof of any one of claims 1 to 9, such as a host cell comprising the vector of claim 14.

16. The isolated antibody or antigen fragment thereof of any one of claims 1 to 9, the immunoconjugate of claim 10, the pharmaceutical composition of claim 11, the isolated polynucleotide of claim 12 or claim 13, the vector of claim 14, or the host cell of claim 15 for use in a method of:

(a) preventing the binding of VEGFA to a VEGFR1 in a subject in need thereof, comprising an effective amount of the isolated antibody or antigen fragment thereof, the immunoconjugate, the pharmaceutical composition, the isolated polynucleotide, the vector, or the host cell to be administered to the subject to thereby prevent the binding of VEGFA to the VEGFR1;

(b) treating a Chronic Kidney Disease (CKD) in a subject in need thereof, comprising a therapeutically effective amount of the isolated antibody or antigen fragment thereof, the immunoconjugate, the pharmaceutical composition, the isolated polynucleotide, the vector, or the host cell to be administered to the subject for a time sufficient to treat the CKD; or

(c) decreasing proteinuria in a subject in need thereof, comprising a therapeutically effective amount of the isolated antibody or antigen fragment thereof, the immunoconjugate, the pharmaceutical composition, the isolated polynucleotide, the vector, or the host cell, to be administered to the subject for a time sufficient to decrease proteinuria in the subject.

17. The use of claim 16(a), wherein the subject is in need of a treatment of a Chronic Kidney Disease (CKD), in need of decreasing proteinuria, has advanced stage 4 or 5 chronic kidney disease, or has CKD with proteinuria, albuminuria, or diabetes mellitus.

18. The use of claim 16(b), wherein:

(i) the subject has advanced stage 4 or 5 chronic kidney disease;

(ii) the subject has stage 3 chronic kidney disease; and/or

(iii) the subject has CKD with proteinuria, albuminuria, or diabetes mellitus.

19. A kit comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1 to 9, the immunoconjugate of claim 10, the pharmaceutical composition of claim 11, the isolated polynucleotide of claim 12 or claim 13, the vector of claim 14, or the host cell of claim 15.

20. Use of the isolated antibody or antigen fragment thereof of any one of claims 1 to 9, the immunoconjugate of claim 10, the pharmaceutical composition of claim 11, the isolated polynucleotide of claim 12 or claim 13, the vector of claim 14, or the host cell of claim 15 in the manufacture of a medicament for:

(a) preventing the binding of VEGFA to a VEGFR1 in a subject in need thereof;

(b) treating a Chronic Kidney Disease (CKD) in a subject in need thereof; or

(c) decreasing proteinuria in a subject in need thereof.

21. The use of claim 20(a), wherein the subject is in need of a treatment of a Chronic Kidney Disease (CKD), in need of decreasing proteinuria, has advanced stage 4 or 5 chronic kidney disease, or has CKD with proteinuria, albuminuria, or diabetes mellitus.

22. The use of claim 20(b), wherein:

(i) the subject has advanced stage 4 or 5 chronic kidney disease;

(ii) the subject has stage 3 chronic kidney disease; and/or

(iii) the subject has CKD with proteinuria, albuminuria, or diabetes mellitus.