

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of angiotensinogen (AGT) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding AGT, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7.

2. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

3. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

4. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

5. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

6. The dsRNA agent of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide.

7. The dsRNA agent of claim 1 or 6, wherein substantially all of the nucleotides of the sense strand are modified nucleotides; substantially all of the nucleotides of the antisense strand are modified nucleotides; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides.

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8. The dsRNA agent of any one of claims 1, 6 or 7, wherein all of the nucleotides of the sense strand are modified nucleotides; all of the nucleotides of the antisense strand are modified nucleotides; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

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9. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythymidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, a 2'-5'-linked ribonucleotide (3'-RNA), an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a vinyl-phosphonate nucleotide, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), a nucleotide comprising a 2' phosphate, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

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10. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is selected from the group consisting of LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and glycol; and combinations thereof.

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11. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), a nucleotide comprising a 2' phosphate, and a nucleotide comprising a phosphorothioate group; and combinations thereof.

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12. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is a nucleotide modified with a thermally destabilizing nucleotide modification.

13. The dsRNA agent of claim 12, wherein the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; a destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acid (UNA), and a glycerol nucleic acid (GNA).
14. The dsRNA agent of any one of claims 1-13, wherein the double stranded region is 19-30 nucleotide pairs in length.
15. The dsRNA agent of claim 14, wherein the double stranded region is 19-25 nucleotide pairs in length.
16. The dsRNA agent of claim 14, wherein the double stranded region is 19-23 nucleotide pairs in length.
17. The dsRNA agent of claim 14, wherein the double stranded region is 23-27 nucleotide pairs in length.
18. The dsRNA agent of claim 14, wherein the double stranded region is 21-23 nucleotide pairs in length.
19. The dsRNA agent of any one of claims 1-18, wherein each strand is independently no more than 30 nucleotides in length.
20. The dsRNA agent of any one of claims 1-19, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.
21. The dsRNA agent of any one of claims 1-20, wherein the region of complementarity is at least 17 nucleotides in length.
22. The dsRNA agent of any one of claims 1-21, wherein the region of complementarity is between 19 and 23 nucleotides in length.
23. The dsRNA agent of any one of claims 1-22, wherein the region of complementarity is 19 nucleotides in length.

24. The dsRNA agent of any one of claims 1-23, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

25. The dsRNA agent of any one of claims 1-23, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

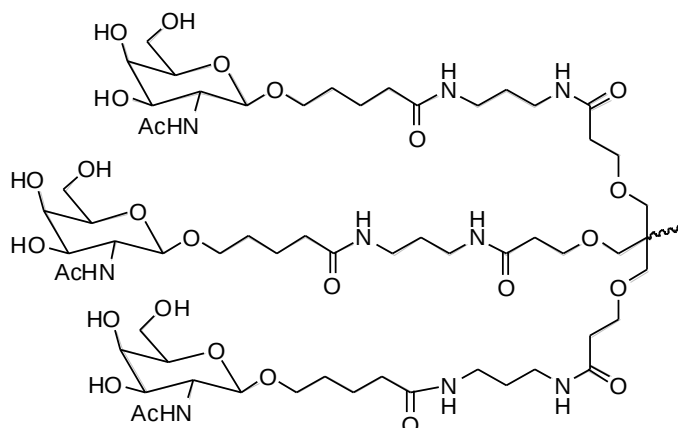
26. The dsRNA agent of any one of claims 1-25, further comprising a ligand.

27. The dsRNA agent of claim 26, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

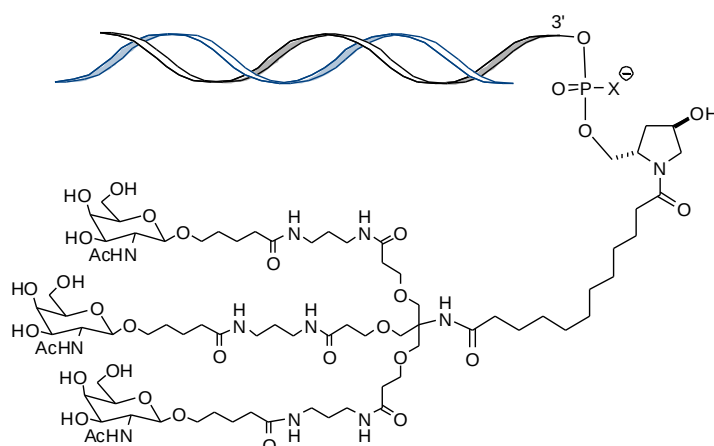
28. The dsRNA agent of claim 26 or 27, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

29. The dsRNA agent of any one of claims 26-28, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

30. The dsRNA agent of claim 28 or 29, wherein the ligand is



31. The dsRNA agent of claim 30, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

32. The dsRNA agent of claim 31, wherein the X is O.

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33. The dsRNA agent of any one of claims 1-32, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

34. The dsRNA agent of claim 33, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

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35. The dsRNA agent of claim 34, wherein the strand is the antisense strand.

36. The dsRNA agent of claim 34, wherein the strand is the sense strand.

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37. The dsRNA agent of claim 33, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

38. The dsRNA agent of claim 37, wherein the strand is the antisense strand.

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39. The dsRNA agent of claim 37, wherein the strand is the sense strand.

40. The dsRNA agent of claim 33, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at both the 5'- and 3'-terminus of one strand.

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41. The dsRNA agent of claim 40, wherein the strand is the antisense strand.

42. The dsRNA agent of any one of claims 1-41, wherein the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.
43. A cell containing the dsRNA agent of any one of claims 1-42.
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44. A pharmaceutical composition for inhibiting expression of a gene encoding angiotensinogen (AGT) comprising the dsRNA agent of any one of claims 1-42 and a pharmaceutically acceptable carrier.
- 10 45. The pharmaceutical composition of claim 44, wherein dsRNA agent is in an unbuffered solution.
46. The pharmaceutical composition of claim 45, wherein the unbuffered solution is saline or water.
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47. The pharmaceutical composition of claim 44, wherein said dsRNA agent is in a buffer solution.
48. The pharmaceutical composition of claim 47, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.
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49. The pharmaceutical composition of claim 48, wherein the buffer solution is phosphate buffered saline (PBS).
- 25 50. Use of the dsRNA agent of any one of claims 1-42, or the pharmaceutical composition of any one of claims 44-49 in the manufacture of a medicament for inhibiting expression of an angiotensinogen (AGT) gene in a cell, wherein the medicament is to be contacted with the cell, thereby inhibiting expression of the AGT gene in the cell.
- 30 51. The use of claim 50, wherein the cell is within a subject.
52. The use of claim 51, wherein the subject is a human.
53. The use of claim 51, wherein the subject has an AGT-associated disorder.
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54. The use of claim 53, wherein the AGT-associated disorder is selected from the group consisting of high blood pressure, hypertension, borderline hypertension, primary hypertension,

secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, hypertension associated with low plasma renin activity or plasma renin concentration, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome.

55. The use of claim 54, wherein the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg.

56. The use of claim 54, wherein the subject has a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 80 mm Hg.

57. The use of claim 54, wherein the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

58. The use of any one of claims 50-57, wherein contacting the cell with the dsRNA agent inhibits the expression of AGT by at least 50%, 60%, 70%, 80%, 90%, or 95%.

59. The use of any one of claims 50-58, wherein inhibiting expression of AGT decreases AGT protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%.

60. Use of the dsRNA agent of any one of claims 1-42, or the pharmaceutical composition of any one of claims 44-49 in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in angiotensinogen (AGT) expression, wherein the medicament is to be administered to the subject in a therapeutically effective amount.

61. Use of the dsRNA agent of any one of claims 1-42, or the pharmaceutical composition of any one of claims 44-49 in the manufacture of a medicament for preventing at least one symptom in a subject having a disorder that would benefit from reduction in angiotensinogen (AGT) expression, wherein the medicament is to be administered to the subject in a prophylactically effective amount.

62. The use of claim 60 or 61, wherein the disorder is an AGT-associated disorder.

63. The use of claim 62, wherein the AGT-associated disorder is selected from the group consisting of high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, hypertension associated with low plasma renin activity or plasma renin concentration, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR), fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome.

64. The use of claim 63, wherein the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg.

65. The use of claim 63, wherein the subject has a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 80 mm Hg.

66. The use of claim 63, the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

67. The use of any one of claims 60-66, wherein the subject is a human.

68. The use of any one of claims 60-67, wherein administration of the dsRNA agent to the subject causes a decrease in AGT protein accumulation in the subject.

69. The use of any one of claims 60-68, wherein the dsRNA agent is to be administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

70. The use of any one of claims 60-69, wherein the dsRNA agent is to be administered to the subject subcutaneously.

71. The use of any one of claims 60-70, further comprising determining the level of AGT in a sample(s) from the subject.
- 5 72. The use of claim 71, wherein the level of AGT in the subject sample(s) is an AGT protein level in a blood or serum or urine or liver tissue sample(s).
73. The use of any one of claims 60-72, wherein the level of bradykinin, prekallikrein, or blood pressure is to be further determined in the subject.
- 10 74. The use of any one of claims 59-72, wherein an additional therapeutic agent for treatment of an AGT-associated disorder is to be further administered to the subject.
75. The use of claim 74, wherein the additional therapeutic agent is selected from the group
15 consisting of a diuretic, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a beta-blocker, a vasodialator, a calcium channel blocker, an aldosterone antagonist, an alpha2-agonist, a renin inhibitor, an alpha-blocker, a peripheral acting adrenergic agent, a selective D1 receptor partial agonist, a nonselective alpha-adrenergic antagonist, a synthetic, a steroidal antimineralocorticoid agent, an angiotensin receptor-neprilysin inhibitors (ARNi),
20 Entresto®, sacubitril/valsartan; or an endothelin receptor antagonist (ERA), sitaxentan, ambrisentan, atrasentan, BQ-123, zibotentan, bosentan, macitentan, and tezosentan; a combination of any of the foregoing; and a hypertension therapeutic agent formulated as a combination of agents.
76. The use of claim 74, wherein the additional therapeutic agent comprises an angiotensin II
25 receptor antagonist.
77. The use of claim 76, wherein the angiotensin II receptor antagonist is selected from the group consisting of losartan, valsartan, olmesartan, eprosartan, and azilsartan.
- 30 78. A kit comprising the dsRNA agent of any one of claims 1-42 or the pharmaceutical composition of any one of claims 44-49.
79. A vial comprising the dsRNA agent of any one of claims 1-42 or the pharmaceutical composition of any one of claims 44-49.

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80. A syringe comprising the dsRNA agent of any one of claims 1-42 or the pharmaceutical composition of any one of claims 44-49.

5 81. An RNA-induced silencing complex (RISC) comprising an antisense strand of any of the dsRNA agents of claims 1-42.

10 82. An *in vitro* method of inhibiting expression of an angiotensinogen (AGT) gene in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-42, or the pharmaceutical composition of any one of claims 44-49, thereby inhibiting expression of the AGT gene in the cell.

83. The dsRNA agent of any one of claims 1-42, or the pharmaceutical composition of any one of claims 44-49 for use in therapy.

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