were developed providing goals for even lower blood pressure to further decrease risk of development of diseases and disorders associated with hypertension (see, *e.g.*, Reboussin *et al.* Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017 Nov 7. pii: S0735-1097(17)41517-8. doi: 10.1016/j.jacc.2017.11.004; and Whelton *et al.* (2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017 Nov 7. pii: S0735-1097(17)41519-1. doi: 10.1016/j.jacc.2017.11.006).

Despite the number of anti-hypertensive drugs available for treating hypertension, more than two-thirds of subjects are not controlled with one anti-hypertensive agent and require two or more anti-hypertensive agents selected from different drug classes. This further reduces the number of subjects with controlled blood pressure as adherence is reduced and side-effects are increased with increasing numbers of medications.

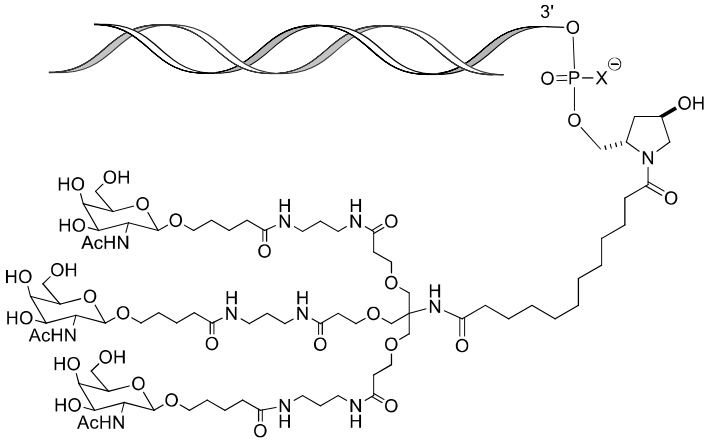
Summary

The present disclosure provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding angiotensinogen (AGT). The AGT may be within a cell, *e.g.*, a cell within a subject, such as a human subject.

In one aspect, the present disclosure refers to a double stranded ribonucleic acid (dsRNA) agent, or a pharmaceutically acceptable salt thereof, for inhibiting expression of angiotensinogen (AGT), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises the nucleotide sequence 5'-gsuscaucCfaCfAfAfugagaguaca-3' of SEQ ID NO:482, and the antisense strand comprises the nucleotide sequence 5'- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' of SEQ ID NO:666, wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer.

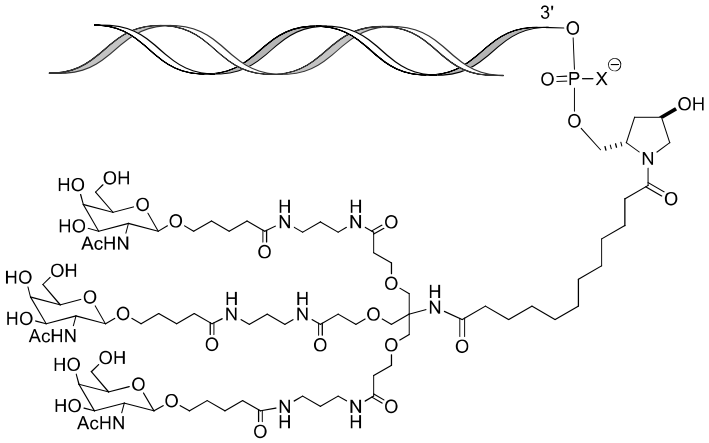
In another aspect, the present disclosure refers to a double stranded RNA (dsRNA) agent, or a pharmaceutically acceptable salt thereof, for inhibiting expression of angiotensinogen (AGT) in a cell, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises the nucleotide sequence 5'-gsuscaucCfaCfAfAfugagaguaca-3' of SEQ ID NO:482, and the antisense strand comprises the nucleotide sequence 5'-usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' of SEQ ID NO:666, wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-

glycol nucleic acid (GNA) S-Isomer; and wherein the 3'-end of the sense strand is conjugated to a ligand as shown in the following schematic



wherein X is O.

In yet another aspect, the present disclosure refers to a double stranded RNA (dsRNA) agent, or a pharmaceutically acceptable salt thereof, for inhibiting expression of angiotensinogen (AGT) in a cell, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand consists of the nucleotide sequence 5'-gsuscaucCfaCfAfAfugagaguaca-3' of SEQ ID NO:482, and the antisense strand consists of the nucleotide sequence 5'- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' of SEQ ID NO:666, wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer; and wherein the 3'-end of the sense strand is conjugated to a ligand as shown in the following schematic



wherein X is O.

In yet another aspect, the present disclosure refers to an isolated cell containing the dsRNA agent, or a pharmaceutically acceptable salt thereof, as disclosed herein.

In yet another aspect, the present disclosure refers to a pharmaceutical composition for inhibiting expression of a gene encoding AGT comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as disclosed herein.

In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as disclosed herein, and a lipid formulation.

In yet another aspect, the present disclosure refers to an *in vitro* method of inhibiting expression of an AGT gene in a cell, the method comprising contacting the cell with the dsRNA agent, or a pharmaceutically acceptable salt thereof, as disclosed herein or the pharmaceutical composition as disclosed herein, thereby inhibiting expression of the AGT gene in the cell.

In yet another aspect, the present disclosure refers to a use of the dsRNA agent or a pharmaceutically acceptable salt thereof, as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject having an AGT-associated disorder.

In yet another aspect, the present disclosure refers to a kit comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as disclosed herein or the pharmaceutical composition as disclosed herein.

In an example, the disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of angiotensinogen (AGT), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 19 contiguous nucleotides from the nucleotide sequence of any one of nucleotides 635-658, 636-658, 642-667, 642-664, 645-667, 1248-1273, 1248-1272, 1248-1270, 1250-1272, 1251-1273, 1580-1602, 1584-1606, 1587-1609, 1601-1623, 1881-1903, 2074-2097, 2074-2096, 2075-2097, 2080-2102, 2272-2294, 2276-2298, 2281-2304, 2281-2303, or 2282-2304 of SEQ ID NO:1 and the antisense strand comprises at least 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:2.

In certain examples, the sense strand comprises at least 21 contiguous nucleotides of any one of nucleotides 635-658, 636-658, 642-667, 642-664, 645-667, 1248-1273, 1248-1272, 1248-1270, 1250-1272, 1251-1273, 1580-1602, 1584-1606, 1587-1609, 1601-1623, 1881-1903, 2074-2097, 2074-2096, 2075-2097, 2080-2102, 2272-2294, 2276-2298, 2281-2304, 2281-2303, or 2282-2304 of SEQ ID NO:1. In certain examples, the antisense strand comprises at least 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:2.

In certain examples, the antisense strand comprises at least 19 contiguous nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent, or a pharmaceutically acceptable salt thereof, for inhibiting expression of angiotensinogen (AGT),

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises the nucleotide sequence 5'-gsuscaucCfaCfAfAfugagaguaca-3' of SEQ ID NO:482, and the antisense strand comprises the nucleotide sequence 5'- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' of SEQ ID NO:666,

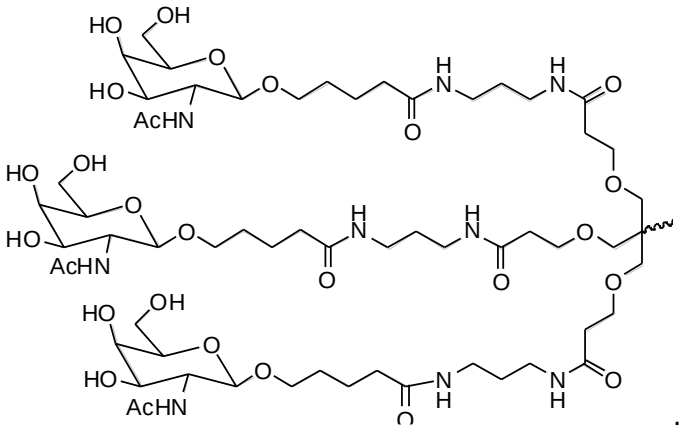
wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer.

2. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 1, further comprising a ligand.

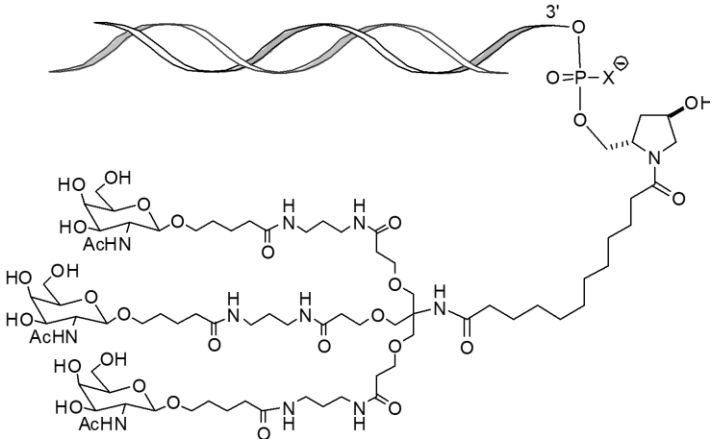
3. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 2, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent, or a pharmaceutically acceptable salt thereof.

4. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 2 or 3, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

5. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 4, wherein the ligand is



6. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 5, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is conjugated to the ligand as shown in the following schematic



, wherein X is O or S.

7. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 2, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent linker.

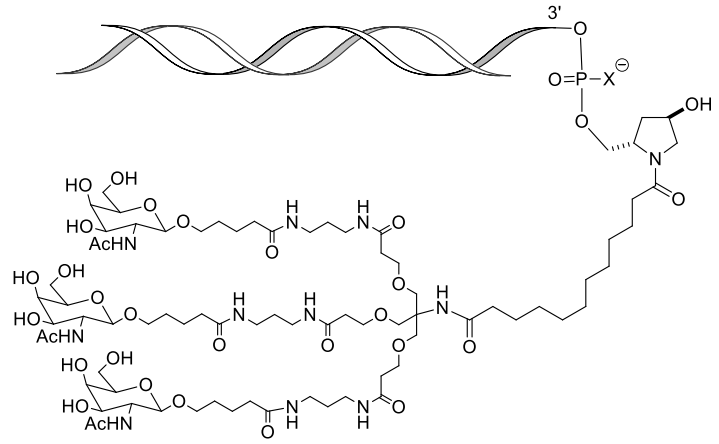
8. A double stranded RNA (dsRNA) agent, or a pharmaceutically acceptable salt thereof, for inhibiting expression of angiotensinogen (AGT) in a cell, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises the nucleotide sequence 5'-gsuscaucCfaCfAfAfugagaguaca-3' of SEQ ID NO:482, and the antisense strand

comprises the nucleotide sequence 5’- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3’ of SEQ ID NO:666,

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer; and

wherein the 3’-end of the sense strand is conjugated to a ligand as shown in the following schematic



wherein X is O.

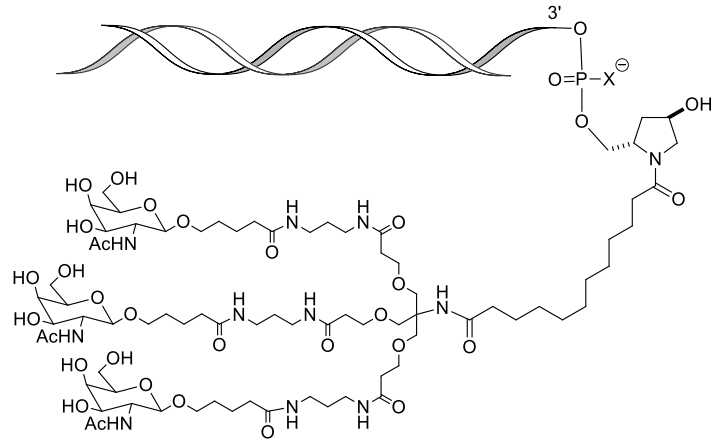
9. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 8, which is in a salt form.

10. A double stranded RNA (dsRNA) agent, or a pharmaceutically acceptable salt thereof, for inhibiting expression of angiotensinogen (AGT) in a cell, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand consists of the nucleotide sequence 5’-gsuscaucCfaCfAfAfugagaguaca-3’ of SEQ ID NO:482, and the antisense strand consists of the nucleotide sequence 5’- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3’ of SEQ ID NO:666,

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer; and

wherein the 3’-end of the sense strand is conjugated to a ligand as shown in the following schematic



wherein X is O.

11. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 10, which is in a salt form.

12. An isolated cell containing the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-11.

13. A pharmaceutical composition for inhibiting expression of a gene encoding AGT comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-11.

14. A pharmaceutical composition for inhibiting expression of a gene encoding AGT comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 8.

15. A pharmaceutical composition for inhibiting expression of a gene encoding AGT comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 10.

16. A pharmaceutical composition comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-11, and a lipid formulation.

17. An *in vitro* method of inhibiting expression of an AGT gene in a cell, the method comprising contacting the cell with the dsRNA agent, or a pharmaceutically

acceptable salt thereof, of any one of claims 1-11 or the pharmaceutical composition of any one of claims 13-16, thereby inhibiting expression of the AGT gene in the cell.

18. The method of claim 17, wherein contacting the cell with the dsRNA agent, or a pharmaceutically acceptable salt thereof, inhibits the expression of the AGT gene by at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%.

19. Use of the dsRNA agent or a pharmaceutically acceptable salt thereof, of any one of claims 1-11 or the pharmaceutical composition of any one of claims 13-16 in the manufacture of a medicament for treating a subject having an AGT-associated disorder.

20. The use of claim 19, wherein the subject has been diagnosed with an AGT-associated disorder.

21. The use of claim 20, 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.

22. The use of any one of claims 19-21, wherein the subject has a systolic blood pressure of at least 130 mm Hg and a diastolic blood pressure of at least 80 mm Hg.

23. The use of any one of claims 19-21, 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.

24. The use of any one of claims 19-23, wherein the subject is human.

25. The use of any one of claims 19-24, wherein the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

26. The use of any one of claims 19-25, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose of 0.01 mg/kg to 50 mg/kg.

27. The use of any one of claims 19-26, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is to be administered to the subject subcutaneously.

28. The use of any one of claims 19-26, further comprising use of an additional therapeutic agent for treatment of hypertension.

29. The use of claim 28, wherein the additional therapeutic agent is selected from the group 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), 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.

30. The use of claim 28, wherein the additional therapeutic agent comprises an angiotensin II receptor antagonist.

31. The use of claim 30, wherein the angiotensin II receptor antagonist is selected from the group consisting of losartan, valsartan, olmesartan, eprosartan, and azilsartan.

32. A kit comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-11, or the pharmaceutical composition of any one of claims 13-16.