CLAIMS

1. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 41, 42, 43, 101, 102, and 103, respectively;

(2) SEQ ID NOs: 44, 45, 46, 104, 105, and 106, respectively; or

(3) SEQ ID NOs: 47, 48, 49, 107, 08, and, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds apelin.

2. The isolated monoclonal antibody or antigen-binding fragment of claim 1, comprising:

(a) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:1, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:2;

(b) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:3, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:4;

(c) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:5, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:6;

(d) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:213, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:216; or

(e) a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:214, and a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:216.

3. An isolated monoclonal antibody or antigen-binding fragment thereof comprising:

a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1, and a light chain variable region having the polypeptide sequence of SEQ ID NO:2;

b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:3, and a light chain variable region having the polypeptide sequence of SEQ ID NO:4;

c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:5, and a light chain variable region having the polypeptide sequence of SEQ ID NO:6;
d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:211, and a light chain variable region having the polypeptide sequence of SEQ ID NO:215;
e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:212, and a light chain variable region having the polypeptide sequence of SEQ ID NO:215;
f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:213, and a light chain variable region having the polypeptide sequence of SEQ ID NO:215;
g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:214, and a light chain variable region having the polypeptide sequence of SEQ ID NO:215;
h. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:213, and a light chain variable region having the polypeptide sequence of SEQ ID NO:216;
i. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:214, and a light chain variable region having the polypeptide sequence of SEQ ID NO:216;
j. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:217, and a light chain variable region having the polypeptide sequence of SEQ ID NO:219; or
k. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:218, and a light chain variable region having the polypeptide sequence of SEQ ID NO:220.

4. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1 or 3, wherein the isolated monoclonal antibody or antigen-binding fragment thereof specifically binds to an epitope with the amino acid sequence of SEQ ID NO:188, wherein binding of the monoclonal antibody or antigen-binding fragment thereof to apelin inhibits apelin-mediated signaling through the apelin receptor and neutralizes apelin activity.

5. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 4, wherein any one of the side chains of residues 11, 12, or 13 of apelin-13 is required for binding to the epitope comprising the amino acid sequence of SEQ ID NO:188.

6. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 4, wherein the monoclonal antibody or antigen-binding fragment thereof binds to the C-terminal end of apelin-13, pyro-apelin-13, apelin-17, apelin-36, apelin-55, and/or other forms of apelin that share the same C-terminal end with apelin-13.

7. The isolated monoclonal antibody or antigen-binding fragment of any one of claims 1-6, wherein the antibody or antigen-binding fragment thereof is chimeric and/or humanized.

8. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment of any one of claims 1-7.

9. A vector comprising the isolated nucleic acid of claim 8.

10. A host cell comprising the vector of claim 9.

11. A pharmaceutical composition, comprising the isolated monoclonal antibody or antigen-binding fragment of any one of claims 1-7 and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 11 for use in a method of blocking binding of apelin to an apelin receptor in a subject in need thereof, wherein the pharmaceutical composition is to be administered to the subject.

13. Use of the pharmaceutical composition of claim 11 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of a diabetic retinopathy (DR), an age-related macular degeneration (AMD), a diabetic macular edema (DME), a macular edema following retinal vein occlusion (RVO), a retinal degeneration, a myopic choroidal neovascularization (mCNV), a diabetic nephropathy, a chronic kidney disease (CKD), a non-alcoholic steatohepatitis (NASH), a liver cirrhosis, a plaque neovascularization, a rubeosis iridis, a neovascular glaucoma, a corneal neovascularization (CNV) a retinopathy of prematurity (ROP), a retinopathy, a macular degeneration, an ovarian hyperstimulation syndrome (OHSS), a uterine bleeding, an endometriosis, an endometrial hyperplasia, a myometrial leiomyomas, an adenomyosis, a tissue fibrosis, and a cancer in a subject in need thereof, wherein the pharmaceutical composition is to be administered to the subject.

14. The use of claim 13, wherein the disease is cancer and the pharmaceutical composition further comprises an anti-cancer agent.

15. The use of claim 14, wherein the anti-cancer agent is an anti-VEGF agent, wherein the anti-VEGF agent is selected from an anti-VEGF antibody, bevacizumab, randibizumab, aflibercept, or conbercept.

16. A method of determining a level of apelin in a subject, the method comprising:

a. obtaining a sample from the subject;

b. contacting the sample with a monoclonal antibody or antigen-binding fragment of any one of claims 1-7; and

c. determining a level of apelin in the subject.

17. The method of claim 16, wherein the sample is a tissue sample or a blood sample.

18. The method of claim 17, wherein the tissue sample is a cancer tissue sample.

19. A method of producing the monoclonal antibody or antigen-binding fragment of any one of claims 1-7, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment of any one of claims 1-7 under conditions to produce the monoclonal antibody or antigen-binding fragment, and recovering the antibody or antigen-binding fragment from the cell or culture.

20. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1 or 3, wherein the monoclonal antibody or antigen-binding fragment thereof specifically binds human apelin.

21. The pharmaceutical composition of claim 11 for use in treating a disease selected from the group consisting of a diabetic retinopathy (DR), an age-related macular degeneration (AMD), a diabetic macular edema (DME), a macular edema following retinal vein occlusion (RVO), a retinal degeneration, a myopic choroidal neovascularization (mCNV), a diabetic nephropathy, a chronic kidney disease (CKD), a non-alcoholic steatohepatitis (NASH), a liver cirrhosis, a plaque neovascularization, a rubeosis iridis, a neovascular glaucoma, a corneal neovascularization (CNV) a retinopathy of prematurity (ROP), a retinopathy, a macular degeneration, an ovarian hyperstimulation syndrome (OHSS), a uterine bleeding, an endometriosis, an endometrial hyperplasia, a myometrial leiomyomas, an adenomyosis, a tissue fibrosis, and a cancer in a subject in need thereof, wherein the pharmaceutical composition is to be administered to the subject.

22. The pharmaceutical composition for use of claim 21, wherein the disease is cancer and the pharmaceutical composition further comprises an anti-cancer agent.

23. The pharmaceutical composition for use of claim 21, wherein the anti-cancer agent is an anti-VEGF agent, wherein the anti-VEGF agent is selected from an anti-VEGF antibody, bevacizumab, randibizumab, aflibercept, or conbercept.