

sequences listed in Tables 1-4, wherein the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent. In certain embodiments, the dsRNA agent comprises any of the sense strand sequences listed in Tables 1-4, wherein the sense strand sequence is completely complementary to the antisense strand sequence in the dsRNA agent. In some embodiments, the dsRNA agent comprises any of the antisense strand sequences listed in Tables 1-4. In some embodiments, the dsRNA agent comprises any of the sequences listed as duplex sequences in Tables 1-4.

In some embodiments, the dsRNA agent comprises a sense strand that differs by 0, 1, 2, or 3 nucleotides from Formula (A): 5'-Z₁AGCUUGUUUGUGAAACZ₂-3' (SEQ ID NO: 656), wherein Z₁ is a nucleotide sequence comprising 0-15 nucleotide motifs, and Z₂ is selected from one of A, U, C, G or does not exist. In certain embodiments, Z₁ is a nucleotide sequence comprising 1-4 nucleotide motifs. In certain embodiments, Z₁ is a nucleotide sequence comprising 1, 2, 3, or 4 nucleotide motifs. In certain embodiments, Z₂ is A. In certain embodiments, Z₁ is a nucleotide sequence comprising a CACC or GACC motif. In certain embodiments, the Z₁ nucleotide sequence is selected from one of the following motifs: C, AC, UC, GC, CC, ACC, UCC, GCC, CCC, GACC, AACC, UACC, CACC, CGACC, CCGACC, ACCGACC, AACCGACC, CAACCGACC, CCAACCGACC (SEQ ID NO: 657), UCCAACCGACC (SEQ ID NO: 658), UUCAACCGACC (SEQ ID NO: 659), AUUCAACCGACC (SEQ ID NO: 660), AAUCCAACCGACC (SEQ ID NO: 661) or GAAUCCAACCGACC (SEQ ID NO: 662). In some embodiments, the dsRNA agent comprises an antisense strand that differs by 0, 1, 2, or 3 nucleotides from Formula (B): 5'-Z₃GUUUCACAAACAAGCUZ₄-3' (SEQ ID NO: 663), wherein Z₃ is selected from one of A, U, C, G or does not exist, and Z₄ is a nucleotide sequence comprising 0-15 nucleotide motifs. In certain embodiments, Z₄ is a nucleotide sequence comprising 1-4 nucleotide motifs. In certain embodiments, Z₄ is a nucleotide sequence comprising 1, 2, 3, or 4 nucleotide motifs. In certain embodiments, Z₃ is U. In certain embodiments, the Z₄ nucleotide sequence is selected from nucleotide sequences comprising a GGUC or GGUG motif. In certain embodiments, the Z₄ nucleotide sequence is selected from one of the following motifs: G, GU, GC, GA, GG, GGU, GGA, GGC, GGG, GGUG, GGUC, GGUU, GGUA, GGUCG, GGUCGG, GGUCGGU, GGUCGGUU, GGUCGGUUG, GGUCGGUUGG (SEQ ID NO: 664), GGUCGGUUGGA (SEQ ID NO: 665), GGUCGGUUGGAA (SEQ ID NO: 666), GGUCGGUUGGAAU (SEQ ID NO: 667), GGUCGGUUGGAAUU (SEQ ID NO: 668) or GGUCGGUUGGAAUUC (SEQ ID NO: 669). In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, the sense strand and the antisense strand respectively comprising nucleotide sequences that differ by 0, 1, 2, or 3 nucleotides from formula (A) and formula (B) as described herein, and optionally comprising a targeting ligand. In certain embodiments, the sense strand (A) and antisense strand (B) of the dsRNA agent are each no more than 35 nucleotides in length. In certain embodiments, the Z₁ and Z₄ nucleotide motifs are fully or partially complementary. In some embodiments, the dsRNA agent comprises a sense strand that differs by 0, 1, 2, or 3 nucleotides

from formula (A'): 5'-Z₁'CAGCUUGUUUGUGAAACA-3 (SEQ ID NO: 670)', and comprises an antisense strand that differs by 0, 1, 2 or 3 nucleotides from formula (B'): 5'-UGUUUCACAAACAAGCUGZ₄'-3' (SEQ ID NO: 671), where Z₁' and Z₄' each independently comprise a nucleotide sequence of 0-13 nucleotide motifs. In certain embodiments, Z₁' and Z₄' each independently comprise a nucleotide sequence of 1, 2, or 3 nucleotide motifs. In certain embodiments, the Z₁' nucleotide sequence is selected from one of the following motifs: A, U, G, C, AC, UC, GC, CC, GAC, AAC, UAC, CAC, CGAC, CCGAC, ACCGAC, AACCGAC, CAACCGAC or GAAUCCAACCGAC (SEQ ID NO: 672). The Z₄' nucleotide sequence is selected from one of the following motifs: U, C, A, G, GU, GA, GC, GG, GUG, GUC, GUU, GUA, GUCG, GUCGG, GUCGGU, GUCGGUU, GUCGGUUG or GUCGGUUGGAAUUC (SEQ ID NO: 673).

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed below:

5'-UACUCAUUAGAAGAAAGGUG-3' (SEQ ID NO: 162);
 5'-UCUUAGACCAAGGAGAAACGG-3' (SEQ ID NO: 163);
 5'-UGUUUCACAAACAAGCUGGUC-3' (SEQ ID NO: 167);
 5'-UGUUUCACAAACAAGCUGGUG-3' (SEQ ID NO: 523);
 5'-UUCGGUUGGAAUUCUUUUUGC-3' (SEQ ID NO: 184);
 5'-GUUUCACAAACAAGCUGG-3' (SEQ ID NO: 653).

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, each of which comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the nucleotide sequences listed below:

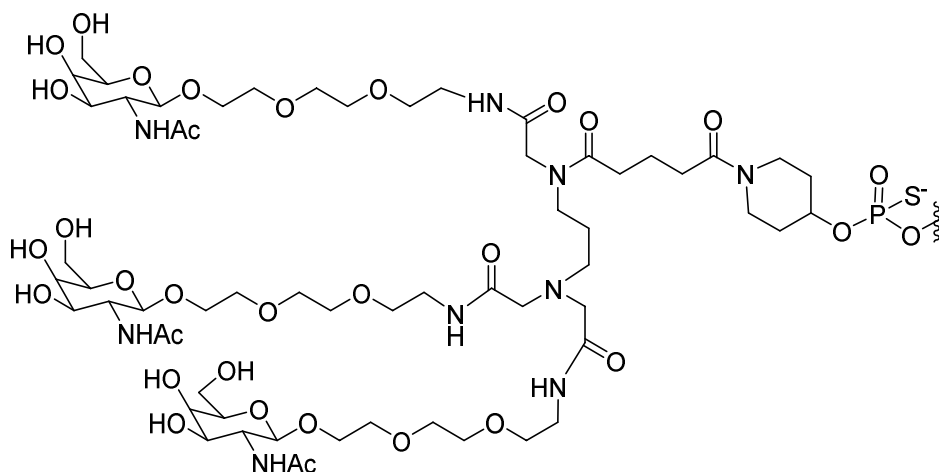
Sense strand: 5'-CACCUUUUCUUCUAAUGAGUA-3' (SEQ ID NO: 65),
 Antisense strand: 5'-UACUCAUUAGAAGAAAAGGUG-3' (SEQ ID NO: 162).

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, each of which comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the nucleotide sequences listed below:

Sense strand: 5'-CCGUUUCUCCUUGGUCUAAGA-3' (SEQ ID NO: 66),
 Antisense strand: 5'-UCUUAGACCAAGGAGAAACGG-3' (SEQ ID NO: 163).

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, each of which comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the nucleotide sequences listed below:

Sense strand: 5'-GACCAGCUUGUUUGUGAAACA-3' (SEQ ID NO: 70),
 Antisense strand: 5'-UGUUUCACAAACAAGCUGGUC-3' (SEQ ID NO: 167).



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In certain embodiments, the dsRNA agent comprises a targeting group conjugated to the 5'-end of the sense strand. In some embodiments, the dsRNA agent comprises a targeting group conjugated to the 3'-end of the sense strand. In some embodiments, the antisense strand comprises an inverted abasic residue at the 3'-end. In certain embodiments, the sense strand comprises one or two inverted abasic residues at the 3' and/or 5' ends. In some embodiments, the dsRNA agent has two blunt ends. In some embodiments, at least one strand includes a 3' overhang that is at least 1 nucleotide long. In some embodiments, at least one strand includes a 3' overhang that is at least 2 nucleotides long.

In certain embodiments, the invention relates to unlocked nucleic acid (UNA) oligomers for use in therapy. Unlocked nucleic acid (UNA) is an acyclic analogue of RNA in which the bond between the C2' and C3' atoms of the ribose ring has been severed. Incorporation of UNA has been shown to be well tolerated and in some cases even enhance the activity of siRNA gene silencing (Meghan A. et al. "Locked vs. unlocked nucleic acids (LNA vs. UNA): contrasting structures work towards common therapeutic goals". *Chem. Soc. Rev.*, 2011, **40**, 5680–5689).

UNA is a thermolabile modification, and replacing ribonucleotides with UNA will reduce base pairing strength and duplex stability. Strategic placement of UNA in the seed region of the siRNA antisense strand can reduce off-target activity in gene silencing mechanisms mediated by microRNA (miRNA). miRNA mainly recognizes target genes through base pairing between the antisense seed region (positions 2-8 from the 5' end) and the target mRNA for gene suppression. Each miRNA has the potential to regulate a large number of genes. The siRNA antisense strand loaded by the RNA-induced silencing complex (RISC) can also potentially regulate a large number of unintended genes through miRNA-mediated mechanisms. Therefore, adding thermolabile nucleotides, such as UNA, to the seed region of siRNA can reduce off-target activity (Lam JK, Chow MY, Zhang Y, Leung SW. siRNA Versus miRNA as Therapeutics for Gene Silencing. *Mol Ther Nucleic Acids*. 2015 Sep 15;4(9):e252. doi: 10.1038/mtna.2015.23. PMID: 26372022; PMCID: PMC4877448.). In particular, such RNA oligonucleotides or complexes of RNA oligonucleotides

some embodiments, the composition is formulated for subcutaneous or intravenous (IV) administration.

According to another aspect of the invention, there is provided a cell comprising any embodiment of the aforescribed dsRNA agent aspect of the invention. In some embodiments, the cell is a mammalian cell, optionally a human cell.

According to another aspect of the present invention, there is provided a method for inhibiting the expression of AGT gene in a cell, said method comprising: (i) preparing a cell comprising an effective amount of any embodiment of the aforementioned dsRNA agent or the aforementioned composition of the invention. In certain embodiments, the method further comprises: (ii) maintaining the prepared cells for a sufficient time to obtain degradation of the mRNA transcript of the AGT gene, thereby inhibiting the expression of the AGT gene in the cell. In some embodiments, the cells are in a subject and the dsRNA agent is administered subcutaneously to the subject. In some embodiments, the cells are in a subject and the dsRNA agent is administered to the subject by IV administration. In certain embodiments, the method further comprises assessing inhibition of the AGT gene after administering the dsRNA agent to the subject, wherein the means of this assessment comprises: (i) determining one or more physiological characteristics of an AGT-associated disease or condition in the subject, and (ii) comparing the determined physiological characteristic to a baseline pre-treatment physiological characteristic of the AGT-associated disease or condition and/or a control physiological characteristic of the AGT-associated disease or condition, wherein the comparison result indicates a presence or absence of inhibition of expression of the AGT gene in the subject. In some embodiments, the physiological characteristic determined is the level of AGT in the blood. In some embodiments, the physiological characteristic determined is blood pressure, which includes systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAPR). A decrease in the AGT level in the blood and/or blood pressure indicates reduction of AGT gene expression in the subject.

According to another aspect of the present invention, there is provided a method for inhibiting the expression of the AGT gene in a subject, which includes administering to the subject an effective amount of an embodiment of the foregoing dsRNA agent aspect or an embodiment of the foregoing composition. In some embodiments, the dsRNA agent is administered subcutaneously to the subject. In certain embodiments, the dsRNA agent is administered to the subject via IV administration. In some embodiments, the method further comprises: assessing inhibition of the AGT gene after administration of the dsRNA agent, wherein the means of assessment includes: (i) determining one or more physiological characteristics of an AGT-associated disease or condition in the subject; (ii) comparing the determined physiological characteristic to a baseline pre-treatment

physiological characteristic of an AGT-associated disease or condition and/or a control physiological characteristic of an AGT-associated disease or condition, wherein the comparison result is indicative of the presence or absence of inhibition of expression of the AGT gene in the subject. In some embodiments, the physiological characteristic determined is the level of AGT in the blood; in some embodiments, the physiological characteristic determined is blood pressure, which includes systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAPR). A decrease in AGT levels in the blood and/or blood pressure indicates a reduction of AGT gene expression in the subject.

According to another aspect of the present invention, there is provided a method of treating a disease or condition associated with the AGT protein, which comprises: administering to a subject an effective amount of any embodiment of the foregoing dsRNA agent aspect of the present invention or the foregoing composition of the invention, so as to inhibit AGT gene expression. In certain embodiments, the AGT-associated disorder is selected from: hypertension, high blood pressure, borderline hypertension, essential hypertension, secondary hypertension, isolated systolic or diastolic hypertension, pregnancy-related hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt's hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, unstable hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy degeneration, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiomyopathy, glomerulosclerosis, aortic stenosis, aortic aneurysm, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth retardation (IUGR), and fetal growth restriction. In some embodiments, the method further comprises administering an additional treatment regimen to the subject. In some embodiments, the additional treatment regimen includes treatment of an AGT-associated disease or condition. In certain embodiments, the additional treatment regimen comprises: administering to the subject one or more AGT antisense polynucleotides of the invention; administering to the subject a non-AGT dsRNA therapeutic agent; and effecting behavioral changes in the subject. In some embodiments, the non-AGT dsRNA therapeutic agent is one of the following: additional therapeutic agents such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, beta-blockers, vasodilators, calcium channel blockers, aldosterone antagonists, α 2-agonists, renin inhibitors, α -blockers, peripherally acting adrenergic agents, selective D1 receptor partial agonists, non-selective alpha-adrenergic antagonists, synthetic steroidal antimineralocorticoids, or combinations of any of the foregoing, and therapeutic agents for hypertension formulated as pharmaceutical combinations..

In some embodiments, the dsRNA agent is administered subcutaneously to the subject. In certain embodiments, the dsRNA agent is administered to the subject via IV administration. In some embodiments, the method further comprises determining the efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject. In some embodiments, the means for
5 determining the efficacy of a treatment in a subject comprises: (i) determining one or more physiological characteristics of an AGT-associated disease or condition in the subject; (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the AGT-associated disease or condition, wherein the comparison result indicates one or more of a presence, absence, and level of efficacy of a double-stranded ribonucleic acid
10 (dsRNA) agent administered to the subject. In some embodiments, the physiological characteristic determined is the level of AGT in the blood; in some embodiments, the physiological characteristic determined is blood pressure, which includes systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAPR). A decrease in AGT levels in the blood and/or blood pressure indicates the presence of effectiveness of the double-stranded ribonucleic acid
15 (dsRNA) agent administered to the subject.

According to another aspect of the invention, there is provided a method of reducing the level of AGT protein in a subject as compared to a baseline pre-treatment level of AGT protein in the subject, comprising administering to the subject an effective amount of any embodiment of the foregoing dsRNA agent aspect of the invention or any embodiment of the foregoing composition of
20 the invention, so as to reduce the level of AGT gene expression. In some embodiments, the dsRNA agent is administered to the subject subcutaneously or by IV.

According to another aspect of the invention, there is provided a method of altering a physiological characteristic of an AGT-associated disease or condition in a subject as compared to a baseline pre-treatment physiological characteristic of the AGT-associated disease or condition in the subject, said method comprising administering to the subject an effective amount of any
25 embodiment of the foregoing dsRNA agent aspect of the invention or any embodiment of the foregoing composition of the invention, so as to alter the physiological characteristic of the AGT-associated disease or condition in the subject. In some embodiments, the dsRNA agent is administered to the subject subcutaneously or by IV. In certain embodiments, the physiological
30 characteristic is the level of AGT in the blood; in some embodiments, the physiological characteristic determined is blood pressure, which includes systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAPR).