What is claimed is:

1. An isolated antibody or antigen-binding fragment thereof that binds specifically to natriuretic peptide receptor 1 (NPR1) protein, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising an amino acid sequence of SEQ ID NO:2; and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising an amino acid sequence of SEQ ID NO:10.

2. The antibody or antigen-binding fragment thereof of claim 1 comprising a HCVR having an amino acid sequence of SEQ ID NO: 2.

3. The antibody or antigen-binding fragment thereof of claim 1 comprising a LCVR having an amino acid sequence of SEQ ID NO: 10.

4. The antibody or antigen-binding fragment thereof of claim 1 comprising:

(a) a HCDR1 having an amino acid sequence of SEQ ID NO: 4;

(b) a HCDR2 having an amino acid sequence of SEQ ID NOs: 6;

(c) a HCDR3 having an amino acid sequence of SEQ ID NOs: 8;

(d) a LCDR1 having an amino acid sequence of SEQ ID NO: 12;

(e) a LCDR2 having an amino acid sequence of SEQ ID NO: 14; and

(f) a LCDR3 having an amino acid sequence of SEQ ID NO: 16.

5. The antibody or antigen-binding fragment thereof of claim 4 comprising a HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 2/10.

6. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof interacts with one or more amino acids contained within the extracellular domain of NPR1 (amino acids 29—-347 of SEQ ID NO: 194), as determined by hydrogen/deuterium exchange, and wherein the antibody or antigen-binding fragment thereof: (i) binds to cells expressing human NPR1 in the presence or absence of atrial natriuretic peptide (ANP); and/or (ii) ~~binds to NPR1 and~~ activates NPR1.

~~2. The isolated antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence selected from the group consisting of (a) amino acids 29 to 45 of SEQ ID NO: 194; (b) amino acids 331 to 347 of SEQ ID NO: 194; (c) amino acids 336 to 347 of SEQ ID NO: 194; (d) amino acids 331 to 335 of SEQ ID NO: 194; and (e) amino acids 70 to 81 of SEQ ID NO: 194.~~

~~3. The isolated antibody or antigen-binding fragment thereof of claim 2, wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence selected~~

~~from the group consisting of (a) amino acids 29 to 45 of SEQ ID NO: 194; and (b) amino acids 336 to 347 of SEQ ID No: 194.~~

~~4. The isolated antibody or antigen-binding fragment thereof of claim 2, wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence selected from the group consisting of (a) amino acids 29 to 45 of SEQ ID NO: 194; and (b) amino acids 331 to 347 of SEQ ID No: 194, in the presence of ANP.~~

~~5. The isolated antibody or antigen-binding fragment thereof of claim 2~~

7. The isolated antibody or antigen-binding fragment thereof of claim 6, wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence selected from the group consisting of (a) amino acids 29 to 45 of SEQ ID NO: 194~~;~~, and (b) amino acids ~~70~~336 to ~~81 of SEQ ID NO: 194; and (c) amino acids 331 to 335~~347 of SEQ ID No: 194~~, in the presence of ANP~~.

~~6. An~~

8. The isolated antibody or antigen-binding fragment thereof ~~that binds specifically to natriuretic peptide receptor 1 (NPR1) protein in the presence of atrial natriuretic peptide (ANP),~~of claim 6, wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence selected from the group consisting of (a) amino acids 29 to 45 of SEQ ID NO: 194~~;~~, and (b) amino acids 331 to 347 of SEQ ID No: 194, ~~but not with amino acids 70 to 81 of SEQ ID NO: 194,as determined by hydrogen/deuterium exchange, and wherein the antibody or antigen-binding fragment thereof: (i) binds to cells expressing human NPR1 in the presence or absence of ANP; and/or (ii) binds to NPR1 and activates NPR1.~~ in the presence of ANP.

~~7.~~

9. The antibody or antigen-binding fragment thereof of ~~any one of claims 1 –~~ claim 6, wherein the antibody is a fully human monoclonal antibody.

~~8.~~

10. The antibody or antigen-binding fragment thereof of ~~any one of claims 1 – 7~~ claim 6, wherein the antibody has one or more properties selected from the group consisting of: (a) is a fully human monoclonal antibody; (b) binds to monomeric human NPR1 in the absence of ANP and/or brain natriuretic peptide (BNP) at 25° C. and at 37° C. with a dissociation constant (KD) of less than 690 nM, as measured in a surface plasmon resonance assay; (c) binds to dimeric human NPR1 in the absence of ANP or BNP at and at 37° C. with a KD of less than 42 nM, as measured in a surface plasmon resonance assay; (d) binds to human NPR1 complexed to ANP at 25° C. and 37° C. with a KD of less than 80 nM, as measured in a surface plasmon resonance assay; (e) binds to human NPR1 complexed to BNP at 25° C. and 37° C. with a KD of less than 20 nM, as measured in a surface plasmon resonance assay; (f) binds to monomeric monkey NPR1 in the absence of ANP and/or BNP at 25° C. and 37° C. with a KD of less than 365 nM, as measured in a surface plasmon resonance assay; (g) binds to dimeric monkey NPR1 in the absence of ANP or BNP at 25° C. and at 37° C. with a KD of less than 30 nM, as measured in a surface plasmon resonance assay; (h) binds to monkey NPR1 complexed to ANP at 25° C. and 37° C. with a KD of less than 10 nM, as measured in a surface plasmon resonance assay; ~~-~~(i) binds to monkey NPR1 complexed to BNP at 25° C. and 37° C. with a KD of less than 10 nM, as measured in a surface plasmon resonance assay; (j) does not bind to mouse NPR1; (k) binds to cells expressing human NPR1 (without ANP) or NPR1-complexed to ANP with a EC50 less than 5 nM; (l) activates NPR1 with a EC50 of less than 385 nM, as measured in a calcium flux cell-based bioassay; (m) reduces the systemic blood pressure when

administered to normotensive and hypertensive mice, wherein the reduction in systemic and mean arterial blood pressures lasts for up to 28 days upon administration of a single dose; and (n) improves glucose tolerance when administered to diet-induced obese mice.

~~9. The antibody or antigen-binding fragment of any one of claims 1—8, wherein the antibody or antigen-binding fragment comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR); and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR), wherein the HCVR has an amino acid sequence selected from the group consisting of HCVR sequences listed in Table 1.~~

~~10. The antibody or antigen-binding fragment thereof of claim 9 comprising a LCVR having an amino acid sequence selected from the group consisting of LCVR sequences listed in Table 1.~~

~~11. The antibody or antigen-binding fragment thereof of claim 9 or 10 comprising:~~

~~(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, and 180;~~

~~(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, and 182;~~

~~(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, and 184;~~

~~(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, and 188;~~

~~(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, and 190; and~~

~~(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, and 192.~~

~~12. The antibody or antigen-binding fragment thereof of claim 11 comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, and 178/186.~~

13. The antibody or antigen-binding fragment thereof of claim 12 comprising CDRs selected from the group consisting of: (a) SEQ ID NOs: 4, 6, 8, 12, 14, and 16; and (b) SEQ ID NOs: 68, 70, 72, 76, 78, and 80.

14. The antibody or antigen-binding fragment thereof of claim 13 comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, and 66/74.

15. An antibody or antigen-binding fragment thereof that binds to natriuretic peptide receptor 1 (NPR1) protein, wherein the antibody or antigen-binding fragment comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR; wherein the HCVR comprises:

(i) an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, and 178;

(ii) an amino acid sequence having at least 90% identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, and 178;

(iii) an amino acid sequence having at least 95% identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, and 178; or

(iv) an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, and 178, said amino acid sequence having no more than 12 amino acid substitutions,

and the LCVR comprises:

(a) an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, and 186;

(b) an amino acid sequence having at least 90% identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, and 186;

(c) an amino acid sequence having at least 95% identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, and 186; or

(d) an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, and 186, said amino acid sequence having no more than 10 amino acid substitutions.

16. The antibody or antigen-binding fragment thereof of claim 15 comprising a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, and 178.

17. The antibody or antigen-binding fragment thereof of claim 15 comprising a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, and 186.

18. The antibody or antigen-binding fragment thereof of any one of claims 15 – 17 comprising three CDRs contained within a HCVR selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, and 178; and three CDRs contained within a LCVR selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, and 186.

19. The antibody or antigen-binding fragment of any one of claims 15 – 18 comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, and 178/186.

20. The antibody or antigen-binding fragment thereof of claim 15 comprising:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, and 180;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, and 182;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, and 184;

~~(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, and 188;~~

~~(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, and 190; and~~

~~(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, and 192.~~

~~21. The antibody or antigen-binding fragment thereof of claim 20 comprising CDRs selected from the group consisting of: (a) SEQ ID NOs: 4, 6, 8, 12, 14, and 16; and (b) SEQ ID NOs: 68, 70, 72, 76, 78, and 80.~~

~~22. The antibody or antigen-binding fragment thereof of claim 21 comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, and 66/74.~~

~~23. An isolated monoclonal antibody or antigen-binding fragment thereof that activates natriuretic peptide receptor 1 (NPR1) protein comprising three CDRs of a HCVR, wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, and 178; and three CDRs of a LCVR, wherein the LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, and 186.~~

~~24. An antibody or antigen-binding fragment thereof that competes for binding to natriuretic peptide receptor 1 (NPR1) protein with an antibody or antigen-binding fragment thereof of any one of claims 1 – 23.~~

~~25. An antibody or antigen-binding fragment thereof that binds to the same epitope as an antibody or antigen-binding fragment thereof of any one of claims 1 – 23.~~

~~26.~~
11. A pharmaceutical composition comprising an isolated antibody or antigen-binding fragment thereof that binds to natriuretic peptide receptor 1 (NPR1) protein according to ~~any one of claims 1 – 25~~ claim 1 and a pharmaceutically acceptable carrier or diluent.

~~27. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a HCVR of an antibody as set forth in any one of claims 1 – 25.~~

28. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a LCVR of an antibody as set forth in any one of claims 1 – 25.

29. A vector comprising the polynucleotide sequence of claim 27 and/or the polynucleotide sequence of claim 28.

30. A host cell expressing the vector of claim 29.

31. A method of producing an anti-NPR1 antibody or antigen-binding fragment thereof, comprising growing the host cell of claim 30 under conditions permitting production of the antibody or fragment, and recovering the antibody or fragment so produced.

32. The method of claim 31, further comprising formulating the antibody or antigen-binding fragment thereof as a pharmaceutical composition comprising an acceptable carrier.

33. A method of treating, preventing or ameliorating at least one symptom or indication of a NPR1-associated disease or disorder, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding fragment thereof of any one of claims 1 – 25 to a subject in need thereof.

34. The method of claim 33, wherein the NPR1-associated disease or disorder is selected from the group consisting of hypertension, heart failure, obesity, renal failure, chronic kidney disease, macular edema, glaucoma, stroke, lung disorders, pulmonary fibrosis, inflammation, asthma, skeletal growth disorders, bone fractures, diabetes, and cancer.

35. The method of claim 33 or 34, wherein the pharmaceutical composition is administered prophylactically or therapeutically to the subject in need thereof.

36. The method of any one of claims 33 – 35, wherein the pharmaceutical composition is administered in combination with a second therapeutic agent.

37. The method of claim 36, wherein the second therapeutic agent is selected from the group consisting of an aldosterone antagonist, an alpha-adrenergic blocker, an angiotensin converting enzyme (ACE) inhibitor, an arteriolar vasodilator, an autonomic ganglionic vasodilator, a beta-adrenergic blocker, a catecholamine-depleting sympatholytic, a central alpha-2 adrenergic agonist, a calcium channel blocker, a diuretic, a renin inhibitor, an anti-coagulant, an anti-platelet agent, a cholesterol lowering agent, a vasodilator, digitalis, surgery, an implantable device, anti-tumor therapy, insulin, a GLP1 agonist, metformin,

~~dialysis, bone marrow stimulant, hemofiltration, a lifestyle modification, and a dietary supplement.~~

~~38. The method of any one of claims 33 – 37, wherein the pharmaceutical composition is administered subcutaneously, intravenously, intradermally, intraperitoneally, or intramuscularly.~~