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.

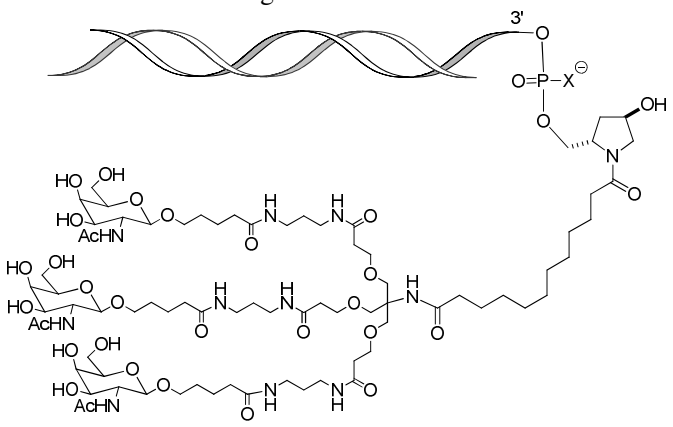
Summary

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 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' (SEQ ID NO:482) , and the antisense strand comprises the nucleotide sequence 5'-usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' (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.

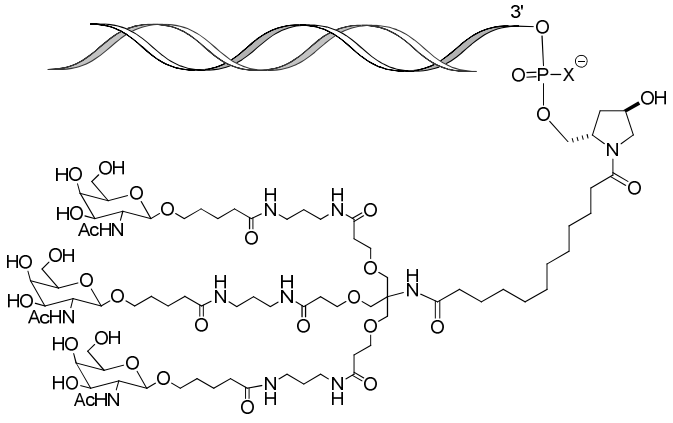
In another aspect, the present disclosure refers to a double stranded RNA (dsRNA) agent, or a salt thereof, for inhibiting expression of angiotensinogen (AGT) in a cell, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises the nucleotide sequence 5'-gsuscaucCfaCfAfAfugagaguaca-3' (SEQ ID NO:482) and the antisense strand comprises the nucleotide sequence 5'- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' (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 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' (SEQ ID NO:482) and the antisense strand consists of the nucleotide sequence 5'- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' (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 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 salt thereof, as disclosed herein.

In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the dsRNA agent, or 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 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 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 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

consisting of AD-85481, AD-84701, AD-84703, AD-84704, AD-84705, AD-84707, AD-84715, AD-84716, AD-84739, AD-84741, AD-84746, AD-85432, AD-85434, AD-85435, AD-85436, AD-85437, AD-85438, AD-85441, AD-85442, AD-85443, AD-85444, AD-85446, AD-85447, AD-85482, AD-85485, AD-85493, AD-85496, AD-85504, AD-85517, AD-85519, AD-85524, AD-85622, AD-85623, AD-85625, AD-85626, AD-85634, AD-85635, AD-85637, AD-85655, AD-126306, AD-126307, AD-126308, AD-126310, AD133360, AD-133361, AD-133362, AD-133374, and AD-133385. In certain examples, the sense strand comprises at least 19 contiguous nucleotides from any one of the sense strand nucleotide sequences of a duplex selected from the group consisting of AD-85481, AD-84701, AD-84703, AD-84704, AD-84705, AD-84707, AD-84715, AD-84716, AD-84739, AD-84741, AD-84746, AD-85432, AD-85434, AD-85435, AD-85436, AD-85437, AD-85438, AD-85441, AD-85442, AD-85443, AD-85444, AD-85446, AD-85447, AD-85482, AD-85485, AD-85493, AD-85496, AD-85504, AD-85517, AD-85519, AD-85524, AD-85622, AD-85623, AD-85625, AD-85626, AD-85634, AD-85635, AD-85637, AD-85655, AD-126306, AD-126307, AD-126308, AD-126310, AD133360, AD-133361, AD-133362, AD-133374, and AD-133385. In certain examples, the sense and antisense strands comprise nucleotide sequences of a duplex selected from the group consisting of AD-85481, AD-84701, AD-84703, AD-84704, AD-84705, AD-84707, AD-84715, AD-84716, AD-84739, AD-84741, AD-84746, AD-85432, AD-85434, AD-85435, AD-85436, AD-85437, AD-85438, AD-85441, AD-85442, AD-85443, AD-85444, AD-85446, AD-85447, AD-85482, AD-85485, AD-85493, AD-85496, AD-85504, AD-85517, AD-85519, AD-85524, AD-85622, AD-85623, AD-85625, AD-85626, AD-85634, AD-85635, AD-85637, AD-85655, AD-126306, AD-126307, AD-126308, AD-126310, AD133360, AD-133361, AD-133362, AD-133374, and AD-133385.

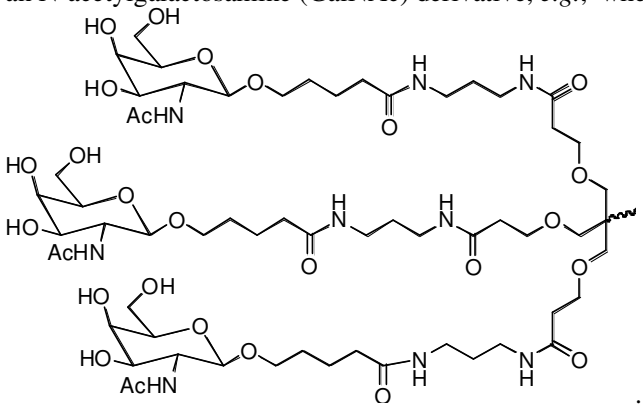
In certain examples, the antisense strand comprises at least 19 contiguous nucleotides from nucleotide sequence of the antisense strand of AD-85481 (5'-UGUACUCUCAUUGUGGAUGACGA-3' (SEQ ID NO: 9)). In certain examples, the sense strand comprises at least 19 contiguous nucleotides from the nucleotide sequences of the sense strand of AD-85481 (5'-GUCAUCCACAAUGAGAGUACA-3' (SEQ ID NO: 10)). In certain examples, the sense and antisense strands comprise the nucleotide sequences of the sense and antisense strands of AD-85481 (5'-UGUACUCUCAUUGUGGAUGACGA-3' (SEQ ID NO: 9) and 5'-GUCAUCCACAAUGAGAGUACA-3' (SEQ ID NO: 10)).

In certain examples, the dsRNA agent comprises at least one modified nucleotide. In certain examples, substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification. In certain examples, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification. In certain examples, at least one of the modified nucleotides is selected from the group of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, 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'-hydroxly-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 thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof. In certain examples, the modifications on the nucleotides are 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, GNA, and combinations thereof. In certain examples, the modifications on the nucleotides are 2′-O-methyl or 2′-fluoro modifications. In certain examples, 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), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof. In certain examples, at least one of the nucleotide modification is a thermally destabilizing nucleotide modification. In certain examples, the thermally destabilizing nucleotide modification is selected from the group consisting of of an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acids (UNA), and a glycerol nucleic acid (GNA)

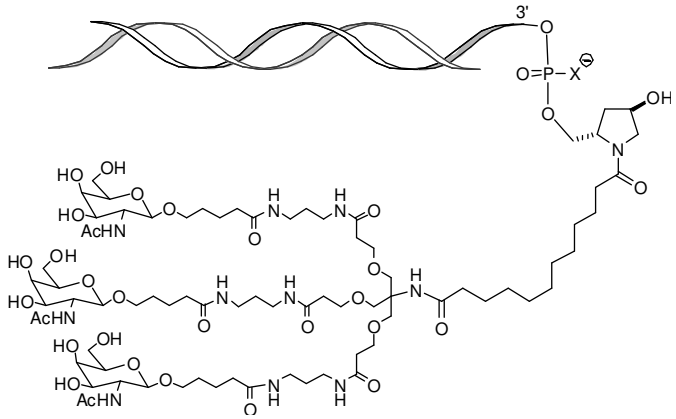
In certain examples, the double stranded region is 19- 21 nucleotides in length. In certain examples, the double stranded region is 21 nucleotides in length. In certain examples, each strand of the dsRNA agent is independently no more than 30 nucleotides in length. In certain examples, at least one strand of the dsRNA agent comprises a 3' overhang of at least 1 nucleotide or at least 2 nucleotides.

In certain examples, dsRNA agent further comprises a ligand. In certain examples, the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent. In certain examples, the ligand is an N-acetylgalactosamine (GalNAc) derivative, *e.g.*, wherein the ligand is



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In certain examples, the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S, *e.g.*, wherein the X is O.

In certain examples, the disclosure provides a dsRNA agent, wherein the antisense strand comprises a region of complementarity to an mRNA encoding human AGT, wherein the region of complementarity comprises at least 19 nucleotides one of the antisense strand sequences of a duplex selected from the group consisting of AD-85481, AD-84701, AD-84703, AD-84704, AD-84705, AD-84707, AD-84715, AD-84716, AD-84739, AD-84741, AD-84746, AD-85432, AD-85434, AD-85435, AD-85436, AD-85437, AD-85438, AD-85441, AD-85442, AD-85443, AD-85444, AD-85446, AD-85447, AD-85482, AD-85485, AD-85493, AD-85496, AD-85504, AD-85517, AD-85519, AD-85524, AD-85622, AD-85623, AD-85625, AD-85626, AD-85634, AD-85635, AD-85637, AD-85655, AD-126306, AD-126307, AD-126308, AD-126310, AD133360, AD-133361, AD-133362, AD-133374, and AD-133385. In certain examples, the antisense strand comprises a region of complementarity to an mRNA encoding human AGT, wherein the region of complementarity comprises any one of the antisense strand sequences of a duplex selected from the group consisting of AD-85481, AD-84701, AD-84703, AD-84704, AD-84705, AD-84707, AD-84715, AD-84716, AD-84739, AD-84741, AD-84746, AD-85432, AD-85434, AD-85435, AD-85436, AD-85437, AD-85438, AD-85441, AD-85442, AD-85443, AD-85444, AD-85446, AD-85447, AD-85482, AD-85485, AD-85493, AD-85496, AD-85504, AD-85517, AD-85519, AD-85524, AD-85622, AD-85623, AD-85625, AD-85626, AD-85634, AD-85635, AD-85637, AD-85655, AD-126306, AD-126307, AD-126308, AD-126310, AD133360, AD-133361, AD-133362, AD-133374, and AD-133385. In certain examples, the region of complementarity consists of any one of the antisense strand sequences of a duplex selected from the group consisting of AD-85481, AD-84701, AD-84703, AD-84704, AD-84705, AD-84707, AD-84715, AD-84716, AD-84739, AD-84741, AD-84746, AD-85432, AD-85434, AD-85435, AD-85436, AD-85437, AD-85438, AD-85441, AD-85442, AD-85443, AD-85444, AD-85446, AD-85447, AD-85482, AD-85485, AD-85493, AD-85496, AD-85504, AD-85517, AD-85519, AD-85524, AD-85622, AD-85623, AD-85625, AD-85626, AD-85634, AD-85635, AD-85637, AD-85655, AD-126306, AD-126307, AD-126308, AD-126310, AD133360, AD-133361, AD-133362, AD-133374, and AD-133385.

In certain examples, the disclosure provides a dsRNA agent, wherein the antisense strand comprises the chemically modified nucleotide sequence of a duplex selected from the group consisting of AD-85481, AD-84701, AD-84703, AD-84704, AD-84705, AD-84707, AD-84715, AD-

84716, AD-84739, AD-84741, AD-84746, AD-85432, AD-85434, AD-85435, AD-85436, AD-85437, AD-85438, AD-85441, AD-85442, AD-85443, AD-85444, AD-85446, AD-85447, AD-85482, AD-85485, AD-85493, AD-85496, AD-85504, AD-85517, AD-85519, AD-85524, AD-85622, AD-85623, AD-85625, AD-85626, AD-85634, AD-85635, AD-85637, AD-85655, AD-126306, AD-126307, AD-126308, AD-126310, AD133360, AD-133361, AD-133362, AD-133374, and AD-133385.

In certain examples, the disclosure provides a dsRNA agent, wherein the antisense strand comprises the chemically modified nucleotide sequence of the duplex AD-85481 (5'-usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' (SEQ ID NO: 11)) wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively; Af, Cf, Gf, and Uf are 2'-O-fluoroadenosine-3'-phosphate, 2'-O-fluorocytidine-3'-phosphate, 2'-O-fluoroguanosine-3'-phosphate, and 2'-O-fluorouridine-3'-phosphate, respectively; dT is a deoxy-thymine; s is a phosphorothioate linkage; and (Tgn) is thymidine-glycol nucleic acid (GNA) S-isomer.

In certain examples, the disclosure provides a dsRNA agent, wherein the antisense strand and the sense strand comprise the chemically modified nucleotide sequences of a duplex selected from the group consisting of AD-85481, AD-84701, AD-84703, AD-84704, AD-84705, AD-84707, AD-84715, AD-84716, AD-84739, AD-84741, AD-84746, AD-85432, AD-85434, AD-85435, AD-85436, AD-85437, AD-85438, AD-85441, AD-85442, AD-85443, AD-85444, AD-85446, AD-85447, AD-85482, AD-85485, AD-85493, AD-85496, AD-85504, AD-85517, AD-85519, AD-85524, AD-85622, AD-85623, AD-85625, AD-85626, AD-85634, AD-85635, AD-85637, AD-85655, AD-126306, AD-126307, AD-126308, AD-126310, AD133360, AD-133361, AD-133362, AD-133374, and AD-133385.

In certain examples, the disclosure provides a dsRNA agent, wherein the antisense strand and the sense strand comprise the chemically modified nucleotide sequences of the duplex AD-85481 (5'-usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' (SEQ ID NO: 11) and 5'-gsuscaucCfaCfAfAfugagaguaca-3' (SEQ ID NO: 12)) wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively; Af, Cf, Gf, and Uf are 2'-O-fluoroadenosine-3'-phosphate, 2'-O-fluorocytidine-3'-phosphate, 2'-O-fluoroguanosine-3'-phosphate, and 2'-O-fluorouridine-3'-phosphate, respectively; dT is a deoxy-thymine; s is a phosphorothioate linkage; and (Tgn) is thymidine-glycol nucleic acid (GNA) S-isomer; and wherein the 3'-end of the sense strand is optionally conjugated to an N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol (L96) ligand.

In certain examples, the disclosure provides a dsRNA agent, wherein the antisense strand and the sense strand consist of the chemically modified nucleotide sequences of the duplex AD-85481 (5'-usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' (SEQ ID NO: 11) and 5'-gsuscaucCfaCfAfAfugagaguaca-3' (SEQ ID NO: 12)), wherein the 3'-end of the sense strand is conjugated to an N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol (L96) ligand, wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-

methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively; Af, Cf, Gf, and Uf are 2'-O-fluoroadenosine-3'-phosphate, 2'-O-fluorocytidine-3'-phosphate, 2'-O-fluoroguanosine-3'-phosphate, and 2'-O-fluorouridine-3'-phosphate, respectively; dT is a deoxy-thymine; s is a phosphorothioate linkage; and (Tgn) is thymidine-glycol nucleic acid (GNA) S-isomer.

In certain examples, the double stranded region of the dsRNA agent is about 19-30 nucleotide pairs in length, about 19-25 nucleotide pairs in length, about 23-27 nucleotide pairs in length, about 19-23 nucleotide pairs in length, about 21-23 nucleotide pairs in length.

In certain examples, each strand of the dsRNA agent is independently 19-30 nucleotides in length.

In certain examples, the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In certain examples, the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage. In certain examples, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. In certain examples, the strand is the antisense strand. In certain examples, the strand is the sense strand. In certain examples, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. In certain examples, the strand is the antisense strand. In certain examples, the strand is the sense strand. In certain examples, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand. In certain examples, the strand is the antisense strand.

In certain examples, the dsRNA agent at the 1 position of the 5′-end of the antisense strand of the duplex comprises a base pair that is an AU base pair.

In certain examples, the dsRNA agent comprises a sense strand has a total of 21 nucleotides and an antisense strand has a total of 23 nucleotides.

In an example, the disclosure provides a cell containing the dsRNA agent of the disclosure.

In an example, the disclosure provides a pharmaceutical composition for inhibiting expression of a gene encoding AGT comprising the dsRNA agent of the disclosure. In certain examples, the pharmaceutical composition comprises the dsRNA agent and a lipid formulation.

In an example, the disclosure provides a method of inhibiting expression of an AGTgene in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent or a pharmaceutical composition of the disclosure; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the AGT gene, thereby inhibiting expression of the AGT gene in the cell.

In certain examples, the cell is within a subject. In certain examples, the subject is a human. In certain examples, the subject has been diagnosed with an AGT-associated disorder.

In certain examples, the AGT –associated disorder is selected from 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, 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.

In certain examples, the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg. In certain examples, the subject has a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 80 mm Hg. In certain examples, the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

In certain examples, contacting the cell with the dsRNA agent inhibits the expression of AGT by at least 50%, 60%, 70%, 80%, 90%, 95% (*e.g.,* as compared to the level of expression of AGT prior to first contacting the cell with the dsRNA agent; *e.g.*, prior to administration of a first dose of the dsRNA agent to the subject). In certain embodiments, inhibiting expression of AGT decreases an AGT protein level in a subject serum sample(s) by at least 50%, 60%, 70%, 80%, 90%, or 95%, *e.g.,* as compared to the level of expression of AGT prior to first contacting the cell with the dsRNA agent.

In an example, the disclosure provides a method of treating a an AGT-associated disorder in a subject, comprising administering to the subject the dsRNA agent or the pharmaceutical composition of the disclosure, thereby treating the AGT-associated disorder in the subject. In certain examples, the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg. In certain examples, the subject has a systolic blood pressure of at least 140 mm Hg and diastolic blood pressure of at least 80 mm Hg. In certain examples, the subject is human. In certain examples, subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

In certain examples of the disclosure, the dsRNA agent is administered at a dose of about 0.01 mg/kg to about 50 mg/kg. In certain examples, the dsRNA agent is administered to the subject subcutaneously. In certain examples, the level of AGT is measured in the subject. In certain examples, the level of AGT in the subject is an AGT protein level in a subject blood sample(s), serum sample(s), or urine sample(s).

In certain examples, an additional therapeutic agent for treatment of hypertension is administered to the subject. In certain examples, the additional therapeutic agent is selected from the group consisting of 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, and steroidal antimineralocorticoid agent; or a combination of any of the foregoing, and a hypertension therapeutic agent formulated as a combination of agents. In certain examples, the additional therapeutic agent comprises an angiotensin II receptor antagonist, *e.g.*, losartan, valsartan, olmesartan, eprosartan, and azilsartan. In certain examples, the additional therapeutic agent is an angiotensin receptor-neprilysin inhibitor (ARNi), *e.g.*, Entresto®, sacubitril/valsartan; or an endothelin receptor antagonist (ERA), *e.g.*, sitaxentan, ambrisentan, atrasentan, BQ-123, zibotentan, bosentan, macitentan, and tezosentan.

The disclosure also provides uses of the dsRNA agents and the pharmaceutical compositions provided herein for treatment of an AGT-associated disorder. In certain examples, the uses include any of the methods provided by the disclosure.

The disclosure provides kits comprising a dsRNA agent of the disclosure. In certain examples, the disclosure provides kits for practicing a method of the disclosure.

Brief Description of the Drawings

Figure 1A is a graph showing serum AGT protein levels in cynomolgus monkeys (n = 3 per group) treated with a single 3 mg/kg dose of the indicated siRNAs. AGT levels are shown as a percent of AGT level prior to treatment.

Figure 1B is a graph showing serum AGT protein levels in cynomolgus monkeys (n = 3 per group) treated with a single 0.3 mg/kg, 1 mg/kg, or 3 mg/kg dose of AD-85481 or AD-67327 on day 1. AGT levels are shown as a percent of AGT level prior to treatment.

Figure 1C is a graph showing serum AGT protein levels in cynomolgus monkeys (n = 3 per group) administered a 1 mg/kg dose of AD-85481 or AD-67327 once every four weeks for three doses. AGT levels are shown as a percent of AGT level prior to treatment.

Figures 2A-2G show the results of a various parameters in a study of spontaneously hypertensive rats (n=9 per group) treated with a vehicle, valsartan (31 mg/kg/day), a rat specific AGT-siRNA (10 mg/kg q2w), captopril (100 mg/kg/day), valsartan and captopril, or valsartan and AGT-siRNA.

Figure 2A shows plasma AGT levels at the start (solid bars) and end (stippled bars) of the study (at four weeks).

Figure 2B shows daily blood pressure readings compared to baseline.

Figure 2C is a graph showing heart weight: tibial length ratios.

Figure 2D is a graph showing plasma renin activity level at the start (solid bars) and end (stippled bars) of the study (at four weeks).

Figure 2E is a graph of heart weight:tibial length graphed against mean arterial pressure (MAP) in mm Hg.

Figure 2F is a graph of cardiomyocyte size.

Figure 2G is a graph of N-terminal pro b-type natriuretic peptide (NT-proBNP) levels.

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent, or 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' (SEQ ID NO:482) , and the antisense strand comprises the nucleotide sequence 5'- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' (SEQ ID NO:666),

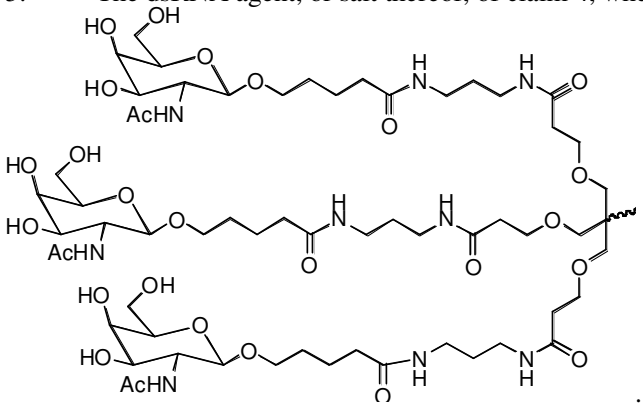
wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer.

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

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

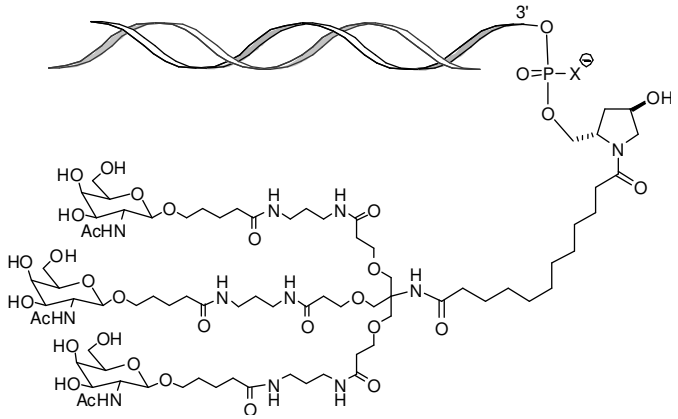
4. The dsRNA agent, or salt thereof, of claim 2 or 3, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

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



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



and, wherein X is O or S.

7. The dsRNA agent, or salt thereof, of claim 6, wherein the X is O.

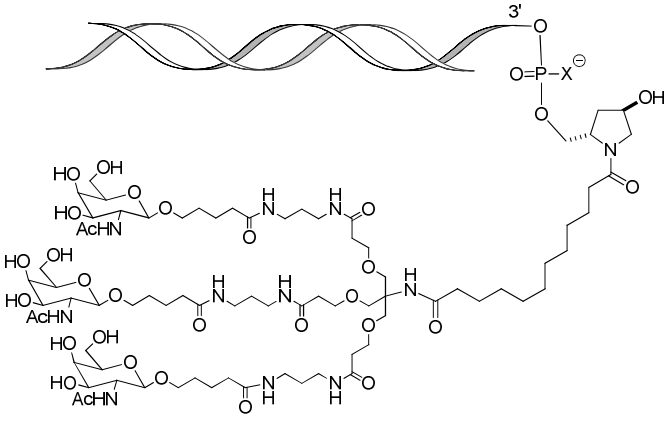
8. The dsRNA agent, or salt thereof, of claim 2, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

9. A double stranded RNA (dsRNA) agent, or a 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' (SEQ ID NO:482) and the antisense strand comprises the nucleotide sequence 5'- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' (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

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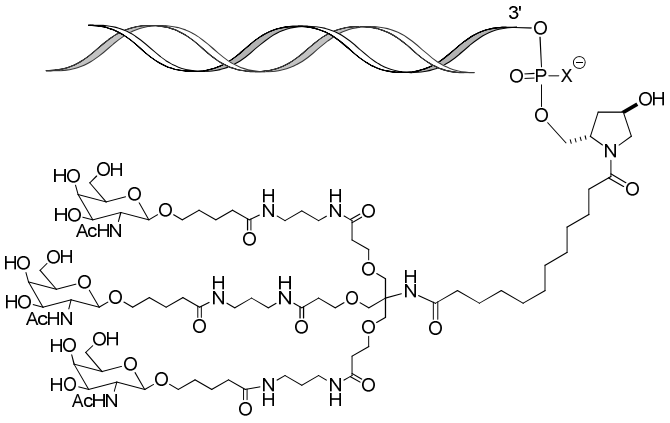
10. The dsRNA agent, or a salt thereof, of claim 9, which is in a salt form.

11. A double stranded RNA (dsRNA) agent, or a 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' (SEQ ID NO:482) and the antisense strand consists of the nucleotide sequence 5'- usGfsuac(Tgn)cucauugUfgGfaugacsgsa-3' (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.

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

13. An isolated cell containing the dsRNA agent, or salt thereof, of any one of claims 1-12.

14. A pharmaceutical composition for inhibiting expression of a gene encoding AGT comprising the dsRNA agent, or salt thereof, of any one of claims 1-12.

15. A pharmaceutical composition for inhibiting expression of a gene encoding AGT comprising the dsRNA agent, or salt thereof, of claim 9.

16. A pharmaceutical composition for inhibiting expression of a gene encoding AGT comprising the dsRNA agent, or salt thereof, of claim 11.

17. A pharmaceutical composition comprising the dsRNA agent, or salt thereof, of any one of claims 1-12, and a lipid formulation.

18. 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 salt thereof, of any one of claims 1-12 or the pharmaceutical composition of any one of claims 14-17, thereby inhibiting expression of the AGT gene in the cell.

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

20. Use of the dsRNA agent or salt thereof, of any one of claims 1-12 or the pharmaceutical composition of any one of claims 14-17 in the manufacture of a medicament for treating a subject having an AGT-associated disorder.

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

22. The use of claim 21, 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.

23. The use of any one of claims 20-22, 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.

24. The use of any one of claims 20-22, 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.

25. The use of any one of claims 20-24, wherein the subject is human.

26. The use of any one of claims 20-25, wherein the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

27. The use of any one of claims 20-26, wherein the dsRNA agent, or salt thereof, is to be administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

28. The method of any one of claims 20-27, wherein the dsRNA agent, or salt thereof, is to be administered to the subject subcutaneously.

29. The use of any one of claims 20-27, further comprising that an additional therapeutic agent for treatment of hypertension is to be administered to the subject.

30. The use of claim 29, 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.

31. The use of claim 29, wherein the additional therapeutic agent comprises an angiotensin II receptor antagonist.

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

33. A kit comprising the dsRNA agent, or salt thereof, of any one of claims 1-12 or the pharmaceutical composition of any one of claims 14-17.