CLAIMS

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 binds to NPR1 and blocks NPR1.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody is a fully human monoclonal antibody.

3. The antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the antibody has one or more properties selected from the group consisting of: (a) is a fully human monoclonal antibody; (b) binds to human NPR1 at 25^{o}C and at 37^{o}C with a dissociation constant (K_D) of less than 1.7nM, as measured in a surface plasmon resonance assay; (c) binds to monkey NPR1 at 25^{o}C and 37^{o}C with a K_D of less than 1.99nM, as measured in a surface plasmon resonance assay; (d) binds to human NPR1 in the presence of ANP at 25^{o}C and at 37^{o}C with a K_D of less than 1.52nM, as measured in a surface plasmon resonance assay; (e) inhibits ligand-induced NPR1 activation, as measured by cGMP accumulation assay; (f) binds to human NPR1 in the presence or absence of ANP or BNP with an EC_{50} of less than 2.9nM, as measured by electrochemiluminescence-based immunoassay; (g) binds to monkey NPR1 in the presence or absence of ANP or BNP with an EC_{50} of less than 4.2nM, as measured by electrochemiluminescence-based immunoassay; (h) increases the systemic blood pressures when the antibody or antigen-binding fragment thereof is to be administered to normotensive and hypotensive mice, wherein the increase in systemic blood pressures lasts for up to about 28 days upon a single dose to be administered; (i) increases the systemic blood pressures when the antibody or antigen-binding fragment thereof is to be administered to ANP overexpression-induced hypotensive mice, wherein the increase in systemic blood pressures lasts for up to about 28 days upon a single dose to be administered; and (j) increases systemic blood pressures in LPS-induced hypotensive mice.

4. The antibody or antigen-binding fragment thereof of any one of claims 1-3, 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); and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR), wherein the HCVR comprises:

(i) an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, 38, and 55;

(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, 22, 38, and 55;

(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, 22, 38, and 55; or

(iv) an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, 38, and 55, 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, 30, 46, and 63;

(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, 30, 46, and 63;

(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, 30, 46, and 63; or

(d) an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 30, 46, and 63, said amino acid sequence having no more than 10 amino acid substitutions.

5. The antibody or antigen-binding fragment thereof of any one of claims 1-4 comprising a heavy chain variability region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, 38, and 55.

6. The antibody or antigen-binding fragment thereof of any one of claims 1-5 comprising a light chain variability region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 30, 46, and 63.

7. The antibody or antigen-binding fragment thereof of any one of claims 1-4 comprising three complementarity determining regions (CDRs) contained within a heavy chain variable region (HCVR) selected from the group consisting of SEQ ID NOs: 2, 22, 38, and 55; and three CDRs contained within a light chain variable region (LCVR) selected from the group consisting of SEQ ID NOs: 10, 30, 46, and 63.

8. The antibody or antigen-binding fragment of any one of claims 1-7 comprising a heavy chain variable region (HCVR)/light chain variable region (LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 38/46, and 55/63.

9. The antibody or antigen-binding fragment thereof of any one of claims 1-7 comprising:

(a) a heavy chain determining region (HCDR)1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 24, 40, and 57;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 26, 42, and 59;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 28, 44, ad 61;

(d) a light chain determining region (LCDR)1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 48, and 65;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of AAS and GAS; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, and 69.

10. The antibody or antigen-binding fragment thereof of any one of claims 1-9 comprising complementarity determining regions (CDRs) selected from the group consisting of: (a) SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 12, AAS, and SEQ ID NO: 16; (b) SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 12, AAS, and SEQ ID NO: 32; (c) SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 48, AAS and SEQ ID NO: 16; and (d) SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, GAS, and SEQ ID NO: 69.

11. The antibody or antigen-binding fragment thereof of any one of claims 1-10 comprising a heavy chain variable region (HCVR)/light chain variable region (LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 38/46, and 55/63.

12. The antibody or antigen-binding fragment thereof of any one of claims 1-11 comprising a heavy chain and a light chain, wherein the heavy chain is selected from the group consisting of SEQ ID NOs: 18, 34, 51 and 71.

13. The antibody or antigen-binding fragment thereof of any one of claims 1-11 comprising a heavy chain and light chain, wherein the light chain is selected from the group consisting of SEQ ID NOs: 20, 36, 53, and 73.

14. The antibody or antigen-binding fragment thereof of any one of claims 1-11 comprising a heavy chain and a light chain, wherein the heavy chain is selected from the group consisting of SEQ ID NOs: 18, 34, 51 and 71; and the light chain is selected from the group consisting of SEQ ID NOs: 20, 36, 53, and 73.

15. The antibody or antigen-binding fragment thereof of any one of claims 1-14, wherein the antibody or antigen-binding fragment thereof binds to residues in the lower lobe of the extracellular domain of NPR1.

16. The antibody or antigen-binding fragment thereof of any one of claims 1-15, wherein the antibody or antigen-binding fragment thereof interacts with at least one of the NPR1 residues selected from the group consisting of Arg143, Leu144, Glu384, Leu401, Val402, Ala103, Ser405, Gly406, Arg407, Lys408, Trp411, Leu413, Gly414, Tyr415, and Pro416.

17. The antibody or antigen-binding fragment thereof of any one of claims 1-16 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 18; and the light chain comprises an amino acid sequence of SEQ ID NO: 20.

18. The antibody or antigen-binding fragment thereof of any one of claims 1-16 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 34; and the light chain comprises an amino acid sequence of SEQ ID NO: 36.

19. The antibody or antigen-binding fragment thereof of any one of claims 1-16 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 51; and the light chain comprises an amino acid sequence of SEQ ID NO: 53.

20. The antibody or antigen-binding fragment thereof of any one of claims 1-16 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 71; and the light chain comprises an amino acid sequence of SEQ ID NO: 73.

21. An antibody or antigen-binding fragment thereof that competes for binding to natriuretic peptide receptor 1 (NPR1) protein with the antibody or antigen-binding fragment thereof of any one of claims 1-20.

22. An antibody or antigen-binding fragment thereof that binds to the same epitope as the antibody or antigen-binding fragment thereof of any one of claims 1-20.

23. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-20 and a pharmaceutically acceptable carrier or diluent.

24. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a heavy chain variable region (HCVR) of an antibody as set forth in any one of claims 1-20.

25. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a light chain variable region (LCVR) of an antibody as set forth in any one of claims 1-20.

26. A vector comprising the polynucleotide molecule of claim 24.

27. A vector comprising the polynucleotide molecule of claim 25.

28. A host cell expressing the vector of claim 26 and/or 27.

29. A method of producing an anti-NPR1 antibody or antigen-binding fragment thereof, comprising growing the host cell of claim 28 under conditions permitting production of the antibody or fragment, and recovering the antibody or fragment so produced.

30. The method of claim 29, further comprising formulating the antibody or antigen-binding fragment thereof as a pharmaceutical composition comprising an acceptable carrier.

31. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-20 for the manufacture of a medicament for the treatment, prevention, or amelioration of at least one symptom or indication of a NPR1-associated disease or disorder.

32. The use of claim 31, wherein the NPR1-associated disease or disorder is selected from the group consisting of hypotension, circulatory shock, septic shock, neurogenic orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS), heart failure, cardiogenic

shock, obesity, renal failure, chronic kidney disease, macular edema, glaucoma, stroke, lung disorders, pulmonary fibrosis, inflammation, asthma, skeletal growth disorders, bone fractures, diabetes, hypoglycemia, and cancer.

33. The use of claim 31 or 32, wherein the medicament is to be administered prophylactically or therapeutically to the subject in need thereof.

34. The use of any one of claims 31-33, wherein the medicament is to be administered in combination with a second therapeutic agent or therapy.

35. The use of claim 34, wherein the second therapeutic agent or therapy is selected from the group consisting of an angiogenesis inhibitor, a vasoconstrictor/vasopressor, an immunosuppressant, ascorbic acid, a calcineurin inhibitor, a corticosteroid, a VEGF inhibitor, a decongestant, an antidepressant, hormonal birth control, a stimulant (including cardiac stimulant), caffeine, extracorporeal membrane oxygenation, ventricular assist device, intra-aortic balloon pump, a lifestyle modification, a dietary supplement, an anti-microbial drug, insulin, and an anti-inflammatory drug.

36. The use of any one of claims 31-35, wherein the medicament is to be administered subcutaneously, intravenously, intradermally, intraperitoneally, or intramuscularly.