

**DOUBLE STRANDED RNA TARGETING ANGIOTENSINOGEN (AGT)
AND METHODS OF USE THEREOF**

RELATED APPLICATIONS

[001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 63/395,445, filed August 5, 2022, the contents of which are incorporated herein by reference in their entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[002] The Sequence Listing XML associated with this application is provided electronically in XML file format and is hereby incorporated by reference in its entirety into the specification. The name of the XML file containing the Sequence Listing XML is "SANB_009_001WO_SeqList_ST26.xml". The XML file is 655,027 bytes in size, created on August 7, 2023.

BACKGROUND

[003] Angiotensinogen (mRNA) is an α 2-globulin precursor of angiotensin, and is a hormone produced in the liver, kidney, adrenal glands, brain, heart and blood vessels, and adipose tissues to cause vasoconstriction and regulate blood pressure. Angiotensinogen is a part of the renin-angiotensin-aldosterone system (RAAS) that plays a crucial role in the regulation of blood pressure. Active renin in the plasma cleaves angiotensinogen (produced by the liver) to angiotensin I, which is then converted by circulating and locally expressed angiotensin-converting enzyme (ACE) to angiotensin II. Angiotensin II exerts its effect on the RAAS are by binding to angiotensin II type 1 receptors (AT1R), leading to arterial vasoconstriction, tubular and glomerular effects, such as enhanced Na⁺ reabsorption or modulation of glomerular filtration rate. In addition, together with other stimuli such as adrenocorticotropin, anti-diuretic hormone, catecholamines, endothelin, serotonin, and levels of Mg²⁺ and K⁺, AT1R stimulation by Angiotensin II leads to aldosterone release which, in turn, promotes Na⁺ and K⁺ excretion in the renal distal convoluted tubule.

[004] Excessive angiotensin II production due to dysregulation of RAAS and/or AT1R stimulation results in hypertension. Hypertension a major risk factor for various diseases,

disorders and conditions such as, shortened life expectancy, chronic kidney disease, stroke, myocardial infarction, heart failure, aneurysms (e.g. aortic aneurysm), peripheral artery disease, heart damage (e.g., heart enlargement or hypertrophy) and other cardiovascular related diseases, disorders and/or conditions. Accordingly, there is a need in the art for alternative therapies and combination therapies for subjects having an angiotensinogen-associated disease.

SUMMARY

[005] The present disclosure provides an isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[006] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[007] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[008] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0009] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0010] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0011] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 166 to 196; b) 394 to 480; c) 744 to 968; d) 1110 to 1331; e) 1410 to 1676; and f) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0012] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 166 to 196; b) 394 to 480; c) 744 to 968; d) 1110 to 1331; e) 1410 to 1676; and f) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0013] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 166 to 196; b) 394 to 480; c) 744 to 968; d) 1110 to 1331; e) 1410 to 1676; and f) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0014] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that substantially identical to a region comprising the sequence between any one of the nucleotide positions selected from: a) 9 to 29; b) 168 to 189; c) 784 to 808; d) 1264 to 1289; e) 1607 to 1630; f) 1814 to 1835; and g) 1843 to 1882, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0015] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising the sequence between any one of the nucleotide positions

selected from: a) 9 to 29; b) 168 to 189; c) 784 to 808; d) 1264 to 1289; e) 1607 to 1630; f) 1814 to 1835; and g) 1843 to 1882, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0016] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is identical to a region comprising the sequence between any one of the nucleotide positions selected from: a) 9 to 29; b) 168 to 189; c) 784 to 808; d) 1264 to 1289; e) 1607 to 1630; f) 1814 to 1835; and g) 1843 to 1882, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0017] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide is capable of inducing degradation of the AGT mRNA.

[0018] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand is a single stranded RNA molecule. In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand is a single stranded RNA molecule. In some embodiments of the isolated oligonucleotide of the present disclosure, both the sense strand and the antisense strand are single stranded RNA molecules.

[0019] In some embodiments of the isolated oligonucleotide of the present disclosure, the single stranded RNA molecule of the sense strand comprises a 3' overhang. In some embodiments, in the single stranded RNA molecule of the sense strand, the 3' overhang comprise at least one nucleotide. In some embodiments, in the single stranded RNA molecule of the sense strand, the 3' overhang comprise two nucleotides.

[0020] In some embodiments of the isolated oligonucleotide of the present disclosure, the single stranded RNA molecule of the antisense strand comprises a 3' overhang. In some embodiments, in the single stranded RNA molecule of the antisense strand, the 3' overhang comprise at least one nucleotide. In some embodiments, in the single stranded RNA molecule of the antisense strand, the 3' overhang comprise two nucleotides.

[0021] In some embodiments of the isolated oligonucleotide of the present disclosure, the 3' overhang comprises any one of thymidine-thymidine (dTdT), Adenine-Adenine (AA), Cysteine-Cysteine (CC), Guanine-Guanine (GG) or Uracil-Uracil (UU).

[0022] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises an RNA sequence of at least 20 nucleotides in length. In some embodiments of

the isolated oligonucleotide of the present disclosure, the sense strand comprises an RNA sequence of 20 nucleotides in length.

[0023] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises an RNA sequence of at least 22 nucleotides in length. In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises an RNA sequence of 22 nucleotides in length.

[0024] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region is between 19 and 21 nucleotides in length. In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region is 20 nucleotides in length.

[0025] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand and a sense strand, according to any one of the pairs of antisense strand and sense strand sequences in Tables 1-4, as described in the detailed description.

[0026] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-56.

[0027] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57-111.

[0028] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-56; and the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57-111, wherein the antisense strand and the sense strand sequences have sufficient complementarity to allow formation of a double stranded region between the antisense and the sense strand.

[0029] In some embodiments, the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a sequence is identical to a region comprising the sequence between any one of the nucleotide positions selected from a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to

50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%), at a dose of 0.02 nM.

[0030] In some embodiments, the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a sequence is identical to a region comprising the sequence between any one of the nucleotide positions selected from a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 99%, 99% to 100%), at a dose of 0.02 nM.

[0031] In some embodiments, the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a sequence is identical to a region comprising the sequence between any one of the nucleotide positions selected from a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%), at a dose of 0.1 nM.

[0032] In some embodiments, the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a sequence is identical to a region comprising the sequence between any one of the nucleotide positions selected from a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 99%, 99% to 100%), at a dose of 0.1 nM.

[0033] The present disclosure also provides an isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is

substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[0034] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%) at a dose of 0.1 nM.

[0035] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071;

and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 100%) at a dose of 0.1 nM.

[0036] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%) at a dose of 0.02 nM.

[0037] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., 50% to

55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 100%) at a dose of 0.02 nM.

[0038] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2, 3, 16, 30, 35, 37, 40, 41, 44 or 55.

[0039] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57, 58, 71, 85, 90, 92, 95, 96, 99 or 110.

[0040] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2, 3, 16, 30, 35, 37, 40, 41, 44 or 55; and the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57, 58, 71, 85, 90, 92, 95, 96, 99 or 110, wherein the antisense strand and the sense strand sequences have sufficient complementarity to allow formation of a double stranded region between the antisense and the sense strand.

[0041] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUUGA 3').

[0042] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3').

[0043] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3').

[0044] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUUGCCCUUUUCAA 3').

[0045] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3').

[0046] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAAUUGGGUUUUA 3').

[0047] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUAAAAUA 3').

[0048] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUAAAAGUAUA 3').

[0049] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUAAAAGUAUAA 3').

[0050] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3').

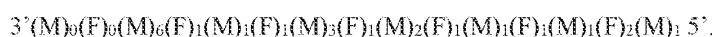
[0051] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise one or more modified nucleotide(s).

[0052] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a mono methyl protected phosphate mimic (5'-MeEP).

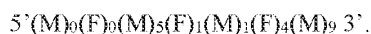
[0053] In some embodiments of the isolated oligonucleotide of the present disclosure, in the sense strand or the antisense strand or both, a terminal or internal nucleotide is linked to a targeting ligand.

[0054] In some embodiments of the isolated oligonucleotide of the present disclosure, the targeting ligand comprises at least one GalNAc G1b moiety.

[0055] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula:



[0056] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula:



[0057] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises any one of: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 447 (5'

[MeEPmUs][fCs][fA][mA][fA][mA][fA][mA][mA][fA][mU][mG][mC][fU][mG][fU][mU][mC][mA][mGs][mCs][mA] 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 448 (5'

[MeEPmUs][fCs][fA][mC][fU][mU][fU][mU][mU][fU][mG][mU][mU][fU][mC][fA][mC][mA][mA][mAs][mCs][mA] 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 449 (5'

[MeEPmUs][fGs][fG][mA][fA][mC][fA][mC][mU][fU][mU][mU][fU][mG][fU][mU][mU][mC][mAs][mCs][mA] 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 450 (5'

[MeEPmUs][fUs][fU][mG][fA][mA][fA][mA][mG][fG][mG][mA][mA][fC][mA][fC][mU][mU][mU][mUs][mUs][mU] 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 451 (5'

[MeEPmUs][fCs][fA][mA][fU][mU][fU][mU][mU][fG][mU][mU][mC][fU][mC][fA][mA][mC][mU][mUs][mGs][mA] 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 452 (5'

[MeEPmUs][fAs][fA][mA][fA][mC][fC][mC][mA][fA][mU][mU][mU][fU][mU][fG][mU][mU][mC][mUs][mCs][mA] 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 453 (5'

[MeEPmUs][fAs][fU][mU][fU][mU][fA][mA][fA][mC][mC][fA][mA][fU][mU][mU][mU][mUs][mGs][mU] 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 454 (5'

[MeEPmUs][fAs][fU][mA][fC][mU][fU][mU][mA][fA][mU][mU][mU][fU][mA][fA][mA][mA][mC][mCs][mCs][mA] 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 455 (5'

[MeEPmUs][fUs][fA][mU][fA][mC][fU][mU][mU][fA][mA][mU][mU][fU][mU][fA][mA][mA][mA][mCs][mCs][mC] 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 456 (5'

[mUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG] 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 457 (5'

[EPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG] 3'); or xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 458 (5'

[MeEPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, "MeEP" is a mono methyl protected phosphate mimic.

[0058] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises any one of: i) a sense strand of nucleic acid sequence according to SEQ ID NO: 460 (5'

[mCs][mUs][mG][mA][mA][fC][mA][fG][fC][fA][fU][mU][mU][mU][mU][mU][mU][mUs][mGs][mA][G1b][G1b][G1b] 3'); ii) a sense strand of nucleic acid sequence according to SEQ ID NO: 461 (5'

[mUs][mUs][mU][mG][mU][fG][mA][fA][fA][fC][fA][mA][mA][mA][mA][mA][mG][mUs][mGs][mA][G1b][G1b][G1b] 3'); iii) a sense strand of nucleic acid sequence according to SEQ ID NO: 462 (5'

[mUs][mGs][mA][mA][mA][fC][mA][fA][fA][fA][fA][mA][mG][mU][mG][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3'); iv) a sense strand of nucleic acid sequence according to SEQ ID NO: 463 (5'

[mAs][mAs][mA][mA][mG][fU][mG][fU][fU][fC][fC][mC][mU][mU][mU][mU][mC][mAs][mAs][mA][G1b][G1b][G1b] 3'); v) a sense strand of nucleic acid sequence according to SEQ ID NO: 464 (5'

[mAs][mAs][mG][mU][mU][fG][mA][fG][fA][fA][fC][mA][mA][mA][mA][mU][mUs][mGs][mA][G1b][G1b][G1b] 3'); vi) a sense strand of nucleic acid sequence according to SEQ ID NO: 465 (5'

[mAs][mGs][mA][mA][mC][fA][mA][fA][fA][fA][fU][mU][mG][mG][mG][mU][mU][mUs][mUs][mA][G1b][G1b][G1b] 3'); vii) a sense strand of nucleic acid sequence according to SEQ ID NO: 466 (5'

[mAs][mAs][mA][mA][mA][fU][mU][fG][fG][fG][fU][mU][mU][mU][mA][mA][mA][mAs][mUs][mA][G1b][G1b][G1b] 3'); viii) a sense strand of nucleic acid sequence according to SEQ ID NO: 467 (5'

[mGs][mGs][mU][mU][mU][fU][mA][fA][fA][fA][fU][mU][mA][mA][mA][mG][mU][mAs][mUs][mA][G1b][G1b][G1b] 3'); ix) a sense strand of nucleic acid sequence according to SEQ ID NO: 468 (5'

[mGs][mUs][mU][mU][mU][fA][mA][fA][fA][fU][fU][mA][mA][mA][mG][mU][mA][mUs][mAs][mA][G1b][G1b][G1b] 3'); or x) a sense strand of nucleic acid sequence according to SEQ ID NO: 469 (5'

[mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fA][fU][mG][mA][mG][mA][mG][mU][mAs][mCs][mA][G1b][G1b][G1b] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, and "G1b" is a GalNac G1b moiety.

[0059] The present disclosure also provides a vector encoding an isolated oligonucleotide disclosed herein.

[0060] The present disclosure also provides a delivery system comprising an isolated oligonucleotide or vector disclosed herein.

[0061] The present disclosure also provides a pharmaceutical composition comprising an isolated oligonucleotide, vector or delivery system disclosed herein, and a pharmaceutically acceptable carrier, diluent or excipient.

[0062] The present disclosure also provides a kit comprising an isolated oligonucleotide, vector, delivery system or a pharmaceutical composition disclosed herein.

[0063] The present disclosure also provides a method of inhibiting or downregulating the expression or level of AGT in a subject in need thereof, wherein the method comprises administering to the subject an effective amount an isolated oligonucleotide, vector, delivery system or a pharmaceutical composition disclosed herein.

[0064] The present disclosure also provides a method of inhibiting or downregulating the expression or level of AGT in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of a first and at least a second oligonucleotides disclosed herein, wherein the first and at least second oligonucleotides comprise different sequences.

[0065] The present disclosure also provides a method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of an isolated oligonucleotide, vector, delivery system or a pharmaceutical composition disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0066] FIG. 1 is a graph showing the efficacy of siRNA compounds listed in Table 2, in silencing human AGT in cultured Huh-7 cells at 0.02 nM. The compounds were transfected into cells at 0.02 nM concentration. Data is presented as % of human AGT mRNA remaining relative to mock transfection when normalized to Gapdh mRNA levels (Mean, +/- SEM). Each bar represents a single compound tested.

[0067] FIG. 2 is a graph showing the efficacy of siRNA compounds listed in Table 2, in silencing human AGT in cultured Huh-7 cells at 0.1 nM. The compounds were transfected into cells at 0.1 nM concentration. Data is presented as % of human AGT mRNA remaining relative to mock transfection when normalized to Gapdh mRNA levels (Mean, +/- SEM). Each bar represents a single compound tested.

[0068] FIG. 3 is a graph showing the *in vivo* potency of compounds listed in Table 3 in mouse HDI liver at 1mg/kg at day 4 post-dosing. Data is presented as % of human AGT mRNA remaining relative to PBS when normalized to NeoR mRNA levels (Mean, +/- SEM).

[0069] FIG. 4 is a graph showing the *in vivo* dose response of compounds listed in Table 3 in mouse HDI liver at 0.3, 1, or 3 mg/kg at day 4 post-dosing. Data is presented as % of human

AGT mRNA remaining relative to PBS when normalized to NeoR mRNA levels (Mean, +/- SEM).

[0070] FIGS. 5A-5B are graphs showing *in vivo* potency evaluations of compounds listed in Table 4 in *Macaca fascicularis* after a 3mg/kg single s.c. dosing. Cyno AGT mRNA remaining in liver (FIG. 5A) and serum AGT protein remaining (FIG. 5B) were measured over time. Data was normalized to pre-dose mRNA or protein levels of each animal.

DETAILED DESCRIPTION

[0071] The present disclosure provides isolated oligonucleotides (oligonucleotide(s)) that form a double stranded region, preferably small interfering RNAs (siRNAs), that can decrease AGT mRNA expression, in turn leading to a decrease in the degree of AGT protein expression in target cells. The oligonucleotides disclosed herein can have therapeutic application in regulating the expression of AGT, for treatment of diseases, including but not limited to cardiovascular disease (CVD), hypertension, atherosclerosis etc.

[0072] The present disclosure has identified specific regions within the AGT mRNA, that provide targets for binding double stranded oligonucleotides, e.g., siRNA, leading to reduction in level of expression of the AGT mRNA.

[0073] The AGT mRNA sequence described herein, is an mRNA sequence of AGT according to accession no. NM_001384479.1:

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1  gaagaagctg cgttgttctt ggttactaca gcagaagggt atgcggaagc gagcacccca
61  gtctgagatg gctcctgcgc gtgtgagcct gagggccacc atcctctgcc tccctggcctg
121 ggcctggcctg gctgcagggtg accgggtgta catacaccac ttccacctcg tcatccacaa
181 tgagagtacc tgtgagcagc tggcaaaggc caatgcgggg aagcccaaag accccacott
241 catacctgct ccaattcagg ccaagacatc ccctgtggat gaaaaggccc tacaggacca
301 gctggtgcta gtcgctgcaa aacttgacac cgaagacaag ttgagggcgc caatggctgg
361 gatgctggcc aacttccttg gcttcogtat atatggcatg cacagtgagc tatggggcgt
421 ggtccatggg gccaccgtcc tctcccaaac ggcctgtctt ggcaccctgg cctctctcta
481 tctggggagc ttggaccaca cagctgacag gctacaggca atcctgggtg ttccttggaa
541 ggacaagaac tgcacctccc ggctggatgc gcacaaggto ctgtctgccc tgcaggctgt
601 acagggcctg ctagtggccc agggcagggc tgatagccag gccagctgc tgotgtccac
661 ggtggtgggc gtgttcacag ccccaggcct gcacctgaag cagcgtttg tgcaggcct
721 ggctctctat acccctgtgg tctcccaacg ctctctggac ttcacagaac tggatgttgc
781 tgctgagaag attgacaggt tcatgcagga tgtgacagga tggaagactg gctgctcct

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841 gatggggagcc agtgtggaca gcacccctggc ttccaacacc tacgtccact tccaagggaa
901 gatgaagggc ttctccctgc tggccgagcc ccaggagtcc tgggtggaca acagcacctc
961 agtgtctgtt cccatgctct ctggcatggg caccctccag cactggagtg acatccagga
1021 caacttctcg gtgactcaag tgcctttcac tgagagcgcc tgcctgctgc tgatccagcc
1081 tcactatgcc tctgacctgg acaaggtgga gggctcact ttccagcaaa actccctcaa
1141 ctggatgaag aaactatctc ccggaccat ccacctgacc atgccccaac tgggtgtgca
1201 aggatcttat gacctgcagg acctgctcgc ccagggtgag ctgcccgcga ttctgcacac
1261 cgagctgaac ctgcaaaaat tgagcaatga ccgcatcagg gtgggggagg tgctgaacag
1321 catttttttt gagcttgaag cggatgagag agagcccaca gagtctaccc aacagcttaa
1381 caagcctgag gtcttggagg tgacctgaa ccgcccattc ctgtttgtct tgtatgatca
1441 aagcgcacct gccctgcact tcttgggccc cgtggccaac ccgtgagca cagcatgagg
1501 ccagggcccc agaacacagt gcttggcaag gcctctgccc ctggccctttg aggcaaaaggc
1561 cagcagcaga taacaacccc ggacaaatca gcatgtgtc acccccagtc tcccaccttt
1621 tcttotaatg agtcgacttt gagctggaaa gcagccgttt ctcttggtc taagtgtgct
1681 gcatggagtg agcagtagaa gccctgcagc gcacaaatgc acctccagc ttgtgggtt
1741 tatttttaga aatgggggtg gggaggcaag aaccagtgt tagcgcggga ctactgttcc
1801 aaaaagaatt ccaaccgacc agcttgtttg tgaaacaaaa aagtgttccc ttttcaagtt
1861 gagaacaaaa attgggtttt aaaattaaag tatacatttt tgcattgctc tcggtttgta
1921 tttagtgtct tgaatgtaag aacatgacct ccgtgtagtg tctgtaatac cttagttttt
1981 tccacagatg cttgtgattt ttgaacaata cgtgaaagat gcaagcaact gaatttctgt
2041 ttgaatgcgg aaccatagct gggtatttct cccttgtgtt agtaataaac gtcttgcac
2101 aataagctc caaaaa (SEQ ID NO: 1) .

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[0074] The present disclosure provides an isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[0075] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0076] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0077] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0078] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0079] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0080] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: (a) 1829 to 1849 and (b) 1837 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0081] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: (a) 1829 to 1849 and (b) 1837 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0082] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: (a) 1829 to 1849 and (b) 1837 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0083] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 166 to 196; b) 394 to 480; c) 744 to 968; d) 1110 to 1331; e) 1410 to 1676; and f) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0084] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 166 to 196; b) 394 to 480; c) 744 to 968; d) 1110 to 1331; e) 1410 to 1676; and f) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0085] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 166 to 196; b) 394 to 480; c) 744 to 968; d) 1110 to 1331; e) 1410 to 1676; and f) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0086] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 166 to 186; b) 176 to 196; c) 493 to 414; d) 460 to 480; e) 744 to 764; f) 778 to 798; g) 929 to 949; h) 948 to 968; i) 1110 to 1130; j) 1134 to 1154; k) 1306 to 1326; l) 1311 to 1331; m) 1410 to 1430; n) 1605 to 1629; o) 1643 to 1676; p) 1726 to 1752; q) 1785 to 1805; r) 1816 to 1894 from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0087] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 166 to 186; b) 176 to 196; c) 493 to 414; d) 460 to 480; e) 744 to 764; f) 778 to 798; g) 929 to 949; h) 948 to 968; i) 1110 to 1130; j) 1134 to 1154; k) 1306 to 1326; l) 1311 to 1331; m) 1410 to 1430; n) 1605 to 1629; o) 1643 to 1676; p) 1726 to 1752; q) 1785 to 1805; r) 1816 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0088] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the

nucleotide positions selected from: a) 166 to 186; b) 176 to 196; c) 493 to 414; d) 460 to 480; e) 744 to 764; f) 778 to 798; g) 929 to 949; h) 948 to 968; i) 1110 to 1130; j) 1134 to 1154; k) 1306 to 1326; l) 1311 to 1331; m) 1410 to 1430; n) 1605 to 1629; o) 1643 to 1676; p) 1726 to 1752; q) 1785 to 1805; r) 1816 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0089] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that substantially identical to a region comprising the sequence between any one of the nucleotide positions selected from: a) 9 to 29; b) 168 to 189; c) 784 to 808; d) 1264 to 1289; e) 1607 to 1630; f) 1814 to 1835; and g) 1843 to 1882, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0090] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising the sequence between any one of the nucleotide positions selected from: a) 9 to 29; b) 168 to 189; c) 784 to 808; d) 1264 to 1289; e) 1607 to 1630; f) 1814 to 1835; and g) 1843 to 1882, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0091] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is identical to a region comprising the sequence between any one of the nucleotide positions selected from a) 9 to 29; b) 168 to 189; c) 784 to 808; d) 1264 to 1289; e) 1607 to 1630; f) 1814 to 1835; and g) 1843 to 1882, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

[0092] The AGT mRNA sequence according to SEQ ID NO: 1, as described herein, is any heterologous mRNA sequence with sufficient identity to an AGT according to Accession No. NM_001384479.1, as described herein, that allows binding to the antisense strand of the oligonucleotides of the present disclosure.

[0093] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide is capable of inducing degradation of the AGT mRNA.

[0094] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand is a single stranded RNA molecule. In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand is a single stranded RNA molecule. In some

embodiments of the isolated oligonucleotide of the present disclosure, both the sense strand and the antisense strand are single stranded RNA molecules.

[0095] In some embodiments, the isolated oligonucleotide of the present disclosure is a small interfering RNA (siRNA). Accordingly, the disclosure provides siRNAs, wherein the siRNA comprises a sense region and antisense region complementary to the sense region that together form an RNA duplex, and wherein the sense region comprises a sequence at least 70% to 100% identical to a AGT mRNA sequence.

Definitions

[0096] “RNAi” or “RNA interference” refers to the process of sequence-specific post-transcriptional gene silencing, mediated by double-stranded RNA (dsRNA). Duplex RNA siRNA (small interfering RNA), miRNA (micro RNA), shRNA (short hairpin RNA), ddRNA (DNA-directed RNA), piRNA (Piwi-interacting RNA), or rasiRNA (repeat associated siRNA) and modified forms thereof are all capable of mediating RNA interference. These dsRNA molecules may be commercially available or may be designed and prepared based on known sequence information, etc. The antisense strand of these molecules can include RNA, DNA, PNA, or a combination thereof. These DNA/RNA chimera polynucleotide includes, but is not limited to, a double-strand polynucleotide composed of DNA and RNA that inhibits the expression of a target gene. These dsRNA molecules can also include one or more modified nucleotides, as described herein, which can be incorporated on either strand.

[0097] In the RNAi gene silencing or knockdown process, dsRNA comprising a first (antisense) strand that is complementary to a portion of a target gene and a second (sense) strand that is fully or partially complementary to the first antisense strand is introduced into an organism. After introduction into the organism, the target gene-specific dsRNA is processed into relatively small fragments (siRNAs) and can subsequently become distributed throughout the organism, decrease messenger RNA of target gene, leading to a phenotype that may come to closely resemble the phenotype arising from a complete or partial deletion of the target gene.

[0098] Certain dsRNAs in cells can undergo the action of Dicer enzyme, a ribonuclease III enzyme. Dicer can process the dsRNA into shorter pieces of dsRNA, i.e. siRNAs. RNAi also involves an endonuclease complex known as the RNA induced silencing complex (RISC). Following cleavage by Dicer, siRNAs enter the RISC complex and direct cleavage of a single stranded RNA target having a sequence complementary to the antisense strand of the siRNA

duplex. The other strand of the siRNA is the passenger strand. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex. siRNAs can thus down regulate or knock down gene expression by mediating RNA interference in a sequence-specific manner.

[0099] As used herein, “target gene” or “target sequence” refers to a gene or gene sequence whose corresponding RNA is targeted for degradation through the RNAi pathway using dsRNAs or siRNAs as described herein. To target a gene, for example using an siRNA, the siRNA comprises an antisense region complementary to, or substantially complementary to, at least a portion of the target gene or sequence, and sense strand complementary to the antisense strand. Once introduced into a cell, the siRNA directs the RISC complex to cleave an RNA comprising a target sequence, thereby degrading the RNA.

[0100] As used herein, “oligonucleotide”, “nucleic acid,” “nucleotide sequence,” and “polynucleotide” are used interchangeably and encompass both RNA and DNA, including cDNA, genomic DNA, mRNA, synthetic (e.g., chemically synthesized) DNA or RNA and chimeras of RNA and DNA. The term polynucleotide, nucleotide sequence, or nucleic acid refers to a chain of nucleotides without regard to length of the chain. The nucleic acid can be double-stranded or single-stranded. Where single-stranded, the nucleic acid can be a sense strand or an antisense strand. The nucleic acid can be synthesized using oligonucleotide analogs or derivatives (e.g., inosine or phosphorothioate nucleotides). Such oligonucleotides can be used, for example, to prepare nucleic acids that have altered base-pairing abilities or increased resistance to nucleases. The present disclosure further provides a nucleic acid that is the complement (which can be either a full complement or a partial complement) of a nucleic acid, nucleotide sequence, or polynucleotide of this disclosure. When dsRNA is produced synthetically, less common bases, such as inosine, 5-methylcytosine, 6-methyladenine, hypoxanthine and others can also be used for antisense, dsRNA, and ribozyme pairing. Other modifications, such as modification to the phosphodiester backbone, or the 2'-fluoro, the 2'-hydroxy or 2'-O-methyl in the ribose sugar group of the RNA can also be made.

[0101] The term “isolated” can refer to a nucleic acid, nucleotide sequence or polypeptide that is substantially free of cellular material, viral material, and/or culture medium (when produced by recombinant DNA techniques), or chemical precursors or other chemicals (when chemically synthesized). Moreover, an “isolated fragment” is a fragment of a nucleic acid, nucleotide

sequence or polypeptide that is not naturally occurring as a fragment and would not be found in the natural state. "Isolated" does not mean that the preparation is technically pure (homogeneous), but it is sufficiently pure to provide the polypeptide or nucleic acid in a form in which it can be used for the intended purpose.

[00102] The term "region" or "fragment" is used interchangeably and as applied to an oligonucleotide.

[00103] The AGT mRNA sequence, as described herein, will be understood to mean a full length AGT mRNA nucleotide sequence, unless indicated otherwise. In some embodiments, the AGT mRNA sequence can be a nucleotide sequence of reduced length relative to a reference nucleic acid or a nucleotide sequence of the AGT mRNA sequence comprising, consisting essentially of, and/or consisting of a nucleotide sequence of contiguous nucleotides identical or almost identical (e.g., 60%, 70%, 80%, 90%, 92%, 95%, 98% or 99% identical) to the reference nucleic acid or nucleotide sequence. Such a nucleic acid fragment according to the disclosure may be, where appropriate, included in a larger polynucleotide of which it is a constituent. In some embodiments, such fragments can comprise, consist essentially of, and/or consist of oligonucleotides having a length of at least about 8, 10, 12, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 150, 200, or more consecutive nucleotides of a nucleic acid or nucleotide sequence according to the disclosure.

[00104] As used herein, "complementary" polynucleotides are those that are capable of base pairing according to the standard Watson-Crick complementarity rules. Specifically, purines will base pair with pyrimidines to form a combination of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. For example, the sequence "A-G-T" binds to the complementary sequence "T-C-A." It is understood that two polynucleotides may hybridize to each other even if they are not completely complementary to each other, provided that each has at least one region that is substantially complementary to the other.

[00105] As used herein, the term "substantially complementary" is at least 90% (e.g., 91, 92, 93, 94, 95, 96, 97, 98 or 99%) complementary to the sense strand that is substantially identical to the nucleotide sequence within the defined regions in SEQ ID NO: 1. As used herein, the term "substantially complementary" means that two nucleic acid sequences are complementary at least at about 90%, 95% or 99% of their nucleotides.

[00106] In some embodiments, the two nucleic acid sequences can be complementary at least at 90%, 95%, 96%, 97%, 98%, 99% or more of their nucleotides. In some embodiments, the two nucleic acid sequences can be between 90% to 95% complementary, between 70% to 100% complementary, between 95% and 96% complementary, between 90% and 100% complementary, between 96% to 97% complementary, between 60% to 80% complementary, between 97% and 98% complementary, between 70% and 90% complementary, between 98% and 99% complementary, between 80% and 100% complementary, or between 99% and 100% complementary.

[00107] The term “substantially complementary” can also mean that two nucleic acid sequences, sense strand and antisense strand have sufficient complementarity that allows binding between the sense strand and antisense strand to form a double stranded region comprising of between 19-25 nucleotides in length. The term “substantially complementary” can also mean that two nucleic acid sequences can hybridize under high stringency conditions, and such conditions are well known in the art.

[00108] As used herein, the term “substantially identical” or “sufficient identity” used interchangeably herein, is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% (e.g., between 70% to 80%, 80% to 90% or 90% to 95% or 95% to 99% or 99% to 100%) identical to the nucleotide sequence within the defined regions in SEQ ID NO: 1.

[00109] As used herein, the term “identity” means that sequences are compared with one another as follows. In order to determine the percentage identity of two nucleic acid sequences, the sequences can first be aligned with respect to one another in order subsequently to make a comparison of these sequences possible. For this e.g., gaps can be inserted into the sequence of the first nucleic acid sequence and the nucleotides can be compared with the corresponding position of the second nucleic acid sequence. If a position in the first nucleic acid sequence is occupied by the same nucleotide as is the case at a position in the second sequence, the two sequences are identical at this position. The percentage identity between two sequences is a function of the number of identical positions divided by the number of all the positions compared in the sequences investigated.

[00110] A “percent identity” or “% identity” as used interchangeably herein, for aligned segments of a test sequence and a reference sequence is the percent of identical components which are shared by the two aligned sequences divided by the total number of components in

reference sequence segment, i.e., the entire reference sequence or a smaller defined part of the reference sequence.

[00111] “Nucleotide sequence” and “nucleic acid sequence” are used interchangeably herein, unless indicated otherwise.

[00112] The percentage identity of two sequences can be determined with the aid of a mathematical algorithm. A preferred, but not limiting, example of a mathematical algorithm which can be used for comparison of two sequences is the algorithm of Karlin et al. (1993), PNAS USA, 90:5873-5877. Such an algorithm is integrated in the NBLAST program, with which sequences which have a desired identity to the sequences of the present disclosure can be identified. In order to obtain a gapped alignment, as described here, the “Gapped BLAST” program can be used, as is described in Altschul et al. (1997), Nucleic Acids Res, 25:3389-3402. If BLAST and Gapped BLAST programs are used, the preset parameters of the particular program (e.g. NBLAST) can be used. The sequences can be aligned further using version 9 of GAP (global alignment program) of the “Genetic Computing Group” using the preset (BLOSUM62) matrix (values -4 to +11) with a gap open penalty of -12 (for the first zero of a gap) and a gap extension penalty of -4 (for each additional successive zero in the gap). After the alignment, the percentage identity is calculated by expressing the number of agreements as a percentage content of the nucleic acids in the sequence claimed. The methods described for determination of the percentage identity of two nucleic acid sequences can also be used correspondingly, if necessary, on the coded amino acid sequences.

[00113] Useful methods for determining sequence identity are also disclosed in Guide to HUGO Computers (Martin J. Bishop, ed., Academic Press, San Diego (1994)), and Carillo, H., and Lipton, D., (Applied Math 48:1073 (1988)). More particularly, preferred computer programs for determining sequence identity include but are not limited to the Basic Local Alignment Search Tool (BLAST) programs which are publicly available from National Center Biotechnology Information (NCBI) at the National Library of Medicine, National Institute of Health, Bethesda, Md. 20894; see BLAST Manual, Altschul et al., NCBI, NLM, NIH; (Altschul et al., J. Mol. Biol. 215:403-410 (1990)); version 2.0 or higher of BLAST programs allows the introduction of gaps (deletions and insertions) into alignments; for peptide sequence BLASTX can be used to determine sequence identity; and, for polynucleotide sequence BLASTN can be used to determine sequence identity. Percent identity can be 70% identity or greater, e.g., at least 70%

identity, at least 75% identity, at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 98% identity, at least 99% identity or 100% identity.

[00114] As used herein, "heterologous" refers to a nucleic acid sequence that either originates from another species or is from the same species or organism but is modified from either its original form or the form primarily expressed in the cell. Thus, a nucleotide sequence derived from an organism or species different from that of the cell into which the nucleotide sequence is introduced, is heterologous with respect to that cell and the cell's descendants. In addition, a heterologous nucleotide sequence includes a nucleotide sequence derived from and inserted into the same natural, original cell type, but which is present in a non-natural state, e.g., a different copy number, and/or under the control of different regulatory sequences than that found in nature.

Double Stranded RNAs Targeting AGT

[00115] The disclosure provides isolated oligonucleotides comprising a double stranded RNAs (dsRNAs) duplex region which target a AGT mRNA sequence for degradation. The double stranded RNA molecule of the disclosure may be in the form of any type of RNA interference molecule known in the art. In some embodiments, the double stranded RNA molecule is a small interfering RNA (siRNA). In other embodiments, the double stranded RNA molecule is a short hairpin RNA (shRNA) molecule. In other embodiments, the double stranded RNA molecule is a Dicer substrate that is processed in a cell to produce an siRNA. In other embodiments the double stranded RNA molecule is part of a microRNA precursor molecule.

[00116] In some embodiments, the dsRNA is a small interfering RNA (siRNA) which targets a AGT mRNA sequence for degradation. In some embodiments, the siRNA targeting AGT is packaged in a delivery system described herein (e.g., nanoparticle).

[00117] The isolated oligonucleotides of the present disclosure targeting AGT for degradation can comprise a sense strand at least 70% identical to any fragment of a AGT mRNA, for example the AGT mRNA of SEQ ID NO: 1. In some embodiments, the sense strand comprises or consists essentially of a sequence at least 70%, at least 80%, at least 90%, at least 95% or is 100% identical to any fragment of SEQ ID NO: 1. The siRNAs targeting AGT for degradation can comprise an antisense strand at least 70% identical to a sequence complementary to any fragment of a AGT mRNA, for example the AGT mRNA of SEQ ID NO: 1. In some embodiments, the antisense strand comprises or consists essentially of a sequence at least 70%,

at least 80%, at least 90%, at least 95% or is 100% identical to a sequence complementary to any fragment of SEQ ID NO: 1. In some embodiments, the sense region and antisense regions are complementary, and base pair to form an RNA duplex structure. The fragment of the AGT mRNA that has percent identity to the sense region of the siRNA, and which is complementary to the antisense region of the siRNA, can be protein coding sequence of the mRNA, an untranslated region (UTR) of the mRNA (5' UTR or 3' UTR), or both.

[00118] In some embodiments, the isolated oligonucleotides of the present disclosure comprises a sense region and antisense region complementary to the sense region that together form an RNA duplex, and the sense region comprises a sequence at least 70% identical to a AGT mRNA sequence. In some embodiments, the sense region is identical to a AGT mRNA sequence.

[00119] As used herein, the term “sense strand” or “sense region” refers to a nucleotide sequence of an siRNA molecule that is partially or fully complementary to at least a portion of a corresponding antisense strand or antisense region of the siRNA molecule. The sense strand of an isolated oligonucleotides of the present disclosure molecule can include a nucleic acid sequence having some percentage identity with a target nucleic acid sequence such as a AGT mRNA sequence. In some cases, the sense region may have 100% identity, i.e. complete identity or homology, to the target nucleic acid sequence. In other cases, there may be one or more mismatches between the sense region and the target nucleic acid sequence. For example, there may be 1, 2, 3, 4, 5, 6, or 7 mismatches between the sense region and the target nucleic acid sequence.

[00120] As used herein, the term “antisense strand” or “antisense region” refers to a nucleotide sequence of the isolated oligonucleotides of the present disclosure, that is partially or fully complementary to at least a portion of a target nucleic acid sequence. The antisense strand of an isolated oligonucleotides of the present disclosure molecule can include a nucleic acid sequence that is complementary to at least a portion of a corresponding sense strand of the isolated oligonucleotides.

[00121] In some embodiments, the sense region comprises a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 97% identical, at least 99% identical or 100% identical to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1, as disclosed herein. In some embodiments, the sense region consists essentially of a sequence that is at least 70% identical, at

least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 97% identical, at least 99% identical or 100% identical to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1, as disclosed herein. In some embodiments, the sense region comprises a sequence that is identical to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1, as disclosed herein. In some embodiments, the sense region consists essentially of a sequence that is identical to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1, as disclosed herein.

[00122] In some embodiments, the sense region of the isolated oligonucleotides of the present disclosure targeting AGT has one or more mismatches between the sequence of the isolated oligonucleotides and the AGT sequence. For example, the sequence of the sense region may have 1, 2, 3, 4 or 5 mismatches between the sequence of the sense region of the isolated oligonucleotides and the AGT sequence. In some embodiments, the AGT sequence is an AGT 3' untranslated region sequence (3' UTR). Without wishing to be bound by theory, it is thought that siRNAs targeting the 3' UTR have elevated mismatch tolerance when compared to mismatches in the isolated oligonucleotides targeting coding regions of a gene. Further, the isolated oligonucleotides RNAs may be tolerant of mismatches outside the seed region. As used herein, the "seed region" of the isolated oligonucleotides refers to base pairs 2-8 of the antisense region of the isolated oligonucleotides, i.e., the strand of the isolated oligonucleotides that is complementary to and hybridizes to the target mRNA.

[00123] In some embodiments, the antisense region comprises a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 97% identical, at least 99% identical or 100% identical to a sequence complementary to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1, as disclosed herein. In some embodiments, the antisense region consists essentially of a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 97% identical, at least 99% or 100% identical to a sequence complementary to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1. In some embodiments, the antisense region comprises a sequence that is identical to a sequence complementary to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1. In some embodiments, the sense region consists essentially of a sequence that is complementary to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1.

[00124] The antisense region of the AGT targeting isolated oligonucleotide of the present disclosure is complementary to the sense region. In some embodiments, the sense region and the antisense region are fully complementary (no mismatches). In some embodiments the antisense region is partially complementary to the sense region, i.e., there are 1, 2, 3, 4 or 5 mismatches between the sense region and the antisense region.

[00125] In general, isolated oligonucleotide of the present disclosure comprise an RNA duplex that is about 16 to about 25 nucleotides in length. In some embodiments, the RNA duplex is between about 17 and about 24 nucleotides in length, between about 18 and about 23 nucleotides in length, or between about 19 and about 22 nucleotides in length. In some embodiments, the RNA duplex is 19 nucleotides in length. In some embodiments, the RNA duplex is 20 nucleotides in length.

[00126] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand is a single stranded RNA molecule. In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand is a single stranded RNA molecule. In some embodiments of the isolated oligonucleotide of the present disclosure, both the sense strand and the antisense strand are single stranded RNA molecules. In some embodiments of the isolated oligonucleotide of the present disclosure is an siRNA targeting AGT, that comprises two different single stranded RNAs, the first comprising the sense region and the second comprising the antisense region, which hybridize to form an RNA duplex.

[00127] In some embodiments, the isolated oligonucleotide of the present disclosure, can have one or more overhangs from the duplex region. The overhangs, which are non-base-paired, single strand regions, can be from one to eight nucleotides in length, or longer. An overhang can be a 3' overhang, wherein the 3'-end of a strand has a single strand region of from one to eight nucleotides. An overhang can be a 5' overhang, wherein the 5'-end of a strand has a single strand region of from one to eight nucleotides.

[00128] The overhangs of the isolated oligonucleotide of the present disclosure can be the same length, or can be different lengths.

[00129] In some embodiments of the isolated oligonucleotide of the present disclosure, the single stranded RNA molecule of the sense strand comprises a 3' overhang. In some embodiments, in the single stranded RNA molecule of the sense strand, the 3' overhang

comprise at least one nucleotide. In some embodiments, in the single stranded RNA molecule of the sense strand, the 3' overhang comprise two nucleotides.

[00130] In some embodiments of the isolated oligonucleotide of the present disclosure, the single stranded RNA molecule of the antisense strand comprises a 3' overhang. In some embodiments, in the single stranded RNA molecule of the antisense strand, the 3' overhang comprise at least one nucleotide. In some embodiments, in the single stranded RNA molecule of the antisense strand, the 3' overhang comprise two nucleotides.

[00131] In additional embodiments, both ends of isolated oligonucleotide of the present disclosure have an overhang, for example, a 3' dinucleotide overhang on each end. The overhangs at the 5'- and 3'-ends may be of different lengths, or be the same length.

[00132] An overhang of an isolated oligonucleotide of the present disclosure can contain one or more deoxyribonucleotides, one or more ribonucleotides, or a combination of deoxyribonucleotides and ribonucleotides. In some embodiments, one, or both, of the overhang nucleotides of an siRNA may be 2'-deoxyribonucleotides.

[00133] In some embodiments, the first single stranded RNA molecule comprises a first 3' overhang. In some embodiments, the second single stranded RNA molecule comprises a second 3' overhang. In some embodiments, the first and second 3' overhangs comprise a dinucleotide.

[00134] In some embodiments of the isolated oligonucleotide of the present disclosure, the 3' overhang comprises any one of thymidine-thymidine (dTdT), Adenine-Adenine (AA), Cysteine-Cysteine (CC), Guanine-Guanine (GG) or Uracil-Uracil (UU). In some embodiments, the isolated oligonucleotide of the present disclosure, the 3' overhang comprises a thymidine-thymidine (dTdT) or a Uracil-Uracil (UU) overhang. In some embodiment, the 3' overhang comprises a Uracil-Uracil (UU) overhang. Without wishing to be bound by theory, it is thought that 3' overhangs, such as dinucleotide overhangs, enhance siRNA mediated mRNA degradation by enhancing siRNA-RISC complex formation, and/or rate of cleavage of the target mRNA by the siRNA-RISC complex.

[00135] In some embodiments, the isolated oligonucleotide of the present disclosure can have one or more blunt ends, in which the duplex region ends with no overhang, and the strands are base paired to the end of the duplex region. In some embodiments, the isolated oligonucleotide of the present disclosure can have one or more blunt ends, or can have one or more overhangs, or can have a combination of a blunt end and an overhang end. For example, the 5' end of the

siRNA can be blunt and the 3' end of the same isolated oligonucleotide comprise an overhang, or *vice versa*.

[00136] In some embodiments, both ends of the isolated oligonucleotide of the present disclosure are blunt ends.

[00137] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand and a sense strand, according to any one of the pairs of antisense strand and sense strand sequences in Tables 1-4, as described below.

Table 1: Exemplary Pairs of Antisense and Sense Strand Sequences of the Disclosure

SEQ ID NO:	Antisense strand (guide) sequence	Guide start position	Guide end position	SEQ ID NO:	Sense strand (passenger) sequence	Passenger start position	Passenger end position
2	UGGAACACUUUUUGUUUCACA	1829	1849	57	UGAAACAAAAAGUUGUCCA	1831	1849
3	UUUGAAAAGGGAAACACUUUUU	1837	1857	58	AAAAGUUUCCCUUUUCAA	1839	1857
4	UCUCUCAUUGUGGAGACGAGG	166	186	59	UCGUCAUCCACAAGAGAGA	168	186
5	UCUCACAGGUACUCUAUUGUG	176	196	60	CAAUGAGAGUACCUUGAGA	178	196
6	UCAUAGCUCACUGUGCAUGCCA	394	414	61	GCAUGCACAGUGAGCUAUGA	396	414
7	UUAGAGAGAGGCCAGGGUGCCA	460	480	62	GCACCCUGGCCUCUCUCUAA	462	480
8	UUGAAGUCCAGAGAGCGUGGGA	744	764	63	CCACGUCUCUGGACUCAA	746	764
9	UCUGUCAAUUCUCAGCAGCA	778	798	64	CUGCUGAGAAGAUUGACAGA	780	798
10	UGUCCACCAGAACUCCUGGGG	929	949	65	CCAGGAGUUCUGGGUGGACA	931	949
11	UCAGACACUGAGGUGCUGUUGU	948	968	66	AACAGCACCUACAGUGUCUGA	950	968
12	UUUUGCUGGAAAGUGAGACCCU	1110	1130	67	GGUUCACUUUCCAGCAAAA	1112	1130
13	UGUUUCUUAUCCAGUUGAGGG	1134	1154	68	CUCAACUGGAGUAGAAACA	1818	1836
14	UAAAAUGCUGUUCAGCACCUCC	1306	1326	69	AGGUGCUGAACAGCAUUUUA	1311	1329
15	UAAAAAAUUGCUGUUCAGCACC	1309	1329	70	UGCUGAACAGCAUUUUUUA	1824	1842
16	UAAAAAAAUUGCUGUUCAGCA	1311	1331	71	CUGAACAGCAUUUUUUUGA	1827	1845
17	UCAGCAACAGGAUUGGGCGGU	1410	1430	72	CGCCCAUUCUGUUUGCUGA	1412	1430
18	UGAAGAAAAGGUGGGAGACUGG	1605	1625	73	AGUCUCCACCCUUUUCUUA	1656	1674
19	UUUAGAAGAAAAGGUGGGAGAC	1608	1628	74	CUCCCAUUCUUUCUUA	1610	1628
20	UAUAGAAGAAAAGGUGGGAGA	1609	1629	75	UCCCAUUCUUUCUUA	1266	1284
21	UGAGAAACGGCUGCUUCCAGC	1643	1663	76	UGGAAAGCAGCCGUUUCUA	1271	1289
22	UUUAGACCAAGGAGAAACGGCU	1653	1673	77	CCGUUUCUCCUUGGUCUAAA	11	29
23	UCUUAGACCAAGGAGAAACGGC	1654	1674	78	CGUUUCUCCUUGGUCUAGA	170	188
24	UCACUUAGACCAAGGAGAAACG	1656	1676	79	UUUCUCCUUGGUCUAGA	1854	1872
25	UAAAAUAAACCCAGCAACUGG	1726	1746	80	AGUUUGCUGGGUUUAUUUA	1840	1858
26	UUUCUUAUUUUAAACCCAGCA	1732	1752	81	CUGGGUUUAUUUAAGAGAAA	1849	1867
27	UUUUUUGGAACAGUAGUCCCGC	1785	1805	82	GGGACUACUUGUCCAAAAA	1855	1873
28	UGUUUCACAAACAGCUGGUCG	1816	1836	83	ACCAGCUUGUUUGUGAACA	1856	1874

[illegible]

[00138] In some embodiments, the sense region comprises a sequence selected from any one of the group of sense strand/passenger strand sequences listed in Tables 1-4. In some embodiments, the antisense region comprises a sequence selected from any one of the group of antisense strand/guide strand sequences listed in Tables 1-4. In some embodiments, the sense and antisense regions comprise complementary sequences selected from the group listed in Tables 1-4.

[00139] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-56.

[00140] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57-111.

[00141] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-56; and the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57-111, wherein the antisense strand and the sense strand sequences have sufficient complementarity to allow formation of a double stranded region between the antisense and the sense strand.

[00142] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3'); or ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCUUUUCAA 3').

[00143] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 166 to 196; b) 394 to 480; c) 744 to 968; d) 1110 to 1331; e) 1410 to 1676; and f) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCUCUCAUUGUGGAUGACGAGG

3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' UCGUCAUCCACAAUGAGAGA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UCUCACAGGUACUCUCAUUGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' CAAUGAGAGUACCUGUGAGA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UCAUAGCUCACUGUGCAUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' GCAUGCACAGUGAGCUAUGA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUAGAGAGAGGCCAGGGUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' GCACCCUGGCCUCUCUCUAA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUGAAGUCCAGAGAGCGUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' CCACGCUCUCUGGACUUCAA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UCUGUCAAUCUUCUCAGCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' CUGCUGAGAAGAUUGACAGA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UGUCCACCCAGAACUCCUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' CCAGGAGUUCUGGGUGGACA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UCAGACACUGAGGUGCUGUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AACAGCACCUCAGUGUCUGA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUUUGCUGGAAAGUGAGACCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' GGUCUCACUUUCCAGCAAAA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UGUUUCUUAUCCAGUUGAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' CUCAACUGGAUGAAGAAACA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAAUGCUGUUCAGCACCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' AGGUGCUGAACAGCAUUUUA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAUGCUGUUCAGCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUA

3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUUGA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UCAGCAAACAGGAAUGGGCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' CGCCCAUUCUGUUUGCUGA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAAGAAAAGGUGGGAGACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' AGUCUCCCACCUUUUCUUCA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UUUAGAAGAAAAGGUGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' CUCCCACCUUUUCUUCUAAA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUAGAAGAAAAGGUGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UCCCACCUUUUCUUCUAAUA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UGAGAAACGGCUGCUUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAAAGCAGCCGUUUCUCA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUUAGACCAAGGAGAAACGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' CCGUUUCUCCUUGGUCUAAA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UCUUAGACCAAGGAGAAACGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' CGUUUCUCCUUGGUCUAAGA 3'); xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UCACUUAGACCAAGGAGAAACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UUUCUCCUUGGUCUAAGUGA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UAAAAUAAACCCAGCAAACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' AGUUUGCUGGGUUUAUUUUA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUCUCUAAAAUAAACCCAGCA 3'), and a sense strand of nucleic acid sequence

according to SEQ ID NO: 81 (5' CUGGGUUUAUUUUAGAGAAA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' GGGACUACUGUCCAAAAAA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UGUUUCACAAACAAGCUGGUCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 83 (5' ACCAGCUUGUUUGUGAAACA 3'); xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUUUUUGUUUCACAAACAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UUGUUUGUGAAACAAAAAAA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAGUGA 3'); xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UCUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' AAAGUGUCCCCUUUUCAAGA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UUGUUCUACAACUUGAAAAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' CCUUUUCAAGUUGAGAACAA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAUUUUUGUUCUACAACUUGAAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCAAGUUGAGAACAAAAUA 3'); xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAUUUUUGUUCUACAACUUGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' CAAGUUGAGAACAAAAUUA 3'); xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUUGUUCUACAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3'); and xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UUUUUAAAACCCAAUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' CAAAAAUUGGGUUUUAAAAA 3'); xxxv) an antisense

strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAUUGGGUUUUAAAAUA 3'); xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' UAAUUUAAAACCCAAUUUUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' AAAAUUGGGUUUUAAAAUUA 3'); xxxvii) an antisense of nucleic acid sequence according to SEQ ID NO: 39 (5' UUUAUUUUAAAACCCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' AAUUGGGUUUUAAAAUUA 3'); xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUUAAGUAUA 3'); xxxix) an antisense of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUA 3'); or xL) an antisense of nucleic acid sequence according to SEQ ID NO: 51 (5' UCUCAUUAGAAGAAAAGGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' CACCUUUUCUUCUAAUGAGA 3').

[00144] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 9 to 29; b) 168 to 189; c) 784 to 808; d) 1264 to 1289; e) 1607 to 1630; f) 1814 to 1835; and g) 1843 to 1882, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' UGUAGUACCCAGAACACGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' CCGUUGUUCUGGGUACUACA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' UUACUCUCAUUGUGGAUGACGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' GUCAUCCACAAUGAGAGUAA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UAUGAACCUGUCAUUCUUCUACA 3').

3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' AGAAGAUUGACAGGUUCAUA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' UCUGCAUGAACCUGUCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' GAUUGACAGGUUCAUGCAGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' UCUCAAUUUUUGCAGGUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UGAACCUGCAAAAAUUGAGA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' UCAUUGCUCAAUUUUUGCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' CUGCAAAAAUUGAGCAAUGA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCCACCUUUUCUUCUAA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' UCAUUAGAAGAAAAGGUGGGAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' CCCACCUUUUCUUCUAAUGA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' UUUAAAACCCAAUUUUUGUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' AACAAAAAUUGGGUUUUAAA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' UUUCACAAACAAGCUGGUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' CGACCAGCUUGUUUGUGAAA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' UUUUCACAAACAAGCUGGUCGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' GACCAGCUUGUUUGUGAAAA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' UCUCAACUUGAAAAGGGAACAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' GUUCCCUUUUCAAGUUGAGA 3'); or xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAUUGGGUUUUA 3').

[00145] In some embodiments, the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a sequence is identical to a region comprising the sequence between any one of the nucleotide positions selected from a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%), at a dose of 0.02 nM.

[00146] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a sequence is identical to a region comprising the sequence between any one of the nucleotide positions selected from a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%), at a dose of 0.02 nM, and that attenuate expression of the AGT mRNA by 20% to 50%, at a dose of 0.02 nM, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UCUCACAGGUACUCUCAUUGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' CAAUGAGAGUACCUGUGAGA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UCAUAGCUCACUGUGCAUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' GCAUGCACAGUGAGCUAUGA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUAGAGAGAGGCCAGGGUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' GCACCCUGGCCUCUCUCUAA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUGAAGUCCAGAGAGCGUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' CCACGCUCUCUGGACUUCAA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UCUGUCAAUUCUUCUCAGCAGCA 3'), and a sense strand of nucleic

acid sequence according to SEQ ID NO: 64 (5' CUGCUGAGAAGAUUGACAGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UGUCCACCCAGAACUCCUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' CCAGGAGUUCUGGGUGGACA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UCAGACACUGAGGUGCUGUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AACAGCACCUCAGUGUCUGA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUUUGCUGGAAAGUGAGACCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' GGUCUCACUUCCAGCAAAA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UGUUUCUUCAUCCAGUUGAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' CUCAACUGGAUGAAGAAACA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UCAGCAAACAGGAAUGGGCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' CGCCCAUCCUGUUUGCUGA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAAGAAAAGGUGGGAGACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' AGUCUCCACCUUUUCUUCA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UUUAGAAGAAAAGGUGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' CUCCCACCUUUUCUUCUAAA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UGAGAAACGGCUGCUUCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAAAGCAGCCGUUUCUCA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUUAGACCAAGGAGAAACGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' CCGUUUCUCCUUGGUCUAAA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UCUUAGACCAAGGAGAAACGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' CGUUUCUCCUUGGUCUAAGA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UCACUAGACCAAGGAGAAACG

3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UUUCUCCUUGGUCUAAGUGA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAUUGGGUUUUA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' GGGACUACUGUCCAAAAA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UUGUUCUCAACUUGAAAAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' CCUUUUCAAGUUGAGAACAA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAUUUUUGUUCUCAACUUGAAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCAAGUUGAGAACAAAAUA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAUUUUUGUUCUCAACUUGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' CAAGUUGAGAACAAAAUUA 3'); xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UUUUUAAAACCCAAUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' CAAAAUUGGGUUUUAAAAA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' UAAUUUUAAAACCCAAUUUUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' AAAAUUGGGUUUUAAAAUUA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' UUUAUUUUAAAACCCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' AAUUGGGUUUUAAAAUUA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUAA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' UGUAGUACCCAGAACACGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' CCGUUGUUCUGGGUACUACA 3'); xxvii) an antisense strand of

nucleic acid sequence according to SEQ ID NO: 47 (5' UCUCAAUUUUUGCAGGUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UGAACCUGCAAAAAUUGAGA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' UCAUUGCUCAAUUUUUGCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' CUGCAAAAAUUGAGCAAUGA 3'); xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UCUCAUUAGAAGAAAAGGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' CACCUUUUCUUCUAAUGAGA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' UUUCACAAACAAGCUGGUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' CGACCAGCUUGUUUGUGAAA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' UUUAAAACCCAAUUUUUGUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' AACAAAAAUUGGGUUUAAA 3'); xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UAAAAUAAACCCAGCAAACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' AGUUUGCUGGGUUUAUUUA 3'); or xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUCUCUAAAAUAAACCCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' CUGGGUUUAUUUUAGAGAAA 3').

[00147] In some embodiments, the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a sequence is identical to a region comprising the sequence between any one of the nucleotide positions selected from a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 99%, 99% to 100%), at a dose of 0.02 nM.

[00148] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a sequence is identical to a region comprising the sequence between

any one of the nucleotide positions selected from a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and that attenuate expression of the AGT mRNA by that attenuate expression of the AGT mRNA by at least 50%, at a dose of 0.02 nM, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCCUUUUCAAA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCUCUCAUUGUGGAUGACGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' UCGUCAUCCACAAUGAGAGA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAAAUGCUGUUCAGCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUUA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUUGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUAGAAGAAAAGGUGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UCCCACCUUUUCUUCUAAUA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUUUUUGUUUCACAAACAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UUGUUUGUGAAACAAAAAAA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UCUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence

according to SEQ ID NO: 86 (5' AAAGUGUCCCCUUUUCAAGA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUCAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAAAAUA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUUAAGUAUA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' UUACUCUCAUUGUGGAUGACGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' GUCAUCCACAAUGAGAGUAA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' UCUGCAUGAACCUGUCAAUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' GAUUGACAGGUUCAUGCAGA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCCACCUUUUCUUCUAA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' UCAUUAGAAGAAAAGGUGGGAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' CCCACCUUUUCUUCUAAUGA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' UCUCAACUUGAAAAGGGAACAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' GUUCCCUUUUCAAGUUGAGA 3'); an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAUGCUGUUCAGCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUUA 3'); or an antisense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UAUGAACCUGUCAAUUCUUCUA 3'), and a sense strand

of nucleic acid sequence according to SEQ ID NO: 100 (5' AGAAGAUUGACAGGUUCAUA 3').

[00149] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a sequence is identical to a region comprising the sequence between any one of the nucleotide positions selected from: a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by the isolated oligonucleotide of the present disclosure attenuates expression of the AGT mRNA by 50% to 75% (e.g., between 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70% or 70% to 75%), at a dose of 0.1 nM.

[00150] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a sequence is identical to a region comprising the sequence between any one of the nucleotide positions selected from: a) 9 to 29; b) 166 to 196; c) 394 to 480; d) 744 to 968; e) 1110 to 1331; f) 1410 to 1676; and g) 1726 to 1894, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and that attenuate expression of the AGT mRNA by at least 50%, at a dose of 0.1 nM, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5'

UGAAACAAAAAAGUGUCCA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCCUUUUCAAA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCUCUCAUUGUGGAUGACGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' UCGUCAUCCACAAUGAGAGA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UCUCACAGGUACUCUCAUUGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' CAAUGAGAGUACCUGUGAGA 3'); v) an antisense strand of nucleic acid sequence

according to SEQ ID NO: 6 (5' UCAUAGCUCACUGUGCAUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' GCAUGCACAGUGAGCUAUGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUAGAGAGAGGCCAGGGUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' GCACCCUGGCCUCUCUCUAA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUGAAGUCCAGAGAGCGUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' CCACGCUCUCUGGACUCAA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UCUGUCAAUCUUCUCAGCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' CUGCUGAGAAGAUUGACAGA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UGUCCACCCAGAACUCCUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' CCAGGAGUUCUGGGUGGACA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UCAGACACUGAGGUGCUGUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AACAGCACCUCAGUGUCUGA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAAUUGGGUUUUA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUUUGCUGGAAAGUGAGACCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' GGUCUCACUUUCCAGCAAAA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UGUUUUCUUAUCCAGUUGAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' CUCAACUGGAUGAAGAAACA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAAUGCUGUUCAGCACCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' AGGUGCUGAACAGCAUUUUA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAUUGCUGUUCAGCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUUA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence

according to SEQ ID NO: 82 (5' GGGACUACUGUCCAAAAAA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUGA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UCAGCAAACAGGAAUGGGCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' CGCCCAUCCUGUUUGCUGA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAAGAAAAGGUGGGAGACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' AGUCUCCACCUUUUCUUCA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UUUAGAAGAAAAGGUGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' CUCCCACCUUUUCUUCUAAA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUAGAAGAAAAGGUGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UCCCACCUUUUCUUCUAAUA 3'); xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UGAGAAACGGCUGCUUCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAAAGCAGCCGUUUCUCA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUUAGACCAAGGAGAAACGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' CCGUUUCUCCUUGGUCUAAA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UCUUAGACCAAGGAGAAACGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' CGUUUCUCCUUGGUCUAAGA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UAAAAUAAACCCAGCAAACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' AGUUUGCUGGGUUUAUUUUA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UCACUUAGACCAAGGAGAAACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UUUCUCCUUGGUCUAAGUGA 3'); xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5'

UUUCUCUAAAAUAAACCCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' CUGGGUUUAUUUUAGAGAAA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UGUUUCACAAACAAGCUGGUCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 83 (5' ACCAGCUUGUUUGUGAAACA 3'); xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUUUUUGUUUCACAAACAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UUGUUUGUGAAACAAAAAAA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UCUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' AAAGUGUCCCCUUUUCAAGA 3'); xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UUGUUCUCAACUUGAAAAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' CCUUUUCAAGUUGAGAACAA 3'); xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAUUUUUGUUCUCAACUUGAAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCAAGUUGAGAACAAAAUA 3'); xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAUUUUUGUUCUCAACUUGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' CAAGUUGAGAACAAAAUUA 3'); xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUCAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3'); xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UUUUUAAAACCCAAUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' CAAAAUUGGGUUUUAAAAA 3'); xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence

according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUAAAAUA 3'); xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' UAAUUUAAAAACCCAAUUUUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' AAAAAUUGGGUUUAAAAUUA 3'); xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' UUUAAUUUAAAAACCCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' AAUUGGGUUUAAAAUUA 3'); xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUAAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUUAAGUAUA 3'); xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUAAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUA 3'); xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' UGUAGUACCCAGAACACGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' CCGUUGUUCUGGGUACUACA 3') (63.2); xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' UUACUCUCAUUGUGGAUGACGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' GUCAUCCACAAUGAGAGUAA 3'); xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3'); xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UAUGAACUGUCAAUUCUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' AGAAGAUUGACAGGUUCAUA 3'); xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' UCUGCAUGAACUGUCAAUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' GAUUGACAGGUUCAUGCAGA 3'); xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' UCUCAAUUUUUGCAGGUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UGAACCUGCAAAAAUUGAGA 3'); xLviii) an antisense

strand of nucleic acid sequence according to SEQ ID NO: 48 (5' UCAUUGCUCAAUUUUUGCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' CUGCAAAAUUGAGCAAUGA 3'); xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCCACCUUUUCUUCUAA 3'); L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' UCAUUAGAAGAAAAGGUGGGAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' CCCACCUUUUCUUCUAAUGA 3'); Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UCUCAUUAGAAGAAAAGGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' CACCUUUUCUUCUAAUGAGA 3'); Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' UUUCACAAACAAGCUGGUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' CGACCAGCUUGUUUGUGAAA 3'); Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' UUUUCACAAACAAGCUGGUCGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' GACCAGCUUGUUUGUGAAAA 3'); Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' UCUCAACUUGAAAAGGGAACAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' GUUCCCUUUUCAAGUUGAGA 3'); or Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' UUUAAAACCCAAUUUUUGUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' AACAAAAAUUGGGUUUAAA 3').

[00151] The present disclosure also provides an isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x)

1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[00152] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%) at a dose of 0.02 nM.

[00153] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%) at a dose of 0.02 nM, the double stranded region comprises: i) an antisense strand of nucleic acid

sequence according to SEQ ID NO: 237 (5' UCUGUAGUACCCAGAACAAACGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 404 (5' GUUGUUCUGGGUACUACAGA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UAUACCCUUCUGCUGUAGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 280 (5' UACUACAGCAGAAGGGUAAU 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 126 (5' UCACAGGUACUCUCAUUGUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 293 (5' CACAAUGAGAGUACCUGUGA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 128 (5' UCAUUGGCCUUGGCCAGCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 295 (5' CAGCUGGCAAAGGCCAAUGA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 268 (5' UCUCAACUUGUCUUCGGUGUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 435 (5' ACACCGAAGACAAGUUGAGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 130 (5' UAGAAGUUGGCCAGCAUCCCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 297 (5' GGGUAGCUGGCCAACUUCUA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 131 (5' UCAAGAAGUUGGCCAGCAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 298 (5' GAUGCUGGCCAACUUCUUGA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UGGAAGCCCAAGAAGUUGGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 299 (5' GCCAACUUCUUGGGCUUCCA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAUAUACGGAAGCCCAAGAAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 300 (5' UUCUUGGGCUUCCGUAAUAUA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 134 (5' UUAUAUACGGAAGCCCAAGAAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 301 (5' UCUUGGGCUUCCGUAAUAUA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 137 (5' UAUGCCAUAUAUACGGAAGCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 304 (5' GCUUCCGUAAUAUAUGGCAUA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 145 (5' UGUGCCAAAGACAGCCGUUGGG

3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 312 (5' CAACGGCUGUCUUUGGCACA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 240 (5' UAUAGAGAGAGGCCAGGGUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 407 (5' CACCCUGGCCUCUCUCUAUA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 241 (5' UGAUUGCCUGUAGCCUGUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 408 (5' UGACAGGCUACAGGCAAUCA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UCAGUUCUUGUCCUCCAAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 409 (5' CUUGGAAGGACAAGAACUGA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 243 (5' UUAUAGAGAGCCAGGCCUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 410 (5' CAGGGCCUGGCUCUCUAUAA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 156 (5' UGAACCUGUCAAUUCUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 323 (5' UGAGAAGAUUGACAGGUUCA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' UGUAGGUGUUGAAAGCCAGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 412 (5' CCUGGCUUUAACACCUACA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 246 (5' UCAGAACUCCUGGGGCUCGGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 413 (5' CCGAGCCCCAGGAGUUCUGA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 160 (5' UGACACUGAGGUGCUGUUGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 327 (5' ACAACAGCACCUAGUGUCA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 247 (5' UCUCUCAGUGAAGGGCACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 414 (5' AAGUGCCCUUCACUGAGAGA 3'); xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAAGUGAGACCCUCCACCUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 332 (5' AAGGUGGAGGGUCUCACUUA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 167 (5' UGGAAAGUGAGACCCUCCACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 334 (5'

GUGGAGGGUCUCACUUUCCA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UCUGGAAAGUGAGACCCUCCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 335 (5' GGAGGGUCUCACUUUCCAGA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 169 (5' UGUUUUGCUGGAAAGUGAGACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 336 (5' UCUCACUUUCCAGCAAAACA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 170 (5' UGAGUUUUGCUGGAAAGUGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 337 (5' UCACUUUCCAGCAAAACUCA 3'); xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAGUUGAGGGAGUUUUGCUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 338 (5' CAGCAAAACUCCCUCAACUA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 172 (5' UCAGUUGAGGGAGUUUUGCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 339 (5' AGCAAAACUCCCUCAACUGA 3'); xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UUUUCUUAUCCAGUUGAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 343 (5' CCUCAACUGGAUGAAGAAAA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' UUAAGAUCUUGCAGCACCAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 415 (5' UGGUCUGCAAGGAUCUUA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UGAAUGGCGGGCAGCUCAGCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 344 (5' GCUGAGCUGCCCGCCAUUCA 3'); xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UUUUUGCAGGUUCAGCUCGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 346 (5' CCGAGCUGAACCUGCAAAAA 3'); xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 180 (5' UUUUUUGCAGGUUCAGCUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 347 (5' CGAGCUGAACCUGCAAAAA 3'); xxxiiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UCUCUCAUCCGCUCAAGCUCA 3'), and a sense strand of nucleic acid sequence according

to SEQ ID NO: 436 (5' AGCUUGAAGCGGAUGAGAGA 3'); xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 270 (5' UCUCUCUCAUCCGCUUCAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 437 (5' CUUGAAGCGGAUGAGAGAGA 3'); xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 186 (5' UGACUCUGUGGGCUCUCUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 353 (5' AGAGAGAGCCCACAGAGUCA 3'); xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 187 (5' UUAGACUCUGUGGGCUCUCUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 354 (5' AGAGAGCCCACAGAGUCUAA 3'); xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 254 (5' UCAAACAGGAAUGGGCGGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 421 (5' AACCGCCCAUCCUGUUUGA 3'); xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 190 (5' UAUCAUACACAGCAAACAGGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 357 (5' CCUGUUUGCUGUGUAUGAUA 3'); xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUCAUACACAGCAAACAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 358 (5' CUGUUUGCUGUGUAUGAUA 3'); xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 195 (5' UCUGGGGCCCCUGGCCUCAUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 362 (5' CAUGAGGCCAGGGCCCCAGA 3'); xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 196 (5' UGUGUUCUGGGGCCCCUGGCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 363 (5' GGCCAGGGCCCCAGAACACA 3'); xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' UAGAAAAGGUGGGAGACUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 367 (5' CCAGUCUCCCACCUUUUCUA 3'); xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 201 (5' UAAGAAAAGGUGGGAGACUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 368 (5' CAGUCUCCCACCUUUUCUUA 3'); xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 259 (5' UCUAAAAUAAACCCAGCAAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 426 (5' UUUGCUGGGUUUAUUUUAGA 3'); xLiv) an antisense strand of

nucleic acid sequence according to SEQ ID NO: 202 (5' UAUUCUCUAAAAUAAACCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 369 (5' UGGGUUUAAUUUUAGAGAAUA 3'); xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 272 (5' UUUUGGAACAGUAGUCCCGCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 439 (5' GCGGGACUACUGUCCAAAA 3'); xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 273 (5' UUUUUGGAACAGUAGUCCCGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 440 (5' CGGGACUACUGUCCAAAAA 3'); Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 274 (5' UCUUUUUGGAACAGUAGUCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 441 (5' GGACUACUGUCCAAAAAGA 3'); xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' UUUCUUUUUGGAACAGUAGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 442 (5' ACUACUGUCCAAAAAGAAA 3'); Lix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' UGUCGGUUGGAAUUCUUUUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' AAAAAGAAUCCAACCGACA 3'); L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCAAACAAGCUGGUCGGUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' CAACCGACCAGCUUGUUUGA 3'); Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 211 (5' UUUUUUGUUUCACAAACAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' CUUGUUUGUGAAACAAAAAA 3'); Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' UAAAAGGGAACACUUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' CAAAAAAGUGUCCCUUUUA 3'); Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' UUUUAAAACCCAAUUUUUGUUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' AAAAAAUUGGGUUUUAAAA 3'); Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' UCUUUAUUUUAAAACCCAAUU 3'), and a sense strand of nucleic acid sequence

according to SEQ ID NO: 386 (5' UUGGGUUUUAAAAUAAAAGA 3'); Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' UAUACAAACCGAAGGCAAUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' CAUUGCCUUCGGUUUGUAUA 3'); Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 221 (5' UAAUACAAACCGAAGGCAAUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 388 (5' AUUGCCUUCGGUUUGUAUUA 3'); Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 223 (5' UCUAAAUACAAACCGAAGGCAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 390 (5' GCCUUCGGUUUGUAUUUAGA 3'); Lviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' UCACUAAAUACAAACCGAAGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' CUUCGGUUUGUAUUUAGUGA 3'); Lix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' UAAGACACUAAAUACAAACCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 392 (5' GGUUUGUAUUUAGUGUCUUA 3'); Lx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 226 (5' UCAAGACACUAAAUACAAACCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 393 (5' GUUUGUAUUUAGUGUCUUGA 3'); Lxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 235 (5' UGAGAAAUAACCAGCUAUGGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 402 (5' CCAUAGCUGGUUAUUUCUCA 3'); or Lxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 236 (5' UAAGACGUUUUUACUAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 403 (5' UGUUAGUAAUAAACGUCUUA 3').

[00154] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y)

1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 100%) at a dose of 0.02 nM.

[00155] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 100%) at a dose of 0.02 nM, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 157 (5' UUUGUCCACCCAGAACUCCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 324 (5' AGGAGUUCUGGGUGGACAAA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCACCUUUUCUUCUAA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 206 (5' UUAACACUGGUUCUUGCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' AGGCAAGAACCAGUGUUUAA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 214 (5' UCAACUUGAAAAGGGAACACUU 3'), and

a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' GUGUCCCCUUUCAAGUUGA 3'); or v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' UUUUAAUUUUAAAACCCAAUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' AUUGGGUUUUAAAAUUAAAA 3').

[00156] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%) at a dose of 0.1 nM.

[00157] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%) at a

dose of 0.1 nM, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 237 (5' UCUGUAGUACCCAGAACAAACGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 404 (5' GUUGUUCUGGGUACUACAGA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 128 (5' UCAUUGGCCUUUGCCAGCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 295 (5' CAGCUGGCAAAGGCCAAUGA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 145 (5' UGUGCCAAAGACAGCCGUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 312 (5' CAACGGCUGUCUUUGGCACA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 240 (5' UAUAGAGAGAGGCCAGGGUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 407 (5' CACCCUGGCCUCUCUCUAUA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 241 (5' UGAUUGCCUGUAGCCUGUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 408 (5' UGACAGGCUACAGGCAAUCA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UCAGUUCUUGUCCUCCAAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 409 (5' CUUGGAAGGACAAGAACUGA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 243 (5' UUAUAGAGAGCCAGGCCUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 410 (5' CAGGGCCUGGCUCUCUAUAA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' UGUAGGUGUUGAAAGCCAGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 412 (5' CCUGGCUUUAACACCUACA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 246 (5' UCAGAACUCCUGGGGCUCGGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 413 (5' CCGAGCCCCAGGAGUUCUGA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 157 (5' UUUGUCCACCCAGAACUCCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 324 (5' AGGAGUUCUGGGUGGACAAA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 160 (5' UGACACUGAGGUGCUGUUGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 327 (5' ACAACAGCACCUCAGUGUCA

3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 247 (5' UCUCUCAGUGAAGGGCACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 414 (5' AAGUGCCCUUCACUGAGAGA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAAGUGAGACCCUCCACCUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 332 (5' AAGGUGGAGGGUCUCACUUA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 167 (5' UGGAAAGUGAGACCCUCCACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 334 (5' GUGGAGGGUCUCACUUUCCA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UCUGGAAAGUGAGACCCUCCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 335 (5' GGAGGGUCUCACUUUCCAGA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAGUUGAGGGAGUUUUGCUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 338 (5' CAGCAAAACUCCCUCAACUA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UGAAUGGCGGGCAGCUCAGCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 344 (5' GCUGAGCUGCCCCGCAUUA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 182 (5' UAAUUUUUGCAGGUUCAGCUCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 349 (5' AGCUGAACCUGCAAAAAUUA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 251 (5' UAUGCUGUUCAGCACCUCCCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 418 (5' GGGAGGUGCUGAACAGCAUA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 187 (5' UUAGACUCUGUGGGCUCUCUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 354 (5' AGAGAGCCCACAGAGUCUAA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 254 (5' UCAAACAGGAAUGGGCGGUUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 421 (5' AACCGCCCAUCCUGUUUGA 3'); xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 190 (5' UAUCAUACACAGCAAACAGGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 357 (5' CCUGUUUGCUGUGUAUGAUA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 201 (5'

UAAGAAAAGGUGGGAGACUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 368 (5' CAGUCUCCCACCUUUUCUUA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 259 (5' UCUAAAAUAAACCCAGCAAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 426 (5' UUUGCUGGGUUUAUUUUAGA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 273 (5' UUUUUGGAACAGUAGUCCCGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 440 (5' CGGGACUACUGUCCAAAAA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' UGUCGGUUGGAAUUCUUUUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' AAAAGAAUCCAACCGACA 3'); xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCAAACAAGCUGGUCGGUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' CAACCGACCAGCUUGUUUGA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' UCUUUAAUUUUAAAACCCAAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' UUGGGUUUUAAAAUUAAAGA 3'); xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' UAUACAAACCGAAGGCAAUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' CAUUGCCUUCGGUUUGUAUA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 221 (5' UAAUACAAACCGAAGGCAAUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 388 (5' AUUGCCUUCGGUUUGUAUUA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' UCACUAAAUACAAACCGAAGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' CUUCGGUUUGUAUUUAGUGA 3'); xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' UAAGACACUAAAUACAAACCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 392 (5' GGUUUGUAUUUAGUGUCUUA 3'); xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 226 (5' UCAAGACACUAAAUACAAACCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 393 (5' GUUUGUAUUUAGUGUCUUGA 3'); xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 120 (5'

UGGAAGGGGUGUAUGUACACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 287 (5' GUGUACAUACACCCCUUCCA 3'); xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 236 (5' UAAGACGUUUAUUACUAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 403 (5' UGUUAGUAAUAAACGUCUUA 3'); xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 122 (5' UGGAUGACGAGGUGGAAGGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 289 (5' CCCUCCACCUCGUCAUCCA 3'); xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 125 (5' UCUCAUUGUGGAUGACGAGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 292 (5' CCUCGUCAUCCACAAUGAGA 3'); xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 276 (5' UACAAGCUGGUCGGUUGGAAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 443 (5' UUCCAACCGACCAGCUUGUA 3'); xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 127 (5' UCUUUGCCAGCUGCUCACAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 294 (5' CUGUGAGCAGCUGGCAAAGA 3'); xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 239 (5' UUUUCAUCCACAGGGGAUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 406 (5' ACAUCCCCUGUGGAUGAAAA 3'); xLI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 267 (5' UGUUUUGCAGCGACUAGCACCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 434 (5' GUGCUAGUCGUGCAAAAACA 3'); xLII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 129 (5' UAAGUUGGCCAGCAUCCCGACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 296 (5' UCGGGAUGCUGGCCAACUUA 3'); xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAUAUACGGAAGCCCAAGAAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 300 (5' UUCUUGGGCUUCCGUUAUAUA 3'); xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 135 (5' UAUAUAUACGGAAGCCCAAGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 302 (5' CUUGGGCUUCCGUUAUAUAUA 3'); xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 136 (5'

UCAUAUAUACGGAAGCCCAAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 303 (5' UUGGGCUUCCGUAUAUAUGA 3'); xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 138 (5' UCAUGCCAUUAUAUACGGAAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 305 (5' CUUCCGUAUAUAUGGCAUGA 3'); xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 139 (5' UCUGUGCAUGCCAUUAUAUACGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 306 (5' GUAUAUAUUGGCAUGCACAGA 3'); xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 144 (5' UCAAAGACAGCCGUUGGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 311 (5' UCCCCAACGGCUGUCUUUGA 3'); xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 277 (5' UUUCCAAGGAACACCCAGGAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 444 (5' UCCUGGGUGUCCUUGGAAA 3'); L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 149 (5' UGACCUUGUGCGCAUCCAGCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 316 (5' GCUGGAUGCGCACAAGGUCA 3'); LI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 151 (5' UCAAACGGCUGCUUCAGGUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 318 (5' CACCUGAAGCAGCCGUUGA 3'); LIJ) an antisense strand of nucleic acid sequence according to SEQ ID NO: 152 (5' UCACAAACGGCUGCUUCAGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 319 (5' CCUGAAGCAGCCGUUUGUGA 3'); LIJ) an antisense strand of nucleic acid sequence according to SEQ ID NO: 153 (5' UUAGAGAGCCAGGCCUGCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 320 (5' UGCAGGGCCUGGCUCUCUAA 3'); LIV) an antisense strand of nucleic acid sequence according to SEQ ID NO: 154 (5' UAAGUCCAGAGAGCGUGGGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 321 (5' UCCCACGCUCUCUGGACUUA 3'); LV) an antisense strand of nucleic acid sequence according to SEQ ID NO: 155 (5' UGUGAAGUCCAGAGAGCGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 322 (5' CACGCUCUCUGGACUUCACA 3'); LVI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 244 (5' UUUCUGUGAAGUCCAGAGAGCG 3'), and a sense strand of nucleic acid sequence

according to SEQ ID NO: 411 (5' CUCUCUGGACUUCACAGAAA 3'); LVII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 278 (5' UUCUCAGCAGCAACAUCAGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 445 (5' CUGGAUGUUGCUGCUGAGAA 3'); LVIII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 158 (5' UCUGUUGUCCACCCAGAACUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 325 (5' AGUUCUGGGUGGACAACAGA 3'); LIX) an antisense strand of nucleic acid sequence according to SEQ ID NO: 164 (5' UGUGAGACCCUCCACCUUGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 331 (5' ACAAGGUGGAGGGUCUCACA 3'); LX) an antisense strand of nucleic acid sequence according to SEQ ID NO: 166 (5' UGAAAGUGAGACCCUCCACCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 333 (5' GGUGGAGGGUCUCACUUUCA 3'); LXI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 173 (5' UAUCCAGUUGAGGGAGUUUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 340 (5' AAAACUCCCUCAACUGGAUA 3'); LXII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 178 (5' UCAGAAUGGCGGGCAGCUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 345 (5' UGAGCUGCCCGCCAUCUGA 3'); LXIII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 250 (5' UCUGUUCAGCACCUCUCCCCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 417 (5' UGGGGGAGGUGCUGAACAGA 3'); LXIV) an antisense strand of nucleic acid sequence according to SEQ ID NO: 184 (5' UAAAAAUGCUGUUCAGCACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 351 (5' GUGCUGAACAGCAUUUUUUA 3'); LXV) an antisense strand of nucleic acid sequence according to SEQ ID NO: 185 (5' UAAAAAUGCUGUUCAGCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 352 (5' GCUGAACAGCAUUUUUUUA 3'); LXVI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 270 (5' UCUCUCUCAUCCGCUUCAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 437 (5' CUUGAAGCGGAUGAGAGAGA 3'); LXVII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 252 (5' UCAGGAAUGGGCGGUUCAGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 419 (5' CCUGAACCGCCCAUCCUGA 3'); LXVIII) an antisense strand of nucleic acid sequence

according to SEQ ID NO: 188 (5' UCACAGCAAACAGGAAUGGGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 355 (5' CCCAUUCCUGUUUGCUGUGA 3'); LXIX) an antisense strand of nucleic acid sequence according to SEQ ID NO: 189 (5' UAUACACAGCAAACAGGAAUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 356 (5' AUUCCUGUUUGCUGUGUAUA 3'); LXX) an antisense strand of nucleic acid sequence according to SEQ ID NO: 192 (5' UUUGAUCAUACACAGCAAACAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 359 (5' GUUUGCUGUGUAUGAUCAAA 3'); LXXI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 193 (5' UUUUGAUCAUACACAGCAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 360 (5' UUUGCUGUGUAUGAUCAAAA 3'); LXXII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 255 (5' UGAAGUGCAGGGCAGUGGCGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 422 (5' CGCCACUGCCCUGCACUUCA 3'); LXXIII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 194 (5' UCAGGAAGUGCAGGGCAGUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 361 (5' CACUGCCCUGCACUUCCUGA 3'); LXXIV) an antisense strand of nucleic acid sequence according to SEQ ID NO: 256 (5' UCUCAUGCUGUGCUCAGCGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 423 (5' CCGCUGAGCACAGCAUGAGA 3'); LXXV) an antisense strand of nucleic acid sequence according to SEQ ID NO: 195 (5' UCUGGGGCCCUGGCCUCAUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 362 (5' CAUGAGGCCAGGGCCCCAGA 3'); LXXVI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 198 (5' UAAAAGGUGGGAGACUGGGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 365 (5' CCCAGUCUCCCACCUUUUA 3'); LXXVII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 199 (5' UGAAAAGGUGGGAGACUGGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 366 (5' CCCAGUCUCCCACCUUUUCA 3'); LXXVIII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 271 (5' UCUUCCAGCUCAAAGUCGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 438 (5' UCGACUUUGAGCUGGAAAGA 3'); LXXIX) an antisense strand of

nucleic acid sequence according to SEQ ID NO: 257 (5' UAAAACCCAGCAAACUGGGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 424 (5' UCCCAGUUUGCUGGGUUUAA 3'); LXXX) an antisense strand of nucleic acid sequence according to SEQ ID NO: 204 (5' UCUGGUUCUUGCCUCCCCACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 371 (5' GUGGGGAGGCAAGAACCAGA 3'); LXXXI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 205 (5' UAAACACUGGUUCUUGCCUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 372 (5' GAGGCAAGAACCAGUGUUUA 3'); LXXXII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 260 (5' UGUUGGAAUUCUUUUUGGAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 427 (5' UUCCAAAAAGAAUCCAACA 3'); LXXXIII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 209 (5' UUUGUUUCACAAACAAGCUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 376 (5' CAGCUUGUUUGUGAAACAAA 3'); LXXXIV) an antisense strand of nucleic acid sequence according to SEQ ID NO: 210 (5' UUUUUGUUUCACAAACAAGCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 377 (5' GCUUGUUUGUGAAACAAAAA 3'); LXXXV) an antisense strand of nucleic acid sequence according to SEQ ID NO: 227 (5' UCUUACAUUCAAGACACUAAAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 394 (5' UUAGUGUCUUGAAUGUAAGA 3'); LXXXVI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 229 (5' UGUCAUGUUCUACAUAUCAAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 396 (5' UUGAAUGUAAGAACAUGACA 3'); LXXXVII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 262 (5' UGAAAUUCAGGUGCUUGCAUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 429 (5' AUGCAAGCACCUGAAUUUCA 3'); LXXXVIII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 263 (5' UAACAGAAAUUCAGGUGCUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 430 (5' AAGCACCUGAAUUUCUGUUA 3'); LXXXIX) an antisense strand of nucleic acid sequence according to SEQ ID NO: 265 (5' UCAUCAAACAGAAAUUCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 432 (5' CUGAAUUUCUGUUUGAAUGA 3'); XC) an antisense

strand of nucleic acid sequence according to SEQ ID NO: 266 (5' UGAAAUAACCAGCUAUGGUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 433 (5' AACCAUAGCUGGUUAUUUCA 3'); XCI) an antisense strand of nucleic acid sequence according to SEQ ID NO: 196 (5' UGUGUUCUGGGGCCCUGGCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 363 (5' GGCCAGGGCCCCAGAACACA 3'); or XCII) an antisense strand of nucleic acid sequence according to SEQ ID NO: 112 (5' UCUUCUGCUGUAGUACCCAGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 279 (5' CUGGGUACUACAGCAGAAGA 3').

[00158] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071; and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 100%) at a dose of 0.1 nM.

[00159] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from a) 11 to 42; b) 144 to 215; c) 264 to 284; d) 303 to 323; e) 325 to 345; f) 355 to 405; g) 441 to 481; h) 503 to 552; i) 560 to 580; j) 690 to 731; k) 742 to 802; l) 863 to 883; m) 922 to 966; n) 1036 to 1056; o) 1099 to 1153; p) 1189 to 1209; q) 1233 to 1255; r) 1258 to 1282; s) 1300 to 1367; t) 1403 to 1465; u) 1479 to 1517; v) 1601 to 1624; w) 1631 to 1651; x) 1722 to 1753; y) 1756 to 1861; z) 1863 to 1890; aa) 1901 to 1948; ab) 2017 to 2047; ac) 2049 to 2071;

and ad) 2075 to 2095, from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 100%) at a dose of 0.1 nM, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UAUACCCUUCUGCUGUAGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 280 (5' UACUACAGCAGAAGGGUAUA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 126 (5' UCACAGGUACUCUCAUUGUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 293 (5' CACAAUGAGAGUACCUGUGA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 268 (5' UCUCAACUUGUCUUCGGUGUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 435 (5' ACACCGAAGACAAGUUGAGA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 130 (5' UAGAAGUUGGCCAGCAUCCCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 297 (5' GGGAUGCUGGCCAACUUCUA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UGGAAGCCCAAGAAGUUGGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 299 (5' GCCAACUUCUUGGGCUUCCA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAUAUACGGAAGCCCAAGAAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 300 (5' UUCUUGGGCUUCCGUAUAUA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 134 (5' UUAUAUACGGAAGCCCAAGAAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 301 (5' UCUUGGGCUUCCGUAUAUAA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 137 (5' UAUGCCAUAUAUACGGAAGCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 304 (5' GCUUCCGUAUAUAUGGCAUA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 156 (5' UGAACCUGUCAAUUCUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 323 (5' UGAGAAGAUUGACAGGUUCA 3'); x) an antisense strand of nucleic acid sequence

according to SEQ ID NO: 169 (5' UGUUUUGCUGGAAAGUGAGACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 336 (5' UCUCACUUUCCAGCAAAACA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 170 (5' UGAGUUUUGCUGGAAAGUGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 337 (5' UCACUUUCCAGCAAAACUCA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UUUUCUUAUCCAGUUGAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 343 (5' CCUCAACUGGAUGAAGAAAA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' UUAAGAUCUUGCAGCACCAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 415 (5' UGGUGCUGCAAGGAUCUUA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UUUUUGCAGGUUCAGCUCGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 346 (5' CCGAGCUGAACCUGCAAAAA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 180 (5' UUUUUUGCAGGUUCAGCUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 347 (5' CGAGCUGAACCUGCAAAAA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 181 (5' UAUUUUUGCAGGUUCAGCUCGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 348 (5' GAGCUGAACCUGCAAAAAUA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 183 (5' UCAAUUUUGCAGGUUCAGCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 350 (5' GCUGAACCUGCAAAAAUUGA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UCUCUCAUCCGCUUCAAGCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 436 (5' AGCUUGAAGCGGAUGAGAGA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 186 (5' UGACUCUGUGGGCUCUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 353 (5' AGAGAGAGCCCACAGAGUCA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 253 (5' UAACAGGAAUGGGCGGUUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 420 (5' UGAACCGCCCAUCCUGUUA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 191 (5'

UGAUCAUACACAGCAAACAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 358 (5' CUGUUUGCUGUGUAUGAUC 3'); xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' UAGAAAAGGUGGGAGACUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 367 (5' CCAGUCUCCCCACCUUUUCUA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' UUUUAAAACCCAAUUUUUGUUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' ACAAAAUUGGGUUUUAAAA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 258 (5' UAAUAAACCCAGCAAACUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 425 (5' CCAGUUUGCUGGGUUUAUUA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 202 (5' UAUUCUCUAAAAUAAACCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 369 (5' UGGGUUUUUUUAGAGAAUA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 206 (5' UAAACACUGGUUCUUGCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' AGGCAAGAACCAGUGUUUAA 3'); xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 272 (5' UUUUGGAACAGUAGUCCCGCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 439 (5' GCGGGACUACUGUCCAAAA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 274 (5' UCUUUUUGGAACAGUAGUCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 441 (5' GGACUACUGUCCAAAAAAGA 3'); xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' UUUCUUUUUGGAACAGUAGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 442 (5' ACUACUGUCCAAAAAGAAA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 211 (5' UUUUUUGUUUCACAAACAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' CUUGUUUGUGAAACAAAAAA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' UAAAAGGGAACACUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' CAAAAAGUGUCCCUUUUA 3'); xxxii) an antisense

strand of nucleic acid sequence according to SEQ ID NO: 214 (5' UCAACUUGAAAAGGGAACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' GUGUCCCCUUUCAAGUUGA 3'); xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' UUUUAAUUUUAAAACCCAAUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' AUUGGGUUUUAAAAUAAAA 3').

[00160] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2, 3, 16, 30, 35, 37, 40, 41, 44 or 55.

[00161] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57, 58, 71, 85, 90, 92, 95, 96, 99 or 110.

[00162] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2, 3, 16, 30, 35, 37, 40, 41, 44 or 55; and the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57, 58, 71, 85, 90, 92, 95, 96, 99 or 110, wherein the antisense strand and the sense strand sequences have sufficient complementarity to allow formation of a double stranded region between the antisense and the sense strand.

[00163] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide comprises: (a) a sense strand comprising X1 nucleotides, wherein at least one nucleotide is modified with a first modification, each of the remaining nucleotides is independently modified with a second modification, and X1 is an integer selected from 13-36, wherein the first modification and the second modification are different; and (b) an antisense strand comprising X2 nucleotides, wherein at least one nucleotide is modified with a third modification, each of the remaining nucleotides is independently modified with a fourth modification, and X2 is an integer selected from 18-31, wherein the third modification and the fourth modification are different.

[00164] In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure is 18-21 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 20-23. In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure is 20 or

21 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 22 or 23. In some embodiments, the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure equals the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure plus 2. In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure is 21 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 23. In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure is 20 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 22.

[00165] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide comprises: (a) a sense strand comprising 20 nucleotides, wherein at least one nucleotide is modified with a first modification, each of the remaining nucleotides is independently modified with a second modification, wherein the first modification and the second modification are the same or different; and (b) an antisense strand comprising 22 nucleotides, wherein at least one nucleotide is modified with a third modification, each of the remaining nucleotides is independently modified with a fourth modification, wherein the third modification and the fourth modification are the same or different.

[00166] In some embodiments, the sense strand of the isolated oligonucleotide of the present disclosure comprises at least one nucleotide having a modified phosphate backbone. In some embodiments, the antisense strand of the isolated oligonucleotide of the present disclosure comprises at least one nucleotide having a modified phosphate backbone. In some embodiments, in the sense strand or the antisense strand or both sense and antisense strands of the isolated oligonucleotide of the present disclosure, the modified phosphate backbone comprises a modified phosphodiester bond. In some embodiments, the modified phosphodiester bond is modified by replacing one or more oxygen atoms with a moiety, wherein the moiety is bonded to the phosphorus atom in the phosphodiester bond with a carbon, nitrogen, or sulfur atom in the moiety, or by forming a 2'-5' linkage. In some embodiments, the modified phosphodiester bond comprises phosphorothioate, phosphorodithioate, methylphosphonate, phosphoramidate diester, mesyl phosphoramidate, or phosphonoacetate.

[00167] In some embodiments, the isolated oligonucleotide of the present disclosure comprises one or more non-natural base-containing nucleotide, a locked nucleotide, or an abasic nucleotide.

In some embodiments, the isolated oligonucleotide of the present disclosure, the terminal nucleotide at the 5' end comprises a phosphate mimic. In some embodiments, the 5'-phosphate mimic is ethylphosphonate, vinylphosphonate or an analog thereof.

[00168] In some embodiments, the antisense strand of the isolated oligonucleotide of the present disclosure comprises at least two single-stranded nucleotides at the 3'-terminus. In some embodiments, the antisense strand of the isolated oligonucleotide of the present disclosure comprises two single-stranded nucleotides at the 3'-terminus.

[00169] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1311 to 1331, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUGA 3').

[00170] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1825 to 1845, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3').

[00171] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1829 to 1849, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3').

[00172] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1837 to 1857, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence

according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCCUUUUCAAA 3').

[00173] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1854 to 1874, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUACAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3').

[00174] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1860 to 1880, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAUUGGGUUUUA 3').

[00175] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1865 to 1885, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAUAAAUA 3').

[00176] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1873 to 1893, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAUAAAAGUAUA 3').

[00177] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1874 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUAA 3').

[00178] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 169 to 189, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3').

[00179] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 169 to 189; b) 1311 to 1331; and c) 1825 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% (e.g., between 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%), at a dose of 0.02 nM.

[00180] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 169 to 189; b) 1311 to 1331; and c) 1825 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region and that attenuates expression of the AGT mRNA by 20% to 50%, at a dose of 0.02 nM, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5'

UCAAAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUGA 3'); ii) an antisense strand of nucleic

acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAGUGA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAGUGUCCA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCUUUUCAA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUACAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAUUGGGUUUUA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAUUGGGUUUUUAAAUA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAUAAGUAUA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAUAAGUAUA 3'); or x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3').

[00181] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 169 to 189; b) 1311 to 1331; and c) 1825 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% (e.g., between 50% to 55%, 55% to 60%, 60% to 65%, 65%

to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 100%), at a dose of 0.1 nM.

[00182] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 169 to 189; b) 1311 to 1331; and c) 1825 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, that attenuate expression of the AGT mRNA by at least 50%, at a dose of 0.1 nM, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUUGA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCCUUUUCAAA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAAUUGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAAUUGGGUUUUA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAAAAUA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUAAAAGUAUA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5'

UUAUACUUUAAUUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUAA 3'); or x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3').

[00183] In some embodiments, the isolated oligonucleotide of the present disclosure can comprises a linker, sometimes referred to as a loop. siRNAs comprising a linker or loop are sometimes referred to as short hairpin RNAs (shRNAs). In some embodiments, both the sense and the antisense regions of the siRNA are encoded by one single-stranded RNA. In these embodiments, the antisense region and the sense region hybridize to form a duplex region. The sense and antisense regions are joined by a linker sequence, forming a "hairpin" or "stem-loop" structure. The siRNA can have complementary sense and antisense regions at opposing ends of a single stranded molecule, so that the molecule can form a duplex region with the complementary sequence portions, and the strands are linked at one end of the duplex region by a linker. The linker can be either a nucleotide or non-nucleotide linker or a combination thereof. The linker can interact with the first, and optionally, second strands through covalent bonds or non-covalent interactions.

[00184] Any suitable nucleotide linker sequence is envisaged as within the scope of the disclosure. An siRNA of this disclosure may include a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the nucleic acid to the antisense region of the nucleic acid. A nucleotide linker can be a linker of ≥ 2 nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 nucleotides in length.

[00185] Examples of a non-nucleotide linker include an abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric agents, for example polyethylene glycols such as those having from 2 to 100 ethylene glycol units. Some examples are described in Seela et al., *Nucleic Acids Research*, 1987, Vol. 15, pp. 3113-3129; Cload et al., *J. Am. Chem. Soc.*, 1991, Vol. 113, pp. 6324-6326; Jaeschke et al., *Tetrahedron Lett.*, 1993, Vol. 34, pp. 301; Arnold et al., WO 1989/002439; Usman et al., WO 1995/006731; Dudycz et al., WO 1995/011910, and Ferentz et al., *J. Am. Chem. Soc.*, 1991, Vol. 113, pp. 4000-4002.

[00186] Examples of nucleotide linker sequences include, but are not limited to, AUG, CCC, UUCG, CCACC, AAGCAA, CCACACC and UUCAAGAGA.

[00187] In some embodiments, the isolated oligonucleotide of the present disclosure is an siRNA that can be a dsRNA of a length suitable as a Dicer substrate, which can be processed to produce a RISC active siRNA molecule. See, e.g., Rossi et al., US2005/0244858.

[00188] A Dicer substrate double stranded RNA (dsRNA) can be of a length sufficient that it is processed by Dicer to produce an active siRNA, and may further include one or more of the following properties: (i) the Dicer substrate dsRNA can be asymmetric, for example, having a 3' overhang on the antisense strand, (ii) the Dicer substrate dsRNA can have a modified 3' end on the sense strand to direct orientation of Dicer binding and processing of the dsRNA to an active siRNA, for example the incorporation of one or more DNA nucleotides, and (iii) the first and second strands of the Dicer substrate ds RNA can from 19-30 bp in length.

[00189] In some embodiments, the isolated oligonucleotide of the present disclosure comprises at least one modified nucleotide. In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise one or more modified nucleotide(s). In some embodiments, only the sense strand comprises one or more modified nucleotide(s). In some embodiments, only the antisense strand comprises one or more modified nucleotide(s). In some embodiments, both the sense strand and antisense strand comprise one or more modified nucleotide(s). In some embodiments, the isolated oligonucleotide is partially chemically modified. In some embodiments, the isolated oligonucleotide is fully chemically modified.

[00190] In some embodiments, the isolated oligonucleotide comprises at least two modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least three modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least four modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least five modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least six modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least seven modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least eight modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least nine modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least ten modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least

eleven modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least twelve modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least thirteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least fourteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least fifteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least sixteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least seventeen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least eighteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least nineteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least twenty modified nucleotides. In some embodiments, the isolated oligonucleotide comprises more than twenty modified nucleotides. In some embodiments, the isolated oligonucleotide comprises between twenty and thirty modified nucleotides. In some embodiments, the isolated oligonucleotide comprises between thirty and forty modified nucleotides. In some embodiments, the isolated oligonucleotide comprises between forty and fifty modified nucleotides.

[00191] In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least one modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least two modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least three modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least four modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least five modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least six modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seven modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eight modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nine modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least ten modified nucleotides. In some

embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eleven modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twelve modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least thirteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fourteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fifteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least sixteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seventeen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eighteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nineteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twenty modified nucleotides.

[00192] In some embodiments, wherein the isolated oligonucleotide comprises more than one modified nucleotide, at least a first nucleotide comprises a first modification and at least a second nucleotide comprises a second modification. In some embodiments, the first modification and second modification are different. In some embodiments, the at least first nucleotide and the at least second nucleotide are located on different strands of the isolated oligonucleotide. In some embodiments, the at least first nucleotide and the at least second nucleotide are located on the same strand of the isolated oligonucleotide.

[00193] In some embodiments of the isolated oligonucleotide, wherein the isolated oligonucleotide comprises more than one modified nucleotide, at least a first modified nucleotide comprises a first modification, and at least a second modified nucleotide comprises a second modification, and at least a third nucleotide comprises a third modification. In some embodiments, the isolated oligonucleotide comprises a first, a second, a third and a fourth modifications. In some embodiments, the isolated oligonucleotide comprises more than four modifications. In some embodiments, all modifications are on the sense strand. In some

embodiments, all modifications are on the antisense strand. Any combination of locations of the modifications between the sense strand and antisense strand is envisaged within the isolated oligonucleotides of the present disclosure.

[00194] In some embodiments, the modified nucleotides are consecutively located on the sense strand or the antisense strand or both. In some embodiments, some but not all of the modified nucleotides are consecutively located on the sense strand or the antisense strand or both. In some embodiments, the modified nucleotides on the sense strand or the antisense strand or both are not consecutively located.

[00195] Envisaged within the present disclosure is an isolated oligonucleotide, wherein any nucleotide on the sense strand or antisense strand can be modified. In some embodiments, any nucleotide on the antisense strand can be modified. In some embodiments, any nucleotide on the antisense strand can be modified.

[00196] In some embodiments, the isolated oligonucleotide of the present disclosure comprises at least one modified nucleotide(s). In some embodiments, the one or more modified nucleotide(s) increases the stability or potency or both of the isolated oligonucleotide. In some embodiments, the one or more modified nucleotide(s) increases the stability of the RNA duplex, and siRNA.

[00197] Modifications that increase RNA stability include, but are not limited to locked nucleic acids. As used herein, the term "locked nucleic acid" or "LNA" includes, but is not limited to, a modified RNA nucleotide in which the ribose moiety comprises a methylene bridge connecting the 2' oxygen and the 4' carbon. This methylene bridge locks the ribose in the 3'-endo confirmation, also known as the north confirmation, that is found in A-form RNA duplexes. The term inaccessible RNA can be used interchangeably with LNA. LNAs having a 2'-4' cyclic linkage, as described in the International Patent Application WO 99/14226, WO 00/56746, WO 00/56748, and WO 00/66604, the contents of which are incorporated herein by reference.

[00198] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise at least one nucleotide having a modified phosphate backbone. In some embodiments, the sense strand of the isolated oligonucleotide comprises at least one nucleotide having a modified phosphate backbone. In some embodiments, the antisense strand of the isolated oligonucleotide comprises at least one nucleotide having a modified phosphate backbone. In some embodiments, wherein the isolated oligonucleotide of the

present disclosure comprises a modified phosphate backbone, the modified phosphate backbone comprises a modified phosphodiester bond. In some embodiments, the modified phosphodiester bond is modified by replacing one or more oxygen atoms with a moiety, wherein the moiety is bonded to the phosphorus atom in the phosphodiester bond with a carbon, nitrogen, or sulfur atom in the moiety, or by forming a 2'-5' linkage. In some embodiments, the modified phosphodiester bond comprises phosphorothioate, phosphorodithioate, methylphosphonate, phosphoramidate diester, mesyl phosphoramidate, or phosphonoacetate.

[00199] In some embodiments, the isolated oligonucleotide of the present disclosure comprises one or more non-natural base-containing nucleotide, a locked nucleotide, or an abasic nucleotide. In some embodiments, the one or more modified nucleotide comprises a phosphorothioate derivative or an acridinine substituted nucleotide. In some embodiments, the isolated oligonucleotides of the present disclosure comprise a phosphate mimic at the 5'-terminus of antisense strand, including but not limited to vinylphosphonate or other phosphate analogues. In some embodiments, the 5'-phosphate mimic is ethylphosphonate, vinylphosphonate or an analog thereof.

[00200] In some embodiments, the modified nucleotide comprises 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, or 2, 6-diaminopurine.

[00201] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise a terminal or internal nucleotide linked to one or more targeting ligands. In some embodiments, the terminal or internal nucleotide is linked to the one or more targeting ligands directly. In some embodiments, the terminal or internal nucleotide

is linked to the one or more targeting ligands indirectly by a linker. In some embodiments, the one or more targeting ligands linked directly or indirectly to the terminal or internal nucleotide can further comprise a PK modulator. In some embodiments, the PK modulator is a competitive modulator, a positive allosteric modulator, a negative allosteric modulator or a neutral allosteric modulator. In some embodiments, the targeting ligand is selected from one or more of a carbohydrate, a peptide, a lipid, an antibody or a fragment thereof, an aptamer, an albumin, a fibrinogen, and a folate.

[00202] Modification of the Nucleotides

[00203] Provided herein is an isolated oligonucleotide, comprising: (a) a sense strand comprising X1 nucleotides, wherein at least one nucleotide is modified with a first modification, each of the remaining nucleotides is independently modified with a second modification, and X1 is an integer selected from 13-36, wherein the first modification and the second modification are different; and (b) an antisense strand comprising X2 nucleotides, wherein at least one nucleotide is modified with a third modification, each of the remaining nucleotides is independently modified with a fourth modification, and X2 is an integer selected from 18-31, wherein the third modification and the fourth modification are different.

[00204] In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure, is 18-21 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 20-23. In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure, is 20 or 21 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 22 or 23. In some embodiments, the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure equals the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure plus 2. In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure is 21 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 23. In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure is 20 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 22.

[00205] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide comprises: (a) a sense strand comprising 20 nucleotides, wherein at least

one nucleotide is modified with a first modification, each of the remaining nucleotides is independently modified with a second modification, wherein the first modification and the second modification are the same or different; and (b) an antisense strand comprising 22 nucleotides, wherein at least one nucleotide is modified with a third modification, each of the remaining nucleotides is independently modified with a fourth modification, wherein the third modification and the fourth modification are the same or different.

[00206] In some embodiments, the first modification is modification of the sugar moiety of the at least one nucleotide at the 2'-position selected from 2'-F modification, 2'-CN modification, 2'-N3 modification, 2'-deoxy modification, and an equivalent thereof, and a combination thereof. In some embodiments, the first modification is 2'-F modification, 2'-CN modification, 2'-N3 modification, or 2'-deoxy modification, or a stereoisomer thereof. In some embodiments, the first modification is 2'-F modification, 2'-CN modification, or 2'-N3 modification, or a stereoisomer thereof. In some embodiments, the first modification is 2'-F modification or a stereoisomer thereof.

[00207] In some embodiments, the second modification is modification of the sugar moiety of one or more of the remaining nucleotides at the 2'-position selected from 2'-C1-C6 alkyl, 2'-OR modification wherein R is C1-C6 alkyl optionally substituted with C1-C6 alkoxy, acetamide, phenyl, or heteroaryl comprising a 5- or 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S, 2'-amino, and morpholino replacement, and an equivalent thereof, and a combination thereof. In some embodiments, the second modification is 2'-OR modification, or morpholino replacement, or a combination thereof. In some embodiments, the second modification is 2'-OR modification. In some embodiments, the second modification is 2'-O-methyl modification or 2'-methoxyethoxy modification. In some embodiments, the second modification is 2'-O-methyl modification. In some embodiments, the second modification is morpholino replacement.

[00208] In some embodiments, the first modification is 2'-F modification or a stereoisomer thereof, and the second modification is 2'-O-methyl modification or 2'-methoxyethoxy modification. In some embodiments, the first modification is 2'-F modification or a stereoisomer thereof, and the second modification is 2'-O-methyl modification.

[00209] In some embodiments, the third modification is modification of the sugar moiety of the at least one nucleotide at the 2'-position selected from 2'-F modification, 2'-CN modification,

2'-N3 modification, 2'-deoxy modification, and an equivalent thereof, and a combination thereof. In some embodiments, the third modification is 2'-F modification, 2'-CN modification, 2'-N3 modification, or 2'-deoxy modification, or a stereoisomer thereof. In some embodiments, the third modification is 2'-F modification, 2'-CN modification, or 2'-N3 modification, or a stereoisomer thereof. In some embodiments, the third modification is 2'-F modification or a stereoisomer thereof.

[00210] In some embodiments, the fourth modification is modification of the sugar moiety of one or more of the remaining nucleotides at the 2'-position selected from 2'-C₁-C₆ alkyl, 2'-OR modification wherein R is C₁-C₆ alkyl optionally substituted with C₁-C₆ alkoxy, acetamide, phenyl, or heteroaryl comprising a 5- or 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S, 2'-amino, and morpholino replacement, and an equivalent thereof, and a combination thereof. In some embodiments, the fourth modification is 2'-OR modification, or morpholino replacement, or a combination thereof. In some embodiments, the fourth modification is 2'-OR modification. In some embodiments, the fourth modification is 2'-O-methyl modification or 2'-methoxyethoxy modification. In some embodiments, the fourth modification is 2'-O-methyl modification. In some embodiments, the fourth modification is morpholino replacement.

[00211] In some embodiments, the third modification is 2'-F modification or a stereoisomer thereof, and the fourth modification is 2'-O-methyl modification or 2'-methoxyethoxy modification. In some embodiments, the third modification is 2'-F modification or a stereoisomer thereof, and the fourth modification is 2'-O-methyl modification.

[00212] Sense strand

[00213] In some embodiments of the isolated oligonucleotide of the present disclosure comprising a sense and an antisense strand, in the sense strand of the isolated oligonucleotide of the present disclosure, at least three nucleotides are modified with the first modification. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least two of the at least three nucleotides modified with the first modification are consecutively located. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least three of the at least three nucleotides modified with the first modification are consecutively located.

[00214] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, in the sense strand at least four nucleotides are modified with the first modification. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least three of the at least four nucleotides modified with the first modification are consecutively located. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least four of the at least four nucleotides modified with the first modification are consecutively located.

[00215] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, in the sense strand at least five nucleotides are modified with the first modification. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least three of the at least five nucleotides modified with the first modification are consecutively located. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least four of the at least five nucleotides modified with the first modification are consecutively located.

[00216] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, the at least three nucleotides, the at least four nucleotides, or the at least five nucleotides modified with the first modification are located from position 10 to position 15 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[00217] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, two of the at least three nucleotides modified with the first modification are located at positions selected from position 10, 11, 12, and 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, three of the at least three nucleotides modified with the first modification are located at positions selected from position 10, 11, 12, and 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least three nucleotides modified with the first modification is located at position 11 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[00218] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, three of the at least three nucleotides modified with the first modification are located

at positions 11, 12 and 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, three of the at least three nucleotides modified with the first modification are located at positions 12, 13 and 14 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, three of the at least three nucleotides modified with the first modification are located at positions 10, 11 and 12 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[00219] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 10 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 11 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 12 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 14 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 15 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[00220] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, the at least four nucleotides modified with the first modification are located at positions 10, 11, 12 and 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[00221] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, the at least five nucleotides modified with the first modification are located at positions 10, 11, 12, 13 and 15 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[00222] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises five nucleotides modified with the first modification, wherein the five nucleotides modified with the first modification are located at positions 10, 11, 12, 13 and 15 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[00223] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, not all of the at least three nucleotides, the at least four nucleotides, or the at least five nucleotides modified with the first modification are consecutively located. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, the at least three nucleotides, the at least four nucleotides, or the at least five nucleotides are modified with 2'-F modification.

[00224] In some embodiments, the sense strand of the isolated oligonucleotide of the present disclosure comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5' (M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3'.

[00225] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5' (M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3'.

[00226] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide,

F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5' (M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57, 58, 71, 85, 90, 92, 95, 96, 99 or 110.

[00227] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5' (M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 71.

[00228] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5' (M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 71, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 16.

[00229] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5' (M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 85.

[00230] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5' (M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide

sequence according to SEQ ID NO: 85, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 30.

[00231] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 57.

[00232] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 57, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 2.

[00233] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 58.

[00234] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide

sequence according to SEQ ID NO: 58, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 3.

[00235] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 90.

[00236] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 90, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 35.

[00237] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 110.

[00238] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide

sequence according to SEQ ID NO: 110, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 55.

[00239] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 92.

[00240] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 92, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 37.

[00241] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 95.

[00242] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide

sequence according to SEQ ID NO: 95, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 40.

[00243] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 96.

[00244] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 96, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 41.

[00245] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 99.

[00246] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' (M)_g(F)_h(M)_e(F)_d(M)_c(F)_b(M)_a 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'(M)₀(F)₀(M)₅(F)₁(M)₁(F)₄(M)₉ 3', and the sense strand comprises a nucleotide

sequence according to SEQ ID NO: 99, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 44.

[00247] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1311 to 1331, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUUGA 3').

[00248] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1825 to 1845, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3').

[00249] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1829 to 1849, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3').

[00250] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1837 to 1857, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCCUUUUCAAA 3').

[00251] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1854 to 1874, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence

according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUCAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3').

[00252] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1860 to 1880, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAUUGGGUUUUA 3').

[00253] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1865 to 1885, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAUAAAUA 3').

[00254] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1873 to 1893, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUUAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAUAUAAAGUAUA 3').

[00255] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1874 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUUAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAUAUAAAGUAUAA 3').

[00256] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 169 to 189, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3').

[00257] Antisense strand

[00258] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at most seven nucleotides are modified with the third modification.

[00259] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at most four of the at most seven nucleotides modified with the third modification are located from position 2 to position 8 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at least one of the at most seven nucleotides are modified with the third modification is located at position 2 from the first nucleotide at the 5'-terminus of the antisense strand.

[00260] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at most two of the at most seven nucleotides modified with the third modification are consecutively located. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, the at most two consecutively located of the at most seven nucleotides modified with the third modification are located at positions 2 and 3 from the first nucleotide at the 5'-terminus of the antisense strand.

[00261] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at least one of the at most seven nucleotides modified with the third modification is located at position 14 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two or three of the at most seven nucleotides modified with the third modification are located at positions selected from position 2, 3, 5, and 6 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, three of the at most seven nucleotides modified with the third modification are located at positions selected from position 2,

3, 5, and 6 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two of the at most seven nucleotides modified with the third modification are located at positions 2 and 5 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two of the at most seven nucleotides modified with the third modification are located at positions 2 and 3 from the first nucleotide at the 5'-terminus of the antisense strand.

[00262] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, three of the at most seven nucleotides modified with the third modification are located at positions 2, 3 and 5 from the first nucleotide at the 5'-terminus of the antisense strand.

[00263] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one or two of the at most seven nucleotides modified with the third modification are located at positions selected from position 14 and 16 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two of the at most seven nucleotides modified with the third modification are located at positions 14 and 16 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, the at most seven nucleotides are modified with 2'-F modification. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 14 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two of the at most seven nucleotides modified with the third modification is located at positions 14 and 16 from the first nucleotide at the 5'-terminus of the antisense strand.

[00264] In some embodiments of the isolated oligonucleotides of the present disclosure, wherein the antisense strand comprises at most seven nucleotides modified with the third modification, the at most seven nucleotides are modified with 2'-F modification. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 2 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the

isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 3 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 5 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 7 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 10 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 14 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 16 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, the at most seven nucleotides modified with the third modification are located at positions 2, 3, 5, 7, 10, 14 and 16 from the first nucleotide at the 5'-terminus of the antisense strand.

[00265] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, the antisense strand comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)_o(F)_o(M)_o(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5'.

[00266] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is

2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', the antisense strand comprises a nucleotide sequence according to any one of SEQ ID NOs: 2, 3, 16, 30, 35, 37, 40, 41, 44 or 55.

[00267] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 16.

[00268] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 16, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 71.

[00269] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 30.

[00270] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 30, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 85.

[00271] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 2.

[00272] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 2, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 57.

[00273] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l,

m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3' (M)_o(F)_o(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 3.

[00274] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3' (M)_o(F)_o(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 3, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 58.

[00275] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3' (M)_o(F)_o(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 35.

[00276] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3' (M)_o(F)_o(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 35, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 90.

[00277] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F

modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 55.

[00278] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 55, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 110.

[00279] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 37.

[00280] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand

comprises a nucleotide sequence according to SEQ ID NO: 37, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 92.

[00281] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 40.

[00282] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 40, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 95.

[00283] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)₀(F)₀(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 41.

[00284] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is

2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)_o(F)_o(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 41, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 96.

[00285] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)_o(F)_o(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 44.

[00286] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' (M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'(M)_o(F)_o(M)₆(F)₁(M)₁(F)₁(M)₃(F)₁(M)₂(F)₁(M)₁(F)₁(M)₁(F)₂(M)₁ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 44, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 99.

[00287] Targeting Ligand

[00288] In some embodiments, in the sense strand or the antisense strand or both of the isolated oligonucleotide of the present disclosure, a terminal or internal nucleotide is linked to a targeting ligand. In some embodiments, the targeting ligand is attached to one or more nucleotides at the 5' end of the sense strand of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand is attached to one or more nucleotides at the 3' end of the sense strand of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand is attached to one or more nucleotides at the 5' end of the antisense strand of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand is

attached to one or more nucleotides at the 3' end of the antisense strand of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand is attached to one or more nucleotides of the at least two single-stranded nucleotides at the 3'-terminus of the antisense strand of the isolated oligonucleotide of the present disclosure.

[00289] In some embodiments, the targeting ligand is selected from one or more of a carbohydrate, a peptide, a lipid, an antibody or a fragment thereof, an aptamer, an albumin, a fibrinogen, and a folate. In some embodiments, the targeting ligand binds to a surface protein on a cell expressing a target mRNA of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand mediates entry of the isolated oligonucleotide of the present disclosure, into a cell expressing a target mRNA of the isolated oligonucleotide of the present disclosure.

[00290] In some embodiments, the targeting ligand is a therapeutic ligand. In some embodiments, the targeting ligand is a therapeutic antibody.

[00291] In some embodiments, the targeting ligand is attached to the isolated oligonucleotide of the present disclosure by a linker. In some embodiments, the linker is any one of a protein, a DNA, an RNA or a chemical compound. In some embodiments, the isolated oligonucleotide, the linker and the targeting ligand, of the present disclosure form a scaffold. As used herein, the term "scaffold" refers to a compound or complex that comprises a linker of the present disclosure, wherein the linker is covalently attached to either a ligand or an isolated oligonucleotide or both.

[00292] In some embodiments, the isolated oligonucleotide, the linker and the targeting ligand, of the present disclosure form a conjugate. As used herein, the term "conjugate" refers to a compound or complex that comprises an isolated oligonucleotide being covalently attached to a ligand via a linker of the present disclosure.

[00293] As used herein, the term "targeting ligand" or "ligand" refers to a moiety that, when being covalently attached to GalNAc an oligonucleotide), is capable of mediating its entry into, or facilitating or allowing its delivery to, a target site (e.g., a target cell or tissue). In some embodiments, the targeting ligand comprises a sugar ligand moiety (e.g., N-acetylgalactosamine (GalNAc)) which may direct uptake of an oligonucleotide into the liver.

[00294] In some embodiments, the targeting ligand binds to the asialoglycoprotein receptor (ASGPR). In some embodiments, the targeting ligand binds to (e.g., through ASGPR) the liver, such as the parenchymal cells of the liver.

[00295] Suitable targeting ligands include, but are not limited to, the ligands disclosed in Winkler (Ther. Deliv., 2013, 4(7): 791-809), PCT Patent Appl'n Pub. Nos. WO/2016/100401, WO/2012/089352, and WO/2009/082607, and U.S. Patent Appl'n Pub. Nos. 2009/0239814, 2012/0136042, 2013/0158824, and 2009/0247608, each of which is incorporated by reference.

[00296] In some embodiments, the targeting ligand comprises a carbohydrate moiety.

[00297] As used herein, "carbohydrate moiety" refers to a moiety which comprises one or more monosaccharide units each having at least six carbon atoms (which may be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. In some embodiments, the carbohydrate moiety comprises a monosaccharide, a disaccharide, a trisaccharide, or a tetrasaccharide. In some embodiments, the carbohydrate moiety comprises an oligosaccharide containing from about 4-9 monosaccharide units. In some embodiments, the carbohydrate moiety comprises a polysaccharide (e.g., a starch, a glycogen, a cellulose, or a polysaccharide gum).

[00298] In some embodiments, the carbohydrate moiety comprises a monosaccharide, a disaccharide, a trisaccharide, or a tetrasaccharide. In some embodiments, the carbohydrate moiety comprises an oligosaccharide (e.g., containing from about four to about nine monosaccharide units). In some embodiments, the carbohydrate moiety comprises a polysaccharide (e.g., a starch, a glycogen, a cellulose, or a polysaccharide gum).

[00299] In some embodiments, the ligand is capable of binding to a human asialoglycoprotein receptor (ASGPR), e.g., human asialoglycoprotein receptor 2 (ASGPR2).

[00300] In some embodiments, the carbohydrate moiety comprises a sugar (e.g., one, two, or three sugar). In some embodiments, the carbohydrate moiety comprises galactose or a derivative thereof (e.g., one, two, or three galactose or the derivative thereof). In some embodiments, the carbohydrate moiety comprises N-acetylgalactosamine or a derivative thereof (e.g., one, two, or three N-acetylgalactosamine or the derivative thereof). In some embodiments, the carbohydrate moiety comprises N-acetyl-D-galactosylamine or a derivative thereof (e.g., one, two, or three N-acetyl-D-galactosylamine or the derivative thereof).

[00301] In some embodiments, the carbohydrate moiety comprises N-acetylgalactosamine (e.g., one, two, or three N-acetylgalactosamine). In some embodiments, the carbohydrate moiety comprises N-acetyl-D-galactosylamine (e.g., one, two, or three N-acetyl-D-galactosylamine).

[00302] In some embodiments, the carbohydrate moiety comprises mannose or a derivative thereof (e.g., mannose-6-phosphate). In some embodiments, the carbohydrate moiety further comprises a linking moiety that connects the one or more sugar (e.g., N-acetyl-D-galactosylamine) with a linker.

[00303] In some embodiments the linker comprises thioether (e.g., thiosuccinimide, or the hydrolysis analogue thereof), disulfide, triazole, phosphorothioate, phosphodiester, ester, amide, or any combination thereof. In some embodiments, the linker is a triantennary linking moiety. Suitable targeting ligands include, but are not limited to, the ligands disclosed in PCT Appl'n Pub. Nos. WO/2015/006740, WO/2016/100401, WO/2017/214112, WO/2018/039364, and WO/2018/045317, each of which is incorporated herein by reference.

[00304] In some embodiments, the targeting ligand comprises a lipid or a lipid moiety (e.g., one, two, or three lipid moiety). In some embodiments the lipid moiety comprises (e.g., one, two, of three of) C8-C24 fatty acid, cholesterol, vitamin, sterol, phospholipid, or any combination thereof.

[00305] In some embodiments, the targeting ligand comprises a peptide or a peptide moiety (e.g., one, two, or three peptide moiety). In some embodiments, the peptide moiety comprises (e.g., one, two, or three of) integrin, insulin, glucagon-like peptide, or any combination thereof. In some embodiments, the targeting ligand comprises an antibody or an antibody moiety (e.g., transferrin). In some embodiments, the targeting ligand comprises one, two, or three antibody moieties (e.g., transferrin).

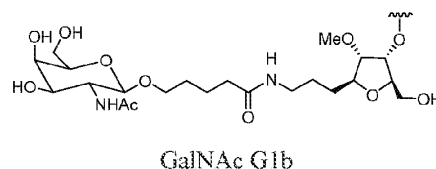
[00306] In some embodiments, the targeting ligand comprises an oligonucleotide (e.g., aptamer or CpG). In some embodiments, the targeting ligand comprises one, two, or three oligonucleotides (e.g., aptamer or CpG).

[00307] In some embodiments, the ligand comprises: one, two, or three sugar (e.g., N-acetyl-D-galactosylamine); one, two, or three lipid moieties; one, two, or three peptide moieties; one, two, or three antibody moieties; one, two, or three oligonucleotides; or any combination thereof.

[00308] In some embodiments, the linker is attached to the isolated oligonucleotide of the present disclosure, via a phosphate group, or an analog of a phosphate group, in the isolated oligonucleotide.

[00309] In some embodiments, the ligand comprises a sugar ligand moiety (e.g., N-acetylgalactosamine (GalNAc)) which may direct uptake of an oligonucleotide into the liver

[00310] In some embodiments, the ligand comprises GalNAc, or a derivative thereof. In some embodiments, the ligand comprises a GalNAc G1b structure shown below.



[00311] In some embodiments, the ligand comprises three GalNAc moieties, or three derivatives thereof. In some embodiments, the ligand comprises three GalNAc G1b moieties. In some embodiments, wherein the ligand comprises three GalNAc G1b moieties, the GalNAc G1b moieties are consecutively located. In some embodiments, the consecutively located GalNAc G1b moieties are located on the 3' end of the sense strand. In some embodiments, wherein the ligand comprises three GalNAc G1b ("G1b") moieties that are consecutively located, the first G1b moiety is linked to the second G1b moiety and the second G1b is linked to the third G1b moiety. In some embodiments, the first GalNAc G1b moiety is linked to the sense strand of the isolated oligonucleotide of the present disclosure.

[00312] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the ligand comprises three GalNAc G1b ("G1b") moieties, wherein the first GalNAc G1b moiety is linked to the sense strand of the isolated oligonucleotide, the first GalNAc G1b moiety is also linked to the second GalNAc G1b moiety, and the second G1b is linked to the third G1b moiety. In some embodiments, wherein the ligand comprises three GalNAc G1b moieties, the three GalNAc G1b moieties are consecutively located on the 3' end of the sense strand.

[00313] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide is linked to the ligand (e.g., GalNAc G1b, or three GalNAc G1b moieties). In some embodiments, the isolated oligonucleotide is linked to the ligand via an internal or terminal nucleotide of the isolated oligonucleotide. In some embodiments, the isolated oligonucleotide is linked to the ligand via a ligand linker. In some embodiments, the

[00314] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the isolated oligonucleotide comprises a sense and an antisense strand, and wherein the ligand comprises three GalNAc G1b moieties, and the three GalNAc G1b moieties are consecutively located on the 3' end of the sense strand, the ligand is linked to a terminal nucleotide on the

sense strand of the isolated oligonucleotide. In some embodiments, the ligand is linked to a terminal nucleotide on the sense strand via a ligand linker. In some embodiments, the ligand linker is a monovalent linker. In some embodiments, the ligand linker is a bivalent linker. In some embodiments, the ligand linker is a trivalent linker.

[00315] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 169 to 189; b) 1311 to 1331; and c) 1825 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, a targeting ligand is attached to the 3' end of the sense strand. In some embodiments, the targeting ligand comprising three GalNAc G1b moieties.

[00316] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 169 to 189; b) 1311 to 1331; and c) 1825 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, wherein the targeting ligand comprises three GalNAc G1b moieties attached to the 3' end of the sense strand, the sense strand comprises a nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUGA 3'); SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3'); SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3'); SEQ ID NO: 58 (5' AAAAGUGUCCCCUUUUCAAA 3'); SEQ ID NO: 90 (5' AAGUUGAGAACAAAAAUUGA 3'); SEQ ID NO: 110 (5' AGAACAAAAUUGGGUUUUA 3'); SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAAAAUA 3'); SEQ ID NO: 95 (5' GGUUUAAAAUUAAGUAUA 3'); SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUAA 3'); or SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3').

[00317] The linkage at the 3' end of the isolated oligonucleotide of the present disclosure may be directly via 5', 3' or 2' hydroxyl groups, or indirectly, via a non-nucleotide linker or a nucleoside, utilizing either the 2' or 3' hydroxyl positions of the nucleoside. Linkages may also utilize a functionalized sugar or nucleobase of a 3' terminal nucleotide. In some embodiments,

the ligand described herein can be attached to the isolated oligonucleotide of the present disclosure with various ligand linkers that can be cleavable or non-cleavable.

[00318] Modification of the Phosphate Groups

[00319] Modified Terminal Phosphate Groups

[00320] The present disclosure further provides oligonucleotides and conjugates containing modified phosphate groups (also referred to as phosphate mimics or phosphate derivatives) for nucleic acid delivery. The present disclosure also relates to uses of oligonucleotides and conjugates containing modified phosphate groups, e.g., in delivering nucleic acid and/or treating or preventing diseases.

[00321] In some embodiments, the present disclosure provides phosphate mimics of 5'-terminal nucleotides. Without wishing to be bound by theory, it is understood that, when being incorporated into oligonucleotides (e.g., at the 5'-terminus of the antisense strand), the phosphate mimics could improve the Ago2 binding/loading and enhance the metabolic stability of the oligonucleotides, thus enhancing the potency and duration of the isolated oligonucleotides (e.g., dsRNA or siRNA).

[00322] In some embodiments of the isolated oligonucleotides of the present disclosure, the oligonucleotides comprise 5'-terminal nucleotide modifications. In some embodiments, the 5'-terminal modifications provide the functional effect of a phosphate group, but are more stable in the environmental conditions that the oligonucleotide will be exposed to when administered to a subject. In some embodiments, the isolated oligonucleotide comprises phosphate mimics that are more resistant to phosphatases and other enzymes while minimizing negative impact on the oligonucleotide's function (e.g., minimizing any reduction in gene target knockdown when used as an RNAi inhibitor molecule).

[00323] In some embodiments, the 5'-terminal modification is a chemical modification. In some embodiments, the chemical modification enhances stability against nucleases or other enzymes that degrade or interfere with the structure or activity of the isolated oligonucleotide.

[00324] In some embodiments, the sense or antisense strand of the isolated oligonucleotides of the present disclosure comprise a 5'-terminal phosphate group. In some embodiments, the 5'-terminal phosphate group comprises an unmodified phosphate having the formula: -O-P(=O)(OH)OH. In some embodiments, the 5'-terminal phosphate group comprises a modified phosphate. In some embodiments, the 5'-terminal phosphate group comprises a modified

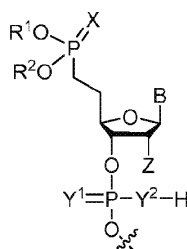
phosphate having the formula $-\text{CH}_2-\text{P}(=\text{X})(\text{OR}^1)\text{OR}^2$, wherein X is O or S, R^1 is H or C₁-C₆ alkyl, and R^2 is H or C₁-C₆ alkyl. In some embodiments, the modified phosphate is referred to as a “phosphate mimic”.

[00325] The term, “halo” or “halogen”, as used herein, refers to fluoro, chloro, bromo and iodo.

[00326] The term, “aryl”, as used herein, includes groups with aromaticity, including “conjugated,” or multicyclic systems with one or more aromatic rings and do not contain any heteroatom in the ring structure. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. Conveniently, an aryl is phenyl.

[00327] The term, “alkyl” or “C₁-C₆ alkyl”, as used herein, is intended to include C₁, C₂, C₃, C₄, C₅ or C₆ straight chain (linear) saturated aliphatic hydrocarbon groups and C₃, C₄, C₅ or C₆ branched saturated aliphatic hydrocarbon groups. For example, C₁-C₆ alkyl is intended to include C₁, C₂, C₃, C₄, C₅ and C₆ alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (e.g., C₁-C₆ for straight chain, C₃-C₆ for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms. In some embodiments, the straight chain alkyl has one carbon atom. In some embodiments, the straight chain alkyl has two carbon atoms.

[00328] In some embodiments, the phosphate mimic is linked to the 5'-terminus of the isolated oligonucleotides (e.g., siRNAs) as shown in the following formula:



wherein:

B is H or a nucleobase moiety;

X is O or S;

R^1 is H or C₁-C₆ alkyl;

R^2 is H or C₁-C₆ alkyl;

Y^1 is O or S;

Y^2 is O or S;

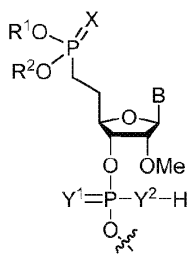
Z is H, halogen, or -OR^Z;

R^Z is H, C₁-C₆ alkyl, or -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), wherein the C₁-C₆ alkyl or -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) is optionally substituted with one or more R^{Za};

each R^{Za} independently is halogen, C₁-C₆ alkyl, or -O-(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl or -O-(C₁-C₆ alkyl) is optionally substituted with one or more halogen; and

 indicates an attachment to a nucleotide of the isolated oligonucleotide (e.g., siRNA).

[00329] In some embodiments, the phosphate mimic is linked to the 5'-terminus of the isolated oligonucleotides (e.g., siRNAs) as shown in the following formula:



wherein:

B is H or a nucleobase moiety;

X is O or S;

R^1 is H or C₁-C₆ alkyl;

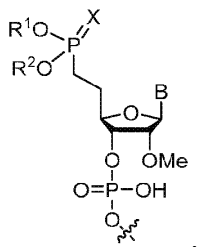
R^2 is H or C₁-C₆ alkyl;

Y^1 is O or S;

Y^2 is O or S; and

 indicates an attachment to a nucleotide of the isolated oligonucleotide (e.g., siRNA).

[00330] In some embodiments, the phosphate mimic is linked to the 5'-terminus of the isolated oligonucleotides (e.g., siRNAs) as shown in the following formula:



wherein:

B is H or a nucleobase moiety;

X is O or S;

R¹ is H or C₁-C₆ alkyl;

R² is H or C₁-C₆ alkyl; and

indicates an attachment to a nucleotide of the isolated oligonucleotide (e.g., siRNA).

[00331] In some embodiments, X is O.

[00332] In some embodiments, X is S.

[00333] In some embodiments, R¹ is H.

[00334] In some embodiments, R¹ is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[00335] In some embodiments, R¹ is methyl.

[00336] In some embodiments, R² is H.

[00337] In some embodiments, R² is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[00338] In some embodiments, R² is methyl.

[00339] In some embodiments, Y¹ is O.

[00340] In some embodiments, Y¹ is S.

[00341] In some embodiments, Y² is O.

[00342] In some embodiments, Y² is S.

[00343] In some embodiments, Z is H.

[00344] In some embodiments, Z is not H.

[00345] In some embodiments, Z is halogen (e.g., F, Cl, Br, or I).

[00346] In some embodiments, Z is F or Cl.

[00347] In some embodiments, Z is F

[00348] In some embodiments, Z is $-OR^Z$.

[00349] In some embodiments, Z is $-OH$.

[00350] In some embodiments, Z is not $-OH$.

[00351] In some embodiments, Z is $-O-(C_1-C_6 \text{ alkyl})$ (e.g., wherein the C_1-C_6 alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

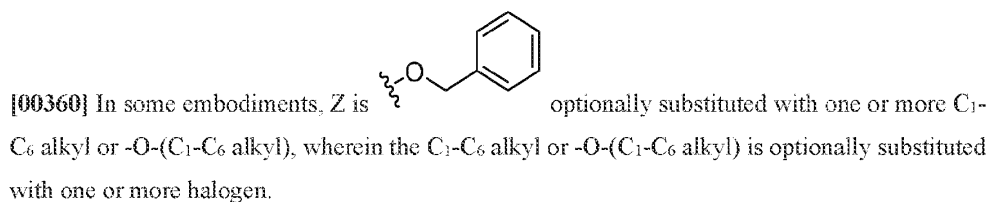
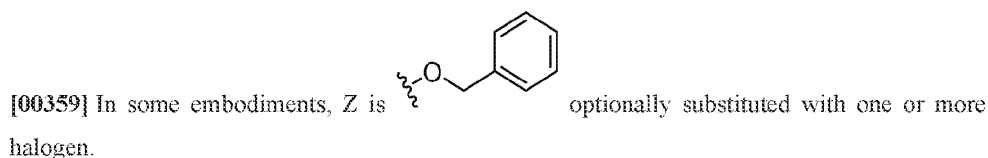
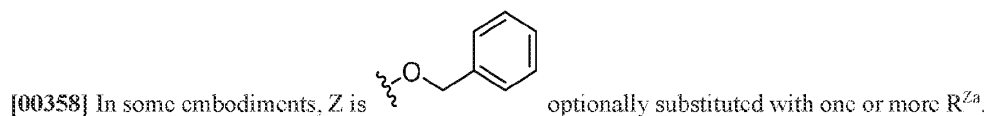
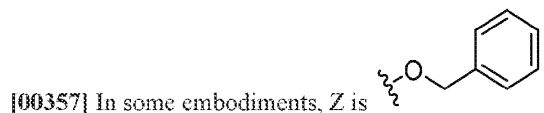
[00352] In some embodiments, Z is $-OCH_3$.

[00353] In some embodiments, Z is $-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ (e.g., wherein the C_1-C_6 alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[00354] In some embodiments, Z is $-OCH_2CH_2OCH_3$.

[00355] In some embodiments, Z is $-O-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$ optionally substituted with one or more R^{Za} .

[00356] In some embodiments, Z is $-O-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$.



[00361] In some embodiments, R^Z is H.

[00362] In some embodiments, R^Z is not H.

[00363] In some embodiments, R^Z is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more R^{Za} .

[00364] In some embodiments, R^Z is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I) or -O-(C₁-C₆ alkyl) (e.g., wherein the C₁-C₆ alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen.

[00365] In some embodiments, R^Z is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[00366] In some embodiments, R^Z is methyl, ethyl, or propyl.

[00367] In some embodiments, R^Z is methyl.

[00368] In some embodiments, R^Z is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[00369] In some embodiments, R^Z is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more -O-(C₁-C₆ alkyl) (e.g., wherein the C₁-C₆ alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), wherein the -O-(C₁-C₆ alkyl) is optionally substituted with one or more halogen.

[00370] In some embodiments, R^Z is -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) optionally substituted with one or more R^{Za} .

[00371] In some embodiments, R^Z is -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I), C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), or -O-(C₁-C₆ alkyl) (e.g., wherein the C₁-C₆ alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), wherein the C₁-C₆ alkyl or -O-(C₁-C₆ alkyl) is optionally substituted with one or more halogen.

[00372] In some embodiments, R^Z is -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl).

[00373] In some embodiments, at least one R^{Za} is halogen (e.g., F, Cl, Br, or I).

[00374] In some embodiments, at least one R^{Za} is F or Cl.

[00375] In some embodiments, at least one R^{Za} is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[00376] In some embodiments, at least one R^{Za} is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[00377] In some embodiments, at least one R^{Za} is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[00378] In some embodiments, at least one R^{Za} is $-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[00379] In some embodiments, at least one R^{Za} is $-O-(C_1-C_6 \text{ alkyl})$.

[00380] In some embodiments, at least one R^{Za} is $-O-(C_1-C_6 \text{ alkyl})$ substituted with one or more halogen (e.g., F, Cl, Br, or I).

[00381] In some embodiments, B is H.

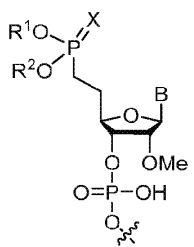
[00382] In some embodiments, B is a nucleobase moiety.

[00383] The term “nucleobase moiety”, as used herein, refers to a nucleobase that is attached to the rest of the isolated oligonucleotides (e.g., dsRNA or siRNA) of the present disclosure, e.g., via an atom of the nucleobase or a functional group thereof.

[00384] In some embodiments, the nucleobase moiety is adenine (A), cytosine (C), guanine (G), thymine (T), or uracil (U).

[00385] In some embodiments, the nucleobase moiety is uracil (U).

[00386] In some embodiments, the phosphate mimic is linked to the 5'-terminus of the isolated oligonucleotides as shown in the following formula:



wherein:

B is a nucleobase moiety, wherein the nucleobase moiety is uracil (U), wherein the uracil is at position 1 from the 5'-terminus of the sense strand or at position 1 from the 5'-terminus of the antisense strand;

X is O;

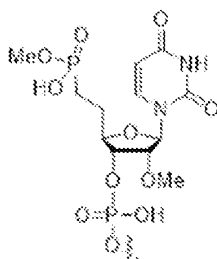
R^1 is C_1 alkyl;

R^2 is H; and

 indicates an attachment to a nucleotide of the isolated oligonucleotide (e.g., siRNA).

[00387] In some embodiments of the isolated oligonucleotides of the present disclosure, the phosphate mimic is attached to the 5'-terminus of the antisense strand of the isolated oligonucleotide.

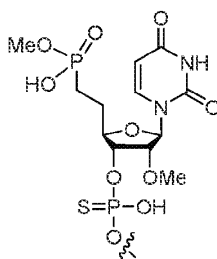
[00388] In some embodiments, the phosphate mimic is attached to a 5'-terminal uridine of the antisense strand of the isolated oligonucleotide, having the following structure (5'-MeEPmU).



5'-MeEPmU,

wherein "mU" is a 2'-O-methyl modified uridine nucleotide and "MeEP" is a mono methyl protected phosphate mimic.

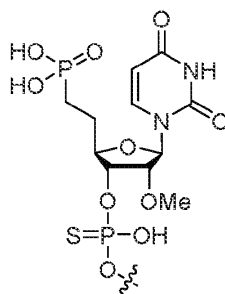
[00389] In some embodiments, the phosphate mimic is attached to a 5'-terminal uridine of the antisense strand of the isolated oligonucleotide, having the following structure (5'-MeEPmUs).



5'-MeEPmUs,

wherein "mU" is a 2'-O-methyl modified uridine nucleotide, "MeEP" is a mono methyl protected phosphate mimic, and "s" is a phosphorothioate internucleotide linkage.

[00390] In some embodiments, the phosphate mimic is attached to a 5'-terminal uridine of the antisense strand of the isolated oligonucleotide, having the following structure (5'-EPmUs).



5'-EPmUs,

wherein "mU" is a 2'-O-methyl modified uridine nucleotide, "EP" is a phosphate mimic, and "s" is a phosphorothioate internucleotide linkage.

[00391] The terms "5'-MeEP", "5' - MeEP", and "5' MeEP" are used interchangeably herein.

[00392] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 169 to 189; b) 1311 to 1331; and c) 1825 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the antisense strand comprises a mono methyl protected phosphate mimic (MeEP). In some embodiments, the MeEP is linked to the 5' end of the antisense strand (5'-MeEP).

[00393] In some embodiments, wherein the MeEP is linked to the 5' end of the antisense strand, the phosphate mimic is attached to a 5'-terminal uridine of the antisense strand.

[00394] In some embodiments, the 5'-terminal uridine is a 2'-O-methyl modified nucleotide.

[00395] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 169 to 189; b) 1311 to 1331; and c) 1825 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, wherein the antisense strand comprises a 5'-MeEP linked to the 5' end of the antisense strand, the antisense strand comprises a nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAAAAUGCUGUUCAGCA 3'); SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'); SEQ ID NO: 2 (5'

UGGAACACUUUUUUGUUUCACA 3'); SEQ ID NO: 3 (5'
 UUUGAAAAGGGAACACUUUUUU 3'); SEQ ID NO: 35 (5'
 UCAAUUUUUGUUCUACUUGA 3'); SEQ ID NO: 55 (5'
 UAAAACCCAAUUUUUGUUCUCA 3'); SEQ ID NO: 37 (5'
 UAUUUUAAAACCCAAUUUUUGU 3'); SEQ ID NO: 40 (5'
 UAUACUUUAAUUUUAAAACCCA 3'); SEQ ID NO: 41 (5'
 UUAUACUUUAAUUUUAAAACCC 3'); or SEQ ID NO: 44 (5'
 UGUACUCUCAUUGUGGAUGACG 3').

[00396] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 169 to 189; b) 1311 to 1331; and c) 1825 to 1894, from the 5' end of a AGT mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, wherein the antisense strand comprises a 5'-MeEP linked to the 5' end of the antisense strand, the sense strand comprises a targeting ligand comprising three GalNAc G1b moieties attached to the 3' end of the sense strand.

[00397] Modified Backbone Phosphate/Phosphodiester Bond

[00398] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise at least one nucleotide having a modified phosphate backbone. In some embodiments, the sense strand of the isolated oligonucleotide comprises at least one nucleotide having a modified phosphate backbone. In some embodiments, the antisense strand of the isolated oligonucleotide comprises at least one nucleotide having a modified phosphate backbone. In some embodiments, wherein the isolated oligonucleotide of the present disclosure comprises a modified phosphate backbone, the modified phosphate backbone comprises a modified phosphodiester bond. A phosphodiester bond comprises a linkage having the formula: $\overset{*}{\underset{\text{Z}^1}{\text{O}}}-\text{P}(=\text{Z}^2)\text{O}-\overset{*}{\underset{\text{Z}^2}{\text{O}}}$, wherein $\overset{*}{\underset{\text{Z}^1}{\text{O}}}$ denotes attachment to a 3' carbon of a first nucleotide in the isolated oligonucleotide of the present disclosure; and $\overset{*}{\underset{\text{Z}^2}{\text{O}}}$ denotes attachment to a 5' carbon of a second nucleotide in the isolated oligonucleotide of the present disclosure. In some embodiments, the phosphodiester bond is unmodified, wherein Z^1 is O and Z^2 is OH or O^- . In some embodiments, the phosphodiester bond is modified, wherein Z^1 is O, S, NH, or N(C₁-C₆

alkyl) and Z^2 is OH, SH, NH_2 , $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, O^- , S^- , HN^- , or $(\text{C}_1\text{-C}_6 \text{ alkyl})\text{N}^-$, and wherein when Z^1 is O, Z^2 is not OH or O^- .

[00399] In some embodiments, Z_1 is O.

[00400] In some embodiments, Z_1 is S.

[00401] In some embodiments, Z_1 is NH.

[00402] In some embodiments, Z_1 is $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})$.

[00403] In some embodiments, Z_2 is OH.

[00404] In some embodiments, Z_2 is SH.

[00405] In some embodiments, Z_2 is NH_2 .

[00406] In some embodiments, Z_2 is $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$.

[00407] In some embodiments, Z_2 is SH, NH_2 , or $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$.

[00408] In some embodiments, Z_2 is O^- .

[00409] In some embodiments, Z_2 is S^- .

[00410] In some embodiments, Z_2 is HN^- .

[00411] In some embodiments, Z_2 is $(\text{C}_1\text{-C}_6 \text{ alkyl})\text{N}^-$.

[00412] In some embodiments, Z_2 is S^- , HN^- , or $(\text{C}_1\text{-C}_6 \text{ alkyl})\text{N}^-$.

[00413] In some embodiments, Z_1 is O and Z_2 is SH.

[00414] In some embodiments, Z_1 is O and Z_2 is NH_2 .

[00415] In some embodiments, Z_1 is O and Z_2 is $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$.

[00416] In some embodiments, Z_1 is S and Z_2 is OH.

[00417] In some embodiments, Z_1 is S and Z_2 is SH.

[00418] In some embodiments, Z_1 is S and Z_2 is NH_2 .

[00419] In some embodiments, Z_1 is S and Z_2 is $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$.

[00420] In some embodiments, Z_1 is NH and Z_2 is OH.

[00421] In some embodiments, Z_1 is NH and Z_2 is SH.

[00422] In some embodiments, Z_1 is NH and Z_2 is NH_2 .

[00423] In some embodiments, Z_1 is NH and Z_2 is $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$.

[00424] In some embodiments, Z_1 is $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})$ and Z_2 is OH.

[00425] In some embodiments, Z_1 is $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})$ and Z_2 is SH.

[00426] In some embodiments, Z_1 is $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})$ and Z_2 is NH_2 .

[00427] In some embodiments, Z_1 is $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})$ and Z_2 is $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$.

[00428] In some embodiments, Z₁ is O and Z₂ is S⁻.

[00429] In some embodiments, Z₁ is O and Z₂ is HN⁻.

[00430] In some embodiments, Z₁ is O and Z₂ is (C₁-C₆ alkyl)N⁻.

[00431] In some embodiments, Z₁ is S and Z₂ is O⁻.

[00432] In some embodiments, Z₁ is S and Z₂ is S⁻.

[00433] In some embodiments, Z₁ is S and Z₂ is HN⁻.

[00434] In some embodiments, Z₁ is S and Z₂ is (C₁-C₆ alkyl)N⁻.

[00435] In some embodiments, Z₁ is NH and Z₂ is O⁻.

[00436] In some embodiments, Z₁ is NH and Z₂ is S⁻.

[00437] In some embodiments, Z₁ is NH and Z₂ is HN⁻.

[00438] In some embodiments, Z₁ is NH and Z₂ is (C₁-C₆ alkyl)N⁻.

[00439] In some embodiments, Z₁ is N(C₁-C₆ alkyl) and Z₂ is O⁻.

[00440] In some embodiments, Z₁ is N(C₁-C₆ alkyl) and Z₂ is S⁻.

[00441] In some embodiments, Z₁ is N(C₁-C₆ alkyl) and Z₂ is HN⁻.

[00442] In some embodiments, Z₁ is N(C₁-C₆ alkyl) and Z₂ is (C₁-C₆ alkyl)N⁻.

[00443] In some embodiments, the modified phosphodiester bond comprises a phosphorothioate internucleotide linkage.

[00444] In some embodiments, the modified phosphodiester bond comprises

$\overset{*}{\underset{\text{Z}}{\text{C}}}\text{-O-P(=S)(OH)O-}\overset{\text{Z}^{**}}{\underset{\text{Z}}{\text{C}}}$ or $\overset{*}{\underset{\text{Z}}{\text{C}}}\text{-O-P(=S)(O)O-}\overset{\text{Z}^{**}}{\underset{\text{Z}}{\text{C}}}$, wherein $\overset{*}{\underset{\text{Z}}{\text{C}}}$ denotes attachment to a 3' carbon of a

first nucleotide in the isolated oligonucleotide of the present disclosure; and $\overset{\text{Z}^{**}}{\underset{\text{Z}}{\text{C}}}$ denotes

attachment to a 5' carbon of a second nucleotide in the isolated oligonucleotide of the present disclosure.

[00445] In some embodiments, the modified phosphodiester bond comprises

$\overset{*}{\underset{\text{Z}}{\text{C}}}\text{-O-P(=S)(OH)O-}\overset{\text{Z}^{**}}{\underset{\text{Z}}{\text{C}}}$, wherein $\overset{*}{\underset{\text{Z}}{\text{C}}}$ denotes attachment to a 3' carbon of a first nucleotide in the

isolated oligonucleotide of the present disclosure; and $\overset{\text{Z}^{**}}{\underset{\text{Z}}{\text{C}}}$ denotes attachment to a 5' carbon of a second nucleotide in the isolated oligonucleotide of the present disclosure.

[00446] In some embodiments, the modified phosphodiester bond comprises

embodiments, the isolated oligonucleotide comprises at least nineteen modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least twenty modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises more than twenty modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises between twenty and thirty modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises between thirty and forty modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises between forty and fifty modified phosphodiester bonds.

[00449] In some embodiments, the isolated oligonucleotide comprises at least two phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least three phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least four phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least five phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least six phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least seven phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least eight phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least nine phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least ten phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least eleven phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least twelve phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least thirteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least fourteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least fifteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least sixteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least seventeen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least eighteen phosphorothioate internucleotide linkages. In some embodiments, the isolated

oligonucleotide comprises at least nineteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least twenty phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises more than twenty phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises between twenty and thirty phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises between thirty and forty phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises between forty and fifty phosphorothioate internucleotide linkages.

[00450] In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least one modified phosphodiester bond(s). In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least two modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least three modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least four modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least five modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least six modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seven modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eight modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nine modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least ten modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eleven modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twelve modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least thirteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each

comprise at least fourteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fifteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least sixteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seventeen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eighteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nineteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twenty modified phosphodiester bonds.

[00451] In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least one phosphorothioate internucleotide linkage(s). In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least two phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least three phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least four phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least five phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least six phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seven phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eight phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nine phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least ten phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide

each comprise at least eleven phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twelve phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least thirteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fourteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fifteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least sixteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seventeen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eighteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nineteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twenty phosphorothioate internucleotide linkages.

[00452] In some embodiments, the modified phosphodiester bonds are consecutively located on the sense strand or the antisense strand or both. In some embodiments, some but not all of the modified phosphodiester bonds are consecutively located on the sense strand or the antisense strand or both. In some embodiments, the modified phosphodiester bonds on the sense strand or the antisense strand or both are not consecutively located.

[00453] Envisaged within the present disclosure is an isolated oligonucleotide, wherein any phosphodiester bond on the sense strand or antisense strand can be modified. In some embodiments, any phosphodiester bond on the antisense strand can be modified. In some embodiments, any phosphodiester bond on the antisense strand can be modified.

[00454] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises between one and twenty, between one and fifteen, between one and ten, between one and five, or less than five modified phosphodiester bonds. In some embodiments, the between one and twenty, between one and fifteen, between one and ten,

between one and five, or less than five modified phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, the antisense strand comprises less than five modified phosphodiester bonds. In some embodiments, the antisense strand comprises one, two, three, or four modified phosphodiester bonds. In some embodiments, wherein the antisense strand comprises one, two, three, or four modified phosphodiester bonds, the one, two, three, or four modified phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, the antisense strand comprises four modified phosphodiester bonds. In some embodiments, wherein the antisense strand comprises four modified phosphodiester bonds, the modified phosphodiester bonds comprise phosphorothioate. [00455] In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 1 and position 2 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide bonds, the phosphorothioate internucleotide linkages connect the nucleotides at position 2 and position 3 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide bonds, the phosphorothioate internucleotide linkages connect the nucleotides at position 20 and position 21 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide bonds, the phosphorothioate internucleotide linkages connect the nucleotides at position 21 and position 22 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four modified phosphodiester bonds, wherein the modified phosphodiester bonds comprise phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 and 2, position 2 and 3, position 20 and 21, and position 21 and 22 from the first nucleotide at the 5'-terminus of the antisense strand.

[00456] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand comprises at least one, at least two, at least three, or at least four

phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 20 to 22 from the first nucleotide at the 5'-terminus of the antisense strand.

[00457] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand comprises at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 20 to 22 from the first nucleotide at the 5'-terminus of the antisense strand.

[00458] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises four phosphorothioate internucleotide linkages. In some embodiments, wherein the antisense strand comprises four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 20 to 22 from the first nucleotide at the 5'-terminus of the antisense strand.

[00459] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises between one and twenty, between one and fifteen, between one and ten, between one and five, or less than five modified phosphodiester bonds. In some embodiments, the between one and twenty, between one and fifteen, between one and ten, between one and five, or less than five modified phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, the sense strand comprises less than five modified phosphodiester bonds. In some embodiments, wherein the sense strand comprises less than five modified phosphodiester bonds, the sense strand comprises one, two, three, or four modified phosphodiester bonds. In some embodiments, wherein the sense strand comprises one, two, three, or four modified phosphodiester bonds, the one, two, three, or four modified phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, the sense strand comprises four modified phosphodiester bonds. In some embodiments, wherein the sense strand comprises four modified phosphodiester bonds, the modified phosphodiester bonds comprise phosphorothioate internucleotide linkages.

[00460] In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four modified phosphodiester bonds, the phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, wherein the sense strand

comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 1 and position 2 from the first nucleotide at the 5'-terminus of the sense strand. In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 2 and position 3 from the first nucleotide at the 5'-terminus of the sense strand. In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 18 and position 19 from the first nucleotide at the 5'-terminus of the sense strand. In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 19 and position 20 from the first nucleotide at the 5'-terminus of the sense strand. In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four modified phosphodiester bonds, wherein the modified phosphodiester bonds comprise phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 and 2, position 2 and 3, position 18 and 19, and position 19 and 20 from the first nucleotide at the 5'-terminus of the sense strand.

[00461] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 18 to 20 from the first nucleotide at the 5'-terminus of the sense strand.

[00462] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises at least four phosphorothioate internucleotide linkages, the at least four phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 18 to 20 from the first nucleotide at the 5'-terminus of the sense strand.

[00463] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises four phosphorothioate internucleotide linkages. In some embodiments, wherein

the sense strand comprises four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 18 to 20 from the first nucleotide at the 5'-terminus of the sense strand.

[00464] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand and the sense strand comprise four phosphorothioate internucleotide linkages, the antisense strand comprises phosphorothioate internucleotide linkages located between nucleotides at position 1 to 3 and nucleotides at position 20 to 22 from the first nucleotide at the 5'-terminus of the antisense strand, and the sense strand comprises phosphorothioate internucleotide linkages located between nucleotides at position 1 to 3 and nucleotides at position 18 to 20 from the first nucleotide at the 5'-terminus of the sense strand.

[00465] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises any one of: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 447 (5'

[MeEPmUs][fCs][fA][mA][fA][mA][fA][mA][mA][fA][mU][mG][mC][fU][mG][fU][mU][mC][mA][mGs][mCs][mA] 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 448 (5'

[MeEPmUs][fCs][fA][mC][fU][mU][fU][mU][mU][fU][mG][mU][mU][fU][mC][fA][mC][mA][mA][mAs][mCs][mA] 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 449 (5'

[MeEPmUs][fGs][fG][mA][fA][mC][fA][mC][mU][fU][mU][mU][mU][fU][mG][fU][mU][mU][mC][mAs][mCs][mA] 3'),

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 450 (5'

[MeEPmUs][fUs][fU][mG][fA][mA][fA][mA][mG][fG][mG][mA][mA][fC][mA][fC][mU][mU][mU][mUs][mUs][mU] 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 451 (5'

[MeEPmUs][fCs][fA][mA][fU][mU][fU][mU][mU][fG][mU][mU][mC][fU][mC][fA][mA][mC][mU][mUs][mGs][mA] 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 452 (5'

[MeEPmUs][fAs][fA][mA][fA][mC][fC][mC][mA][fA][mU][mU][mU][fU][mU][fG][mU][mU][mC][mUs][mCs][mA] 3'),

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 453 (5' [MeEPmUs][fAs][fU][mU][fU][mU][fA][mA][mA][fA][mC][mC][mC][fA][mA][fU][mU][mU][mU][mUs][mGs][mU] 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 454 (5' [MeEPmUs][fAs][fU][mA][fC][mU][fU][mU][mA][fA][mU][mU][mU][fU][mA][fA][mA][mA][mC][mCs][mCs][mA] 3'); or

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 455 (5' [MeEPmUs][fUs][fA][mU][fA][mC][fU][mU][mU][fA][mA][mU][mU][fU][mU][fA][mA][mA][mA][mCs][mCs][mC] 3'),

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 456 (5' [mUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG] 3'),

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 457 (5' [EPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG] 3'), or xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 458 (5'

[MeEPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, "MeEP" is a mono methyl protected phosphate mimic.

[00466] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises any one of: i) a sense strand of nucleic acid sequence according to SEQ ID NO: 460 (5'

[mCs][mUs][mG][mA][mA][fC][mA][fG][fC][fA][fU][mU][mU][mU][mU][mU][mU][mUs][mGs][mA][G1b][G1b][G1b] 3');

ii) a sense strand of nucleic acid sequence according to SEQ ID NO: 461 (5'

[mUs][mUs][mU][mG][mU][fG][mA][fA][fA][fC][fA][mA][mA][mA][mA][mA][mG][mUs][mGs][mA][G1b][G1b][G1b] 3');

iii) a sense strand of nucleic acid sequence according to SEQ ID NO: 462 (5'

[mUs][mGs][mA][mA][mA][fC][mA][fA][fA][fA][fA][mA][mG][mU][mG][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3'),

iv) a sense strand of nucleic acid sequence according to SEQ ID NO: 463 (5'

[mAs][mAs][mA][mA][mG][fU][mG][fU][fU][fC][fC][mC][mU][mU][mU][mU][mC][mAs][mAs][mA][G1b][G1b][G1b] 3');

v) a sense strand of nucleic acid sequence according to SEQ ID NO: 464 (5'

[mAs][mAs][mG][mU][mU][fG][mA][fG][fA][fA][fC][mA][mA][mA][mA][mA][mU][mUs][mGs][mA][G1b][G1b][G1b] 3');

vi) a sense strand of nucleic acid sequence according to SEQ ID NO: 465 (5'

[mAs][mGs][mA][mA][mC][fA][mA][fA][fA][fA][fU][mU][mG][mG][mG][mU][mU][mUs][mUs][mA][G1b][G1b][G1b] 3'),

vii) a sense strand of nucleic acid sequence according to SEQ ID NO: 466 (5'

[mAs][mAs][mA][mA][mA][fU][mU][fG][fG][fG][fU][mU][mU][mU][mA][mA][mA][mAs][mUs][mA][G1b][G1b][G1b] 3');

viii) a sense strand of nucleic acid sequence according to SEQ ID NO: 467 (5'

[mGs][mGs][mU][mU][mU][fU][mA][fA][fA][fA][fU][mU][mA][mA][mA][mG][mU][mAs][mUs][mA][G1b][G1b][G1b] 3');

ix) a sense strand of nucleic acid sequence according to SEQ ID NO: 468 (5'

[mGs][mUs][mU][mU][mU][fA][mA][fA][fA][fU][fU][mA][mA][mA][mG][mU][mA][mUs][mAs][mA][G1b][G1b][G1b] 3'), or

x) a sense strand of nucleic acid sequence according to SEQ ID NO: 469 (5'

[mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fA][fU][mG][mA][mG][mA][mG][mU][mAs][mCs][mA][G1b][G1b][G1b] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, and "G1b" is a GalNac G1b moiety.

[00467] In some embodiments of the isolated oligonucleotide of the present disclosure is selected from:

i) an antisense strand of SEQ ID NO: 447 (5'

[McEPmUs][fCs][fA][mA][fA][mA][fA][mA][mA][fA][mU][mG][mC][fU][mG][fU][mU][mC][mA][mGs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID

NO: 460 (5'

[mCs][mUs][mG][mA][mA][fC][mA][fG][fC][fA][fU][mU][mU][mU][mU][mU][mU][mUs][mGs][mA][G1b][G1b][G1b] 3');

ii) an antisense strand of SEQ ID NO: 448 (5'

[MeEPmUs][fCs][fA][mC][fU][mU][fU][mU][fU][mG][mU][mU][fU][mC][fA][mC][mA]
[mA][mAs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID
NO: 461 (5'

[mUs][mUs][mU][mG][mU][fG][mA][fA][fA][fC][fA][mA][mA][mA][mA][mA][mG][mUs][m
Gs][mA][G1b][G1b][G1b] 3');

iii) an antisense strand of SEQ ID NO: 449 (5'

[MeEPmUs][fGs][fG][mA][fA][mC][fA][mC][mU][fU][mU][mU][fU][mG][fU][mU][mU]
[mC][mAs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID
NO: 462 (5'

[mUs][mGs][mA][mA][mA][fC][mA][fA][fA][fA][fA][mA][mG][mU][mG][mU][mU][mCs][m
Cs][mA][G1b][G1b][G1b] 3');

iv) an antisense strand of SEQ ID NO: 450 (5'

[MeEPmUs][fUs][fU][mG][fA][mA][fA][mA][mG][fG][mG][mA][mA][fC][mA][fC][mU][mU]
[mU][mUs][mUs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID
NO: 463 (5'

[mAs][mAs][mA][mA][mG][fU][mG][fU][fU][fC][fC][mC][mU][mU][mU][mU][mC][mAs][m
As][mA][G1b][G1b][G1b] 3');

v) an antisense strand of SEQ ID NO: 451 (5'

[MeEPmUs][fCs][fA][mA][fU][mU][fU][mU][mU][fG][mU][mU][mC][fU][mC][fA][mA][mC]
[mU][mUs][mGs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID
NO: 464 (5'

[mAs][mAs][mG][mU][mU][fG][mA][fG][fA][fA][fC][mA][mA][mA][mA][mA][mU][mUs][m
Gs][mA][G1b][G1b][G1b] 3');

vi) an antisense strand of SEQ ID NO: 452 (5'

[MeEPmUs][fAs][fA][mA][fA][mC][fC][mC][mA][fA][mU][mU][mU][fU][mU][fG][mU][mU]
[mC][mUs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID
NO: 465 (5'

[mAs][mGs][mA][mA][mC][fA][mA][fA][fA][fA][fU][mU][mG][mG][mG][mU][mU][mUs][m
Us][mA][G1b][G1b][G1b] 3');

vii) an antisense strand of SEQ ID NO: 453 (5'

[MeEPmUs][fAs][fU][mU][fU][mU][fA][mA][mA][fA][mC][mC][mC][fA][mA][fU][mU][mU]
[mU][mUs][mGs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID
NO: 466 (5'

[mAs][mAs][mA][mA][mA][fU][mU][fG][fG][fG][fU][mU][mU][mU][mA][mA][mA][mAs][
mUs][mA][G1b][G1b][G1b] 3');

viii) an antisense strand of SEQ ID NO: 454 (5'

[MeEPmUs][fAs][fU][mA][fC][mU][fU][mU][mA][fA][mU][mU][mU][fU][mA][fA][mA][mA]
[mC][mCs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID
NO: 467 (5'

[mGs][mGs][mU][mU][mU][fU][mA][fA][fA][fA][fU][mU][mA][mA][mA][mG][mU][mAs][
mUs][mA][G1b][G1b][G1b] 3');

ix) an antisense strand of SEQ ID NO: 455 (5'

[MeEPmUs][fUs][fA][mU][fA][mC][fU][mU][mU][fA][mA][mU][mU][fU][mU][fA][mA][mA]
[mA][mCs][mCs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID
NO: 468 (5'

[mGs][mUs][mU][mU][mU][fA][mA][fA][fA][fU][fU][mA][mA][mA][mG][mU][mA][mUs][
mAs][mA][G1b][G1b][G1b] 3');

x) an antisense strand of SEQ ID NO: 456 (5'

[mUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][
mAs][mCs][mG] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 469
(5'

[mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fA][fU][mG][mA][mG][mA][mG][mU][mAs][m
Cs][mA][G1b][G1b][G1b] 3');

xi) an antisense strand of SEQ ID NO: 457 (5'

[EPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][m
G][mAs][mCs][mG] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO:
469 (5'

[mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fA][fU][mG][mA][mG][mA][mG][mU][mAs][m
Cs][mA][G1b][G1b][G1b] 3');

xii) an antisense strand of SEQ ID NO: 458 (5'

[MeEPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU]
[mG][mAs][mCs][mG] 3'), and a sense strand of nucleic acid sequence according to SEQ ID
NO: 469 (5'

[mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fA][fU][mG][mA][mG][mA][mG][mU][mAs][m
Cs][mA][G1b][G1b][G1b] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F
modified nucleotide, "s" is a phosphorothioate internucleotide linkage, "MeEP" is a mono
methyl protected phosphate mimic, and "G1b" is a GalNAc G1b moiety.

Nucleic Acids and Vectors

[00468] The present disclosure also provides a vector encoding an isolated oligonucleotide disclosed herein. In some embodiments, the vector is any one of a plasmid, a cosmid or a viral vector. In some embodiments, the vector is an adenoviral vector. In some embodiments, the vector is a lentiviral vector. In some embodiments, the plasmid is an expression plasmid.

[00469] The disclosure provides nucleic acids comprising the sequences encoding the isolated oligonucleotides of the present disclosure (e.g., dsRNAs or siRNAs) targeting AGT described herein.

[00470] In some embodiments, the nucleic acids are ribonucleic acids (RNAs). In some embodiments, the nucleic acids are deoxyribonucleic acids (DNAs). The DNAs may be a vector or a plasmid, e.g., an expression vector.

[00471] A "vector" is any nucleic acid molecule for the cloning of and/or transfer of a nucleic acid into a cell. A vector may be a replicon to which another nucleotide sequence may be attached to allow for replication of the attached nucleotide sequence. A "replicon" can be any genetic element (e.g., plasmid, phage, cosmid, chromosome, viral genome) that functions as an autonomous unit of nucleic acid replication in vivo, i.e., capable of replication under its own control. The term "vector" includes both viral and nonviral (e.g., plasmid) nucleic acid molecules for introducing a nucleic acid into a cell in vitro, ex vivo, and/or in vivo. A large number of vectors known in the art may be used to manipulate nucleic acids, incorporate response elements and promoters into genes, etc. For example, the insertion of the nucleic acid fragments corresponding to response elements and promoters into a suitable vector can be accomplished by ligating the appropriate nucleic acid fragments into a chosen vector that has complementary cohesive termini. Alternatively, the ends of the nucleic acid molecules may be enzymatically

modified or any site may be produced by ligating nucleotide sequences (linkers) to the nucleic acid termini. Such vectors may be engineered to contain sequences encoding selectable markers that provide for the selection of cells that contain the vector and/or have incorporated the nucleic acid of the vector into the cellular genome. Such markers allow identification and/or selection of host cells that incorporate and express the proteins encoded by the marker. A “recombinant” vector refers to a viral or non-viral vector that comprises one or more heterologous nucleotide sequences (i.e., transgenes), e.g., two, three, four, five or more heterologous nucleotide sequences.

[00472] By the term “express” or “expression” of a polynucleotide coding sequence, it is meant that the sequence is transcribed, and optionally, translated. Typically, according to the present disclosure, expression of a coding sequence of the disclosure will result in production of the polypeptide of the disclosure. The entire expressed polypeptide or fragment can also function in intact cells without purification.

[00473] In some embodiments, the vector is an expression vector for manufacturing siRNAs of the disclosure. Exemplary expression vectors may comprise a sequence encoding the sense and/or antisense strand of the isolated oligonucleotide of the present disclosure, under the control of a suitable promoter for transcription. Interfering RNAs may be expressed from a variety of eukaryotic promoters known to those of ordinary skill in the art, including pol III promoters, such as the U6 or H1 promoters, or pol II promoters, such as the cytomegalovirus promoter. Those of skill in the art will recognize that these promoters can also be adapted to allow inducible expression of the interfering RNA.

[00474] The isolated oligonucleotide of the present disclosure (e.g., dsRNAs and siRNAs) can be expressed endogenously from plasmid or viral expression vectors, or from minimal expression cassettes, for example, PCR generated fragments comprising one or more promoters and an appropriate template or templates for transcribing the siRNA. Examples of commercially available plasmid-based expression vectors for shRNA include members of the pSilencer series (Ambion, Austin, Tex.) and pCpG-siRNA (InvivoGen, San Diego, Calif.). Examples of kits for production of PCR-generated shRNA expression cassettes include Silencer Express (Ambion, Austin, Tex.) and siXpress (Mirus, Madison, Wis.).

[00475] Viral vectors for the in vivo expression of the isolated oligonucleotides (e.g., siRNAs and dsRNAs) in eukaryotic cells are also contemplated as within the scope of the instant

disclosure. Viral vectors may be derived from a variety of viruses including adenovirus, adeno-associated virus, lentivirus (e.g., HIV, FIV, and EIAV), and herpes virus. Examples of commercially available viral vectors for shRNA expression include pSilencer adeno (Ambion, Austin, Tex.) and pLenti6/BLOCK-iT™-DEST (Invitrogen, Carlsbad, Calif.). Selection of viral vectors, methods for expressing the siRNA from the vector and methods of delivering the viral vector, for example incorporated within a nanoparticle, are within the ordinary skill of one in the art.

[00476] It will be apparent to those skilled in the art that any suitable vector, optionally incorporated into a nanoparticle, can be used to deliver the isolated oligonucleotides of the present disclosure (e.g., dsRNAs or siRNAs) described herein to a cell or subject. The vector can be delivered to cells *in vivo*. In other embodiments, the vector can be delivered to cells *ex vivo*, and then cells containing the vector are delivered to the subject. The choice of delivery vector can be made based on a number of factors known in the art, including age and species of the target host, *in vitro* versus *in vivo* delivery, level and persistence of expression desired, intended purpose (e.g., for therapy or screening), the target cell or organ, route of delivery, size of the isolated polynucleotide, safety concerns, and the like.

Delivery Systems

[00477] The present disclosure also provides a delivery system comprising the isolated oligonucleotide disclosed herein or vector of the present disclosure encoding an isolated oligonucleotide disclosed herein. In some embodiments, the delivery system is any one of a liposome, a nanoparticle, a polymer based delivery system or a ligand-conjugate delivery system. In some embodiments, the ligand-conjugate delivery system comprises one or more of an antibody, a peptide, a sugar moiety or a combination thereof.

[00478] In some embodiments, the delivery system of the present disclosure comprises nanoparticles comprising the isolated oligonucleotides of the present disclosure (e.g., siRNA or dsRNAs) targeting a AGT mRNA for degradation.

[00479] In some embodiments, the nanoparticle comprises a polymer-based nanoparticle, a lipid-polymer based nanoparticle, a metal based nanoparticle, a carbon nanotube based nanoparticle, a nanocrystal or a polymeric micelle. In some embodiments, the polymer-based nanoparticle comprises a multiblock copolymer, a diblock copolymer, a polymeric micelle or a hyperbranched macromolecule. In some embodiments, the polymer-based nanoparticle comprises a multiblock

copolymer a diblock copolymer. In some embodiments, the polymer-based nanoparticle is pH responsive. In some embodiments, the polymer-based nanoparticle further comprises a buffering component.

[00480] In some embodiments, the delivery system comprises a liposome. Liposomes are spherical vesicles having at least one lipid bilayer, and in some embodiments, an aqueous core. In some embodiments, the lipid bilayer of the liposome may comprise phospholipids. An exemplary but non-limiting example of a phospholipid is phosphatidylcholine, but the lipid bilayer may comprise additional lipids, such as phosphatidylethanolamine. Liposomes may be multilamellar, i.e. consisting of several lamellar phase lipid bilayers, or unilamellar liposomes with a single lipid bilayer. Liposomes can be made in a particular size range that makes them viable targets for phagocytosis. Liposomes can range in size from 20 nm to 100 nm, 100 nm to 400 nm, 1 μ M and larger, or 200 nm to 3 μ M. Examples of lipidoids and lipid-based formulations are provided in U.S. Published Application 20090023673. In other embodiments, the one or more lipids are one or more cationic lipids. One skilled in the art will recognize which liposomes are appropriate for siRNA encapsulation.

[00481] In some embodiments, the liposome or the nanoparticle of the present disclosure comprises a micelle. A micelle is an aggregate of surfactant molecules. An exemplary micelle comprises an aggregate of amphiphilic macromolecules, polymers or copolymers in aqueous solution, wherein the hydrophilic head portions contact the surrounding solvent, while the hydrophobic tail regions are sequestered in the center of the micelle.

[00482] In some embodiments, the nanoparticle comprises a nanocrystal. Exemplary nanocrystals are crystalline particles with at least one dimension of less than 1000 nanometers, preferably of less than 100 nanometers.

[00483] In some embodiments, the nanoparticle comprises a polymer based nanoparticle. In some embodiments, the polymer comprises a multiblock copolymer, a diblock copolymer, a polymeric micelle or a hyperbranched macromolecule. In some embodiments, the particle comprises one or more cationic polymers. In some embodiments, the cationic polymer is chitosan, protamine, polylysine, polyhistidine, polyarginine or poly(ethylene)imine. In other embodiments, the one or more polymers contain the buffering component, degradable component, hydrophilic component, cleavable bond component or some combination thereof.

[00484] In some embodiments, the nanoparticles or some portion thereof are degradable. In other embodiments, the lipids and/or polymers of the nanoparticles are degradable.

[00485] In some embodiments, any of these delivery systems of the present disclosure can comprise a buffering component. In other embodiments, any of the of the present disclosure can comprise a buffering component and a degradable component. In still other embodiments, any of the of the present disclosure can comprise a buffering component and a hydrophilic component. In yet other embodiments, any of the of the present disclosure can comprise a buffering component and a cleavable bond component. In yet other embodiments, any of the of the present disclosure can comprise a buffering component, a degradable component and a hydrophilic component. In still other embodiments, any of the of the present disclosure can comprise a buffering component, a degradable component and a cleavable bond component. In further embodiments, any of the of the present disclosure can comprise a buffering component, a hydrophilic component and a cleavable bond component. In yet another embodiment, any of the of the present disclosure can comprise a buffering component, a degradable component, a hydrophilic component and a cleavable bond component. In some embodiments, the particle is composed of one or more polymers that contain any of the aforementioned combinations of components.

[00486] In some embodiments of the isolated oligonucleotides of the present disclosure, the delivery system comprises a ligand-conjugate delivery system. In some embodiments, the ligand-conjugate delivery system comprises one or more of an antibody, a peptide, a sugar moiety, lipid or a combination thereof

[00487] In further embodiments, the isolated oligonucleotide of the present disclosure targeting a AGT mRNA (e.g., siRNA or dsRNA) is conjugated to, complexed to, or encapsulated by the one or more lipids or polymers of the delivery system. In further embodiments, the isolated oligonucleotide of the present disclosure targeting a AGT mRNA (e.g., siRNA or dsRNA) can be encapsulated in the hollow core of a nanoparticle. Alternatively, or in addition, the isolated oligonucleotide of the present disclosure targeting a AGT mRNA (e.g., siRNA or dsRNA) can be incorporated into the lipid or polymer-based shell of the delivery system, for example via intercalation. Alternatively, or in addition, the isolated oligonucleotide of the present disclosure targeting a AGT mRNA (e.g., siRNA or dsRNA) can be attached to the surface of the delivery system. In some embodiments, the isolated oligonucleotide of the present disclosure targeting a

AGT mRNA (e.g., siRNA or dsRNA) is conjugated to one or more lipids or polymers of the delivery system, e.g. via covalent attachment.

[00488] In some embodiments, the ligand conjugate delivery system further comprises a targeting agent. In some embodiments, the targeting agent comprises a peptide ligand, a nucleotide ligand, a polysaccharide ligand, a fatty acid ligand, a lipid ligand, a small molecule ligand, an antibody, an antibody fragment, an antibody mimetic or an antibody mimetic fragment.

[00489] In some embodiments, the isolated oligonucleotide disclosed herein may further comprise a ligand that facilitates delivery or uptake of the isolated oligonucleotide to a particular tissue or cell, such as a liver cell. In certain embodiments, the ligand targets delivery of the RNAi construct to hepatocytes. In these and other embodiments, the ligand may comprise galactose, galactosamine or N-acetyl-galactosamine (GalNAc). In certain embodiments, the ligand comprises a multivalent galactose or multivalent GalNAc moiety, such as a trivalent or tetravalent galactose or GalNAc moiety. The ligand can be covalently attached to the 5' or 3' end of the sense strand of the RNAi construct, optionally via a linker.

[00490] In some embodiments, the targeting agent comprises a binding partner for a cell surface protein that is upregulated or overexpressed or normally expressed in a target cell encoding AGT mRNA and expressing AGT protein. In some embodiments, the binding partner can be a transmembrane peptidoglycan expressed on the surface of many types of such cells. Targeting of cell surface protein by the delivery system of the present disclosure thus provides superior delivery and specificity of the compositions of the disclosure to target cells. In some embodiments, the target cell can be any one of an intestinal cell, an arterial cell, a cell of the cardiovascular system, a hepatocyte, a pancreatic cell or a combination thereof.

[00491] In some embodiments, the delivery system of the present disclosure comprises a polymer based delivery system. In some embodiments, polymer based delivery system comprises a blending polymer. In some embodiments, the blending polymer is a copolymer comprising a degradable component and hydrophilic component. In some embodiments, the degradable component of the blending polymer is a polyester, poly(ortho ester), poly(ethylene imine), poly(caprolactone), polyanhydride, poly(acrylic acid), polyglycolide or poly(urethane). In some embodiments, the degradable component of the blending polymer is poly(lactic acid) (PLA) or poly(lactic-co-glycolic acid) (PLGA). In some embodiments, the hydrophilic component of the

blending polymer is a polyalkylene glycol or a polyalkylene oxide. In some embodiments, the polyalkylene glycol is polyethylene glycol (PEG). In other embodiments, the polyalkylene oxide is polyethylene oxide (PEO).

[00492] In some embodiments, the delivery system of the present disclosure is a polymer-based nanoparticle. Polymer based nanoparticles comprise one or more polymers. In some embodiments, the one or more polymers comprise a polyester, poly(ortho ester), poly(ethylene imine), poly(caprolactone), polyanhydride, poly(acrylic acid), polyglycolide or poly(urethane). In still other embodiments, the one or more polymers comprise poly(lactic acid) (PLA) or poly(lactic-co-glycolic acid) (PLGA). In some embodiments, the one or more polymers comprise poly(lactic-co-glycolic acid) (PLGA). In some embodiments, the one or more polymers comprise poly(lactic acid) (PLA). In some embodiments, the one or more polymers comprise polyalkylene glycol or a polyalkylene oxide. In some embodiments, the polyalkylene glycol is polyethylene glycol (PEG) or the polyalkylene oxide is polyethylene oxide (PEO).

[00493] In some embodiments, the polymer-based nanoparticle comprises poly(lactic-co-glycolic acid) PLGA polymers. In some embodiments, the PLGA nanoparticle further comprises a targeting agent, as described herein.

[00494] In some embodiments, the delivery system of the present disclosure is a nanoparticle of average characteristic dimension of less than about 500 nm, 400 nm, 300 nm, 250 nm, 200 nm, 180 nm, 150 nm, 120 nm, 100 nm, 90 nm, 80 nm, 70 nm, 60 nm, 50 nm, 40 nm, 30 nm or 20 nm. In other embodiments, the nanoparticle has an average characteristic dimension of 10 nm, 20 nm, 30 nm, 40 nm, 50 nm, 60 nm, 70 nm, 80 nm, 90 nm, 100 nm, 120 nm, 150 nm, 180 nm, 200 nm, 250 nm or 300 nm. In further embodiments, the nanoparticle has an average characteristic dimension of 10-500 nm, 10-400 nm, 10-300 nm, 10-250 nm, 10-200 nm, 10-150 nm, 10-100 nm, 10-75 nm, 10-50 nm, 50-500 nm, 50-400 nm, 50-300 nm, 50-200 nm, 50-150 nm, 50-100 nm, 50-75 nm, 100-500 nm, 100-400 nm, 100-300 nm, 100-250 nm, 100-200 nm, 100-150 nm, 150-500 nm, 150-400 nm, 150-300 nm, 150-250 nm, 150-200 nm, 200-500 nm, 200-400 nm, 200-300 nm, 200-250 nm, 200-500 nm, 200-400 nm or 200-300 nm.

Therapeutic Agents

[00495] In some embodiments, the delivery system of the present disclosure are administered with one or more additional therapeutic agents. In some embodiments, the additional therapeutic

agents can be a steroid, an anti-inflammatory agent, an antibody, a fusion protein, a small molecule or combination thereof.

[00496] In some embodiments, the additional therapeutic agent is incorporated into a delivery system of the present disclosure comprising at least one isolated oligonucleotide targeting AGT, disclosed herein. In some embodiments, the additional therapeutic agent is conjugated to, complexed to, or encapsulated by the one or more lipids or polymers of the delivery system. Additional therapeutic agents can be encapsulated in the hollow core of delivery system. Alternatively, or in addition, Additional therapeutic agents can be incorporated into the lipid or polymer based shell of the delivery system, for example via intercalation. Alternatively, or in addition, additional therapeutic agents can be attached to the surface of the delivery system. In some embodiments, the additional therapeutic agents are conjugated to one or more lipids or polymers of the delivery system, e.g. via covalent attachment.

[00497] In some embodiments, the additional therapeutic agent and the delivery system at least one isolated oligonucleotide targeting AGT, disclosed herein, are formulated in the same composition. For example, the delivery system comprising isolated oligonucleotide of the present disclosure targeting AGT and the additional therapeutic agent can be formulated in the same pharmaceutical composition.

[00498] In some embodiments, the additional therapeutic agent and the delivery system comprises at least one isolated oligonucleotide targeting AGT, disclosed herein are formulated as separate compositions, e.g., for separate administration to a subject.

Pharmaceutical Compositions

[00499] The present disclosure also provides a pharmaceutical composition comprising: an isolated oligonucleotide disclosed herein, a vector of the present disclosure encoding an isolated oligonucleotide disclosed herein, or a delivery system of the present disclosure, and a pharmaceutically acceptable carrier, diluent, or excipient.

[00500] The pharmaceutical compositions of the disclosure can optionally comprise therapeutic agents, pharmaceutical agents, carriers, adjuvants, dispersing agents, diluents, and the like.

[00501] In some embodiments, the pharmaceutical composition comprises a therapeutic agent, such as a chemotherapeutic agent. In some embodiments, the therapeutic agent is formulated in the delivery system comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT of the present disclosure.

[00502] In some embodiments, an additional therapeutic agent is not formulated in the delivery system comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT of the present disclosure, but both the delivery system and the therapeutic agent are formulated in the same pharmaceutical composition. In some embodiments, an additional therapeutic agent is not formulated in the delivery system comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT of the present disclosure, and the delivery system and the therapeutic agent are formulated in separate pharmaceutical compositions.

[00503] Pharmaceutical compositions can contain any of the reagents discussed above, and one or more of a pharmaceutically acceptable carrier, a diluent or an excipient.

[00504] A pharmaceutical composition is in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (e.g., a formulation of the disclosed agent) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active agent is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[00505] As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00506] “Pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[00507] A pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), intraperitoneal (into the body cavity) and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, intraperitoneal or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. These preparations can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions can include suspending agents and thickening agents. The formulations can be presented in unit/dose or multi-dose containers, for example sealed ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection immediately prior to use.

[00508] The pharmaceutical compositions containing the nanoparticles described herein may be manufactured in a manner that is generally known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active agents into preparations that can be used

pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[00509] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required nanoparticle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00510] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active agent can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the agents in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or agents of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent

such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00511] For administration by inhalation, the agents are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[00512] The pharmaceutical compositions of the present disclosure can be prepared with pharmaceutically acceptable carriers that will protect the one or more isolated oligonucleotides (e.g., dsRNAs or siRNAs) targeting AGT mRNA of the present disclosure against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art, and the materials can be obtained commercially. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[00513] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active agent calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active agent and the particular therapeutic effect to be achieved.

[00514] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[00515] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the

conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids.

[00516] Techniques for formulation and administration of the disclosed compositions of the disclosure can be found in Remington: the Science and Practice of Pharmacy, 19th edition, Mack Publishing Co., Easton, PA (1995).

[00517] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

Methods of Making Isolated Oligonucleotides

[00518] Provided herein are methods of making the one or more oligonucleotides of (e.g., dsRNAs or siRNAs) targeting AGT of the present disclosure, and delivery systems comprising same.

[00519] The one or more oligonucleotides of (e.g., dsRNAs or siRNAs) targeting AGT of the present disclosure, may be generated exogenously by chemical synthesis, by in vitro transcription, or by cleavage of longer double-stranded RNA with Dicer or another appropriate nuclease with similar activity. Chemically synthesized siRNAs, produced from protected ribonucleoside phosphoramidites using a conventional DNA/RNA synthesizer, may be obtained from commercial suppliers. The siRNAs can be purified by extraction with a solvent or resin, precipitation, electrophoresis, chromatography, or a combination thereof, for example. Alternatively, siRNAs may be used with little if any purification to avoid losses due to sample processing.

[00520] In some embodiments, the one or more oligonucleotides of (e.g., dsRNAs or siRNAs) targeting AGT of the present disclosure can be produced using an expression vector into which a nucleic acid encoding the double stranded RNA has been cloned, for example under control of a suitable promoter.

[00521] In some embodiments, the one or more oligonucleotides of (e.g., dsRNAs or siRNAs) targeting AGT of the present disclosure can be incorporated in a delivery system of the present disclosure (e.g., a nanoparticle).

[00522] Delivery systems comprising dsRNAs or siRNAs of the disclosure can be prepared by any suitable means known in the art. For example, polymeric nanoparticles can be prepared using various methods including, but not limited to, solvent evaporation, spontaneous emulsification, solvent diffusion, desolation, dialysis, ionic gelation, nanoprecipitation, salting out, spray drying and supercritical fluid methods. The dispersion of preformed polymers and the polymerization of monomers are two additional strategies for preparation of polymeric nanoparticles. However, the choice of an appropriate method depends upon various factors, which will be known to the person of ordinary skill in the art.

[00523] Sterile injectable solutions comprising a delivery system of the disclosure can be prepared by incorporating the one or more isolated oligonucleotides (e.g. dsRNA and siRNA) targeting AGT disclosed herein, in the delivery systems (e.g. nanoparticle) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated herein, as required, followed by filtered sterilization. Alternatively, or in addition, sterilization can be achieved through other means such as radiation or gas. Generally, dispersions are prepared by incorporating the delivery particles into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze drying that yields a powder of delivery system comprising the one or more isolated oligonucleotides (e.g. dsRNA and siRNA) targeting AGT disclosed herein, plus any additional desired ingredient from a previously sterile filtered solution thereof.

Methods of Use

[00524] The present disclosure also provides a method of inhibiting or downregulating the expression or level of AGT in a subject in need thereof, wherein the method comprises administering to the subject an effective amount an isolated oligonucleotide disclosed herein, a vector of the of the present disclosure encoding an isolated oligonucleotide disclosed herein, a delivery system of the present disclosure, or a pharmaceutical composition of the present disclosure.

[00525] The present disclosure also provides a method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role in a subject in need thereof, wherein the method comprises administering to the subject an effective amount an isolated oligonucleotide disclosed herein, a

vector of the of the present disclosure encoding an isolated oligonucleotide disclosed herein, a delivery system of the present disclosure, or a pharmaceutical composition of the present disclosure.

[00526] The present disclosure also provides an isolated oligonucleotide disclosed herein, a vector of the of the present disclosure encoding an isolated oligonucleotide disclosed herein, a delivery system of the present disclosure, or a pharmaceutical composition of the present disclosure, for use in treatment or prevention of a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role, in a subject in need thereof.

[00527] The present disclosure also provides use of an isolated oligonucleotide disclosed herein, a vector of the of the present disclosure encoding an isolated oligonucleotide disclosed herein, a delivery system of the present disclosure, or a pharmaceutical composition of the present disclosure, in the manufacture of a medicament for treatment or prevention of a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role in a subject in need thereof.

[00528] Provided herein are methods of inhibiting or downregulating AGT expression or activity in a cell, comprising contacting the cell with the one or more oligonucleotides (e.g., dsRNA or siRNA) targeting AGT as described herein. The one or more oligonucleotides (e.g., dsRNA or siRNA) targeting AGT as described herein can reduce or inhibit AGT activity through the RNAi pathway. The cell can be *in vitro*, *in vivo* or *ex vivo*. For example, the cell can be from a cell line, or *in vivo* in a subject in need thereof.

[00529] In some embodiments, the one or more oligonucleotides (e.g., dsRNA or siRNA) targeting AGT as described herein are capable of inducing RNAi-mediated degradation of an AGT mRNA in a cell of a subject.

[00530] As used herein, the terms “contacting,” “introducing” and “administering” are used interchangeably, and refer to a process by which dsRNA or siRNA of the present disclosure or a nucleic acid molecule encoding a dsRNA or siRNA of this disclosure is delivered to a cell, in order to inhibit or alter or modify expression of a target gene. The dsRNA may be administered in a number of ways, including, but not limited to, direct introduction into a cell (i.e., intracellularly) and/or extracellular introduction into a cavity, interstitial space, or into the circulation of the organism.

[00531] “Introducing” in the context of a cell or organism means presenting the nucleic acid molecule to the organism and/or cell in such a manner that the nucleic acid molecule gains access to the interior of a cell. Where more than one nucleic acid molecule is to be introduced these nucleic acid molecules can be assembled as part of a single polynucleotide or nucleic acid construct, or as separate polynucleotide or nucleic acid constructs, and can be located on the same or different nucleic acid constructs. Accordingly, these polynucleotides can be introduced into cells in a single transformation event or in separate transformation events. Thus, the term “transformation” as used herein refers to the introduction of a heterologous nucleic acid into a cell. Transformation of a cell may be stable or transient.

[00532] The term “inhibit” or “reduce” or grammatical variations thereof, as used herein, refer to a decrease or diminishment in the specified level or activity of at least about 5%, about 10%, about 15%, about 25%, about 35%, about 40%, about 50%, about 60%, about 75%, about 80%, about 90%, about 95% or more. In some embodiments, the inhibition or reduction results in little or essentially no detectable activity (at most, an insignificant amount, *e.g.*, less than about 10% or even 5%).

[00533] In contrast, the term “increase” or grammatical variations thereof as used herein refers to an increase or elevation in the specified level or activity of at least about 5%, about 10%, about 15%, about 25%, about 35%, about 40%, about 50%, about 60%, about 75%, about 80%, about 90%, about 95% or more. Increases in activity can be described in terms of fold change. For example, activity can be increased 1.2X, 1.5X, 2X, 3X, 5X, 6X, 7X, 8X, 9X, 10X or more compared to a baseline level of activity.

[00534] As used herein, the term “IC₅₀” or “IC₅₀ value” refers to the concentration of an agent where cell viability is reduced by half. The IC₅₀ is thus a measure of the effectiveness of an agent in inhibiting a biological process. In an exemplary model, cell lines are cultured using standard techniques, treated with any of the one or more oligonucleotides (*e.g.*, dsRNA or siRNA) targeting AGT as described herein, and the IC₅₀ value of the oligonucleotides (*e.g.*, dsRNA or siRNA) targeting AGT is calculated after 24, 48 and/or 72 hours to determine its effectiveness in downregulating or inhibiting the level of AGT mRNA or protein to 50%, as compared to the level of AGT mRNA or protein in an untreated cell or in the same cell before initiation of treatment with the isolated oligonucleotide.

[00535] Methods of monitoring of AGT mRNA and/or protein expression can be used to characterize gene silencing, and to determine the effectiveness of the compositions described herein. Expression of AGT may be evaluated by any known technique. Examples thereof include immunoprecipitations methods, utilizing AGT antibodies in assays such as ELISAs, Western Blot, or immunohistochemistry to visualize AGT protein expression in cells, or flow cytometry. Additional methods include various hybridization methods utilizing a nucleic acid that specifically hybridizes with a nucleic acid encoding AGT or a unique fragment thereof, or a transcription product (e.g., mRNA) or splicing product of said nucleic acid, Northern Blot methods, Southern blot methods, and various PCR-based methods such as RT-PCR, qPCR or digital droplet PCR. AGT mRNA expression may additionally be assessed using high throughput sequencing techniques.

[00536] Methods of assaying the effect of individual isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT include transfecting representative cell lines with isolated oligonucleotides, and measuring viability. For example, cells from representative cell lines can be transfected using methods known in the art, such as the RNAiMAX Lipofectamine kit (Invitrogen, Carlsbad, CA), and cultured using any suitable technique known in the art. Optionally additional therapeutic agents as described herein can be added at variable concentrations to cell culture media following transfection. Following a suitable incubation period, such as 24-96 hours, cell viability can be measured using methods such as Cell Titer Glo 2.0 (Promega, CA) to determine cell viability, and/or AGT mRNA and protein levels can be assessed using the methods described herein.

[00537] In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, wherein the isolated oligonucleotide, the vector, the delivery system, or the pharmaceutical composition is administered parenterally.

[00538] In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, wherein the parenteral administration is intravenous, subcutaneous, intraperitoneal, or intramuscular.

[00539] In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, the subject is a human. In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, the subject has hypertension, and related cardiovascular disorders and conditions.

[00540] In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, the method comprises administering the isolated oligonucleotide, the vector, the delivery system, or the pharmaceutical composition, in combination with at least a second therapeutic agent.

[00541] In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, the second therapeutic agent is an antibody, a small molecule drug, a peptide, a nucleotide molecule, or a combination thereof.

[00542] In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, the second therapeutic agent is an isolated oligonucleotide of the present disclosure.

[00543] The present disclosure also provides a method of inhibiting or downregulating the expression or level of AGT in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of a first and at least a second oligonucleotides disclosed herein, wherein the first and at least second oligonucleotides comprise different sequences.

[00544] In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, wherein the first and at least second oligonucleotides are administered simultaneously.

[00545] In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, wherein the first and at least second oligonucleotides are administered sequentially.

[00546] In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, the subject is a human. In some embodiments of the methods of inhibiting or downregulating AGT expression or activity in a cell of the present disclosure, the subject has hypertension, and related cardiovascular disorders and conditions. In some embodiments of the method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role of the present disclosure, the subject is a human. In some embodiments of the method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role of the present disclosure, the disease or disorder is hypertension, and related cardiovascular disorders and conditions. In some

embodiments of the use for treating or preventing a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role of the present disclosure, the subject is a human. In some embodiments of the use for treating or preventing a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role of the present disclosure, the disease or disorder is hypertension and related conditions.

[00547] In some embodiments of the use in the manufacture of a medicament for treatment or prevention of a disease or disorder associated with aberrant or increased expression or activity of AGT of the present disclosure, the subject is a human. In some embodiments of the use in the manufacture of a medicament for treatment or prevention of a disease or disorder associated with aberrant or increased expression or activity of AGT of the present disclosure of the present disclosure, the disease or disorder is hypertension and related conditions. treatment or prevention of a disease or disorder associated with aberrant or increased expression or activity of AGT.

Routes of administration

[00548] Nanoparticles comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT mRNA of the present disclosure can be administered to a subject by many of the well-known methods currently used for therapeutic treatment. For example, for treatment of mammalian diseases associated with expression or activity of AGT, a compositions comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT mRNA of the present disclosure may be injected directly into cells, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[00549] The compositions comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT mRNA of the present disclosure can be administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In some embodiments, the parenteral administration comprises intramuscular, intraperitoneal, subcutaneous or intravenous administration. One skilled in the art will recognize the advantages of certain routes of administration.

[00550] Compositions of the disclosure may be administered parenterally. Systemic administration of compositions comprising nanoparticles of the disclosure can also be by intravenous, transmucosal, subcutaneous, intraperitoneal, intramuscular or transdermal means. For intravenous parenteral administration, compositions comprising nanoparticles may be administered by injection or by infusion. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories.

Dosages

[00551] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing or treatment of the condition or symptom associated with expression or activity of AGT. Dosages may vary depending on the age and size of the subject and the type and severity of the disease or disorder associated with AGT expression.

[00552] The term “effective amount” or “therapeutically effective amount”, as used interchangeably herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, inhibit, downregulate or control the expression of AGT or symptoms associated with aberrant or abnormal expression of AGT in a subject, or to exhibit a detectable therapeutic or inhibitory effect in a subject. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[00553] For any of the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT mRNA of the present disclosure, the therapeutically effective amount can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate

concentration range and route of administration. In some embodiments, a standard xenograft or patient derived xenograft mouse model can be used to determine the effectiveness of the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT mRNA of the present disclosure. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., the maximum tolerated dose and no observable adverse effect dose. Pharmaceutical compositions that exhibit large therapeutic windows are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[00554] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[00555] The dosage of nanoparticles comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT mRNA of the present disclosure, required depends on the choice of the route of administration; the nature of the formulation; the nature of the patient's illness; the subject's size, weight, surface area, age, and sex; other drugs being administered; and the judgment of the attending physician. Wide variations in the needed dosage are to be expected in view of the differing efficiencies of various routes of administration. For example, oral administration would be expected to require higher dosages than administration by intravenous injection (e.g., 2-, 3-, 4-, 6-, 8-, 10-, 20-, 50-, 100-, 150-, or more fold). Variations in these dosage levels can be adjusted using standard empirical routines for optimization as is well understood in the art. Administrations can be single or multiple. Encapsulation of the inhibitor in a suitable delivery vehicle (e.g., capsules or implantable devices) may increase the efficiency of delivery, particularly for oral delivery.

[00556] A therapeutically effective dose of the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT mRNA of the present disclosure, can optionally be combined with approved amounts of therapeutic agents, and described herein.

Kits and Articles of Manufacture

[00557] The present disclosure also provides a kit comprising an isolated oligonucleotide disclosed herein, a vector of the present disclosure encoding an isolated oligonucleotide disclosed herein, a delivery system of the present disclosure, or a pharmaceutical composition of the present disclosure.

[00558] The kits are for use in the treatment of diseases related to abnormal or aberrant expression of AGT, in a mammal. The kits are for use in downregulating or inhibiting expression of AGT partially or completely, in a mammal. In some embodiments, the mammal is a human, a mouse, a rat, a rabbit, a pig, a bovine, a canine, a feline, an ungulate, an ape, a monkey or an equine species. In some embodiments, the mammal is a human

[00559] Nanoparticles comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting AGT mRNA of the present disclosure, can be lyophilized before being packaged in the kit, or can be provided in solution with a pharmaceutically acceptable carrier, diluent or excipient.

[00560] In some embodiments of the kits of the disclosure, the kit comprises a therapeutically effective amount of a composition comprising the delivery system of the present disclosure comprising one or more of the isolated oligonucleotides of the present disclosure targeting AGT (dsRNA or siRNA), and instructions for use of the same. In some embodiments, the kit further comprises at least one additional therapeutic agents, as described herein.

[00561] Articles of manufacture include, but are not limited to, instructions for use of the kit in treating diseases related to abnormal or aberrant expression of AGT or diseases related to expression of AGT.

[00562] In some embodiments, the kits further comprise instructions for administering the isolated oligonucleotides, the vector, the delivery systems and the pharmaceutical compositions of the disclosure.

[00563] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

EXAMPLES

[00564] **Example 1: Design and testing of siRNA compounds against AGT mRNA.**

[00565] *Compound Design*

[00566] A set of 221 siRNAs compounds against human AGT transcript (Accession No: NM_001384479.1) were designed (See Table 2)

[00567] *Oligonucleotide Synthesis*

[00568] Oligonucleotides were prepared by solid-phase synthesis according to standard protocols. Briefly, oligonucleotide synthesis was conducted on a solid support to incorporate each nucleoside phosphoramidites from 3'-end to 5'-end to prepare oligo single strands. ETT or BTT was used as an activator for the coupling reaction. Iodine in water/pyridine/THF was used to oxidize phosphite-triester (P(III)) to afford phosphate backbones and DDTT was used for the preparation of phosphorothioate linkages. Aqueous ammonium was used to cleave oligos from solid support and to remove protecting groups globally. The oligonucleotide crude was then concentrated by Genevac and purified by AEX-HPLC. The pure fractions were combined and concentrated, and their purity was analyzed by LC-MS. The oligonucleotides were then dialyzed against water using MidiTrap G-25 column, concentrated, and their OD amounts were measured.

[00569] To prepare siRNA duplexes, the sense and antisense strands were annealed at 95 °C for 10 min, based on equal molar amounts, and cooled down to room temperature. The duplex purity was determined by AEX-HPLC, and the solutions were lyophilized to afford the desired siRNA duplex powder.

[00570] *In vitro Screening*

[00571] The compounds were diluted into the desired concentration with PBS. The diluted compounds were then transfected into the cultured Huh-7 cells with Lipofectamine RNAiMAX (Invitrogen-13778-150) reagents on Day 0. Each compound was tested at four concentrations of 0.02 nM and 0.1 nM. At 24 hours post transfection on Day 1, mRNA was extracted from the transfected cells using RNeasy 96 kit (Qiagen-74182). TaqMan RT-qPCR gene expression assay was conducted to analyze the compound potency in silencing AGT mRNA.

[00572] The percentage of human AGT mRNA remaining in cells relative to mock transfection when normalized to Gapdh mRNA levels, was determined for each compound at a concentration of either 0.02 nM and 0.1 nM. The results identified several compounds that were able to reduce the level of human AGT mRNA in transfected cells by 20% to 50% or more than 50% at the

defined concentrations as described in **Table 2** and **FIG. 1** and **FIG. 2**). Also, several compounds from **Table 1** (shown in bold in **Table 2**) were able to reduce the level of human AGT mRNA in transfected cells by between 20% to 50% or at least 50% at 0.02 nM and 0.1 nM (See **Table 2**, and **FIG. 1** and **FIG. 2**).

[00573] *In vivo HDI screening*

[00574] A subset of compounds with GalNAc conjugations as described in **Table 3** were formulated in 1X PBS dosed on day 1 through subcutaneous dosing to BALB/c female animals (6–8 weeks old). Animals then received 10µg of pcDNA3.1-hsAGT plasmids on day 4. Liver biopsies were taken on day 5 for mRNA remaining analysis through RT-qPCR.

[00575] For dose response study, 6–8 weeks old female BALB/c mice were dosed subcutaneously at 0.3 mg/kg (grey triangles), 1 mg/kg (grey squares) or 3 mg/kg (black circles) (**FIG. 4**). The control animals were dosed with PBS. Animals were sacrificed 4 days post-dose and liver samples were collected for RNA extraction and human AGT mRNA expression analysis by RT-qPCR. The results of the experiments are shown in **FIG. 3** and **FIG. 4**. The tested compounds were able to reduce the level of human AGT mRNA.

[00576] *In vivo potency and duration evaluation in Macaca fascicularis*

[00577] To determine AGT knockdown in non-human primates, a nonterminal study was conducted in cynomolgus macaques. A liver biopsy was taken from cyno monkeys in the study to determine the baseline mRNA expression level one week before dosing (Day -7). Blood samples were collected one week before dosing (Day -7) and Day 1 (date to dose) before dosing to determine the baseline serum AGT protein. Animals were dosed with a single dose of 3mg/kg subcutaneously a week after a biopsy (Day 0). A biopsy of the liver was taken at 14, 28, 56, 84 and 112 dates post dose and blood samples were taken one week post dose and then weekly until day 112 post dose. Liver samples were used for mRNA remaining analysis by RT-qPCR and blood samples were used for serum AGT protein analysis by ELISA.

[00578] *RT-qPCR*

[00579] Liver mRNA samples were prepared with RNeasy Plus mini kit (Qiagen, 74104). mRNAs were reverse transcribed into cDNAs using High-Capacity cDNA Reverse transcription kits with RNase Inhibitors (Thermo, 4374967). TaqMan multiplex qPCR assays (Thermo, 4444558) were performed to determine the relative AGT mRNA levels over time.

[00580] *ELISA*

[00581] Serum AGT protein was analyzed using commercially available ELISA kit (Immuno-Biological Laboratories Co., 27412) following manufacturer's instructions

[00582] The results of the experiment are shown in FIGS. 5A and 5B. As shown in FIG. 5A by Day 15, all compounds had reduced liver AGT mRNA by at least 40% relative to pre-dosing levels (Day -7). The maximum reduction in AGT mRNA for all compounds was seen at Day 29 post-dosing, as shown in FIG. 5B. As shown in FIG. 5B by Day 8, all compounds had reduced serum AGT protein by at least 40% relative to pre-dosing levels (Day -7). The maximum reduction in serum AGT protein for all compounds was seen at Day 15 post-dosing, as shown in FIG. 5B.

[00583] *Ex vivo potency evaluation in primary human hepatocytes (PHH) and primary cyno hepatocytes (PCH)*

[00584] A subset of the compounds with GalNAc conjugations listed in Table 3 were tested through free-uptake in PHH and PCH. The compounds were directly added to the cultured primary hepatocytes at 8 doses (20, 4, 0.8, 0.16, 0.03, 0.006, 0.001, 0.0003nM). 48hrs later, the cells were harvested for mRNA analysis through RT-qPCR. The results of the uptake in PHH and PCH are shown in Table 3.

Table 2: Exemplary Sequence of the Present Application and Their *in vitro* Potency in Silencing Human AGT mRNA

Guide Strand position	Start	End	Guide strand sequence (5'-3')	SEQ ID	Passenger strand sequence (5'-3')	SEQ ID	% of gene remaining at 0.02nM		% of gene remaining at 0.1nM	
							Mean	SEM	Mean	SEM
38	17	37	UCUUCUGCUGUAGUACCCAGAA	112	CUGGGUACUACAGCAGAAGA	279	80.20	0.71	62.57	0.95
43	22	42	UAUACCCUUCUGCUGUAGUACC	113	UACUACAGCAGAAGGUUAUA	280	67.23	0.78	45.97	2.48
107	86	106	UGAGGAUGGUGGCCCCUCAGGCU	114	CCUGAGGCCACCAUCCUCA	281	86.50	2.67	81.47	3.70
113	92	112	UGAGGCAGAGGAUGGUGGCCCU	115	GGCCACCAUCCUCUGCCUCA	282	93.90	1.69	90.30	5.60
156	135	155	UGUAUGUACACCCGGUCACCU	116	GGUGACCCGGUGUACAUACA	283	99.03	2.93	96.60	3.86
158	137	157	UGUGUAUGUACACCCGGUCACC	117	UGACCCGGUGUACAUACACA	284	81.83	0.74	100.53	11.51
163	142	162	UAAGGGGUGUAUGUACACCCGG	118	GGGUGUACAUACACCCCUUA	285	90.10	0.64	87.37	6.56
164	143	163	UGAAGGGGUGUAUGUACACCCG	119	GGUGUACAUACACCCCUUA	286	84.10	1.61	83.00	2.91
165	144	164	UGGAAGGGGUGUAUGUACACCC	120	GUGUACAUACACCCCUUCCA	287	102.77	7.40	79.77	0.98
175	154	174	UAUGACGAGGUGGAAGGGGUGU	121	ACCCUUCACCCUCUGUCAUA	288	92.70	4.10	84.43	1.49
177	156	176	UGGAUGACGAGGUGGAAGGGGU	122	CCCUCCACCCUCUGUCAUCCA	289	86.80	3.21	74.33	1.72
179	158	178	UGUGGAUGACGAGGUGGAAGGG	123	CUUCCACCCUCUGUCAUCCA	290	88.07	1.35	98.40	5.28
182	161	181	UAUUGUGGAUGACGAGGUGGAA	124	CCACCCUGUCAUCCACAUAUA	291	84.23	4.52	87.40	11.06
185	164	184	UCUCAUUGUGGAUGACGAGGUG	125	CCUCUGUCAUCCACAUAUGAGA	292	85.20	2.14	77.60	2.01
187	166	186	UCUCUCAUUGUGGAUGACGAGG	4	UCGUCAUCCACAUAUGAGAGA	59	36.67	2.60	22.00	0.95
189	168	188	UUAUCUCAUUGUGGAUGACGA	43	GUCAUCCACAUAUGAGAGUAA	98	44.47	0.83	26.73	0.46
190	169	189	UGUAUCUCAUUGUGGAUGACG	44	UCAUCCACAUAUGAGAGUACA	99	29.83	0.77	15.17	0.47
195	174	194	UCACAGGUACUCUCAUUGUGGA	126	CACAAUGAGAGUACCCUGUGA	293	64.97	5.03	44.80	2.55
197	176	196	UCUCACAGGUACUCUCAUUGUG	5	CAAUGAGAGUACCCUGUGAGA	60	57.50	5.66	37.57	1.17
209	188	208	UCUUUGCCAGCUGCUCACAGGU	127	CUGUGAGCAGCUGGCAAGA	294	81.13	0.55	64.20	4.45
216	195	215	UCAUUGGCCUUUGCCAGCUGCU	128	CAGCUGGCAAGGCCAAUGA	295	76.10	5.60	60.50	2.82

376	355	375	UAAGUUGGCCAGCAUCCCGACC	129	UCGGGAUGCUGGCCAACUUUA	296	84.00	3.38	74.83	1.78
378	357	377	UAGAAGUUGGCCAGCAUCCCGA	130	GGGAUGCUGGCCAACUUUA	297	75.60	2.96	49.20	4.07
380	359	379	UCAAGAAGUUGGCCAGCAUCCC	131	GAUGCUGGCCAACUUUUGA	298	78.03	1.99	83.40	2.40
387	366	386	UGGAAGCCCAAGAAAGUUGGCCA	132	GCCAAUUUUUGGGCUUCCA	299	66.03	1.22	42.37	0.41
393	372	392	UAUAACGGAAGCCCAAGAAAU	133	UUUUUGGGUUCCGUUAUA	300	78.20	1.48	50.00	0.86
394	373	393	UAUAUACGGAAGCCCAAGAAAG	134	UCUUUGGGUUCCGUUAUAA	301	65.03	1.39	41.17	1.66
395	374	394	UAUAUACGGAAGCCCAAGAA	135	CUUGGGUUCCGUUAUUA	302	83.83	2.47	66.40	0.99
396	375	395	UCAUAUACGGAAGCCCAAGA	136	UUUGGGUUCCGUUAUUAUGA	303	89.07	1.82	60.80	2.84
400	379	399	UAUGCAUAUAACGGAAGCCC	137	GCUUCCGUUAUAUGGCAUA	304	74.17	2.17	48.60	1.96
401	380	400	UCAUGCAUAUAACGGAAGCCC	138	CUUCCGUUAUAUGGCAUA	305	93.93	5.38	77.07	1.17
406	385	405	UCUUGCAUGCCAUUAUAACGG	139	GUUAUAUGGCAUUGCACAGA	306	87.10	4.28	68.07	1.86
410	389	409	UCUCACUGUGCAUGCCAUUAU	140	AUAUGGCAUUGCACAGUGAGA	307	94.77	0.52	91.07	3.97
415	394	414	UCAUAGCUCACUGUGCAUGCCA	6	GCAUGCACAGUGAGCUAUA	61	57.47	1.20	33.77	0.97
429	408	428	UCAUGGACACGCCCAUAUAGCU	141	CUAUGGGGCGUGGUCCAUA	308	93.20	1.66	99.13	4.12
436	415	435	UUGGGCCCAUGGACCAACGCC	142	GCGUGGUCCAUGGGGCCACA	309	98.57	1.13	104.33	1.22
460	439	459	UAAGACAGCCGUGGGGAGAGG	143	UCUCCCAAGGGCGUGCUUA	310	95.47	2.17	83.87	1.42
462	441	461	UCAAGACAGCCGUGGGGAGA	144	UCCCAACGGCGUGCUUUGA	311	86.50	8.07	54.53	1.14
466	445	465	UGUGCCAAAGACAGCCGUUGGG	145	CAACGGCGUCUUUUGGCACA	312	74.80	6.63	60.97	7.95
470	449	469	UCAGGGUGCCAAAGACAGCCGU	146	GGCUGUCUUUGGCACCCUGA	313	98.43	3.52	89.03	2.23
481	460	480	UAAGAGAGAGCCAGGGUGCCA	7	GCACCCCGGCCUUCUUA	62	69.57	2.74	35.07	2.25
570	549	569	UCAUCCAGCCGGAGGUGCAGU	147	UGCACCUCCGGCGUGGAUA	314	99.73	1.47	81.50	3.09
578	557	577	UCUUGUGCGAUCCAGCCGGGA	148	CCGGUGGAUGCGCACAAAGA	315	100.13	2.54	92.30	0.81
581	560	580	UGACCUUGUGCGCAUCCAGCCG	149	GCUGGAUGCGCACAAAGGUA	316	87.57	2.51	58.07	1.16
605	584	604	UCUGUACAGCCUGCAGGGCAGA	150	UGCCCUGCAGGCGUACACAGA	317	82.13	3.55	84.27	1.01
711	690	710	UCAACGGCGUGCUUCAGGUCCA	151	CACCUAAGCAGCCGUUUGA	318	86.27	6.00	65.27	0.54
713	692	712	UCACAAACGGCGUGCUUCAGGUG	152	CCUGAAGCAGCCGUUUGUGA	319	92.73	0.88	67.43	1.47
730	709	729	UAAGAGAGCCAGGCCUUGCACA	153	UGCAGGCCUGGCUUCUUA	320	85.70	4.05	66.73	2.40
763	742	762	UAAGUCCAGAGAGCGUGGGAGG	154	UCCCAACGCUUCUGGACUUA	321	88.93	1.05	70.20	0.76
765	744	764	UUGAAGUCCAGAGAGCGUGGGA	8	CCACGGCUCUGGACUUA	63	62.03	3.17	34.30	1.27
766	745	765	UGUGAAGUCCAGAGAGCGUGGG	155	CACGCUUCUGGACUUCACA	322	85.33	1.29	71.70	3.58

803	782	802	UGAACCUUGUCAAUUCUUCAGC	156	UGAGAAGAUUGACAGGUUCA	323	68.80	1.90	45.77	1.54
805	784	804	UAUGAACCUUGUCAAUUCUUCUA	45	AGAAGAUUGACAGGUUCAUA	100	25.70	2.31	27.00	3.58
809	788	808	UCUGCAUGAACCUUGUCAAUUCU	46	GAUGACAGGUUCAUGCAGA	101	37.37	7.72	36.43	10.09
950	929	949	UGUCCACCCAGAACUCCUGGGG	10	CCAGGAGUUCUGGGUGGACA	65	50.30	5.25	38.27	8.09
952	931	951	UUUGUCCACCCAGAACUCCUGG	157	AGGAGUUCUGGGUGGACAAA	324	46.60	12.56	67.23	10.40
955	934	954	UCUGUUGUCCACCCAGAACUCC	158	AGUUCUGGGUGGACAAACAGA	325	80.77	3.23	67.85	23.35
963	942	962	UCUGAGGUGUGUUGUCCACCC	159	GUGGACAAACAGCACCUUCAGA	326	89.57	4.85	87.30	2.17
967	946	966	UGACACUGAGGUGUGUUGUCC	160	ACAACAGCACCUUCAGUUA	327	78.80	6.69	65.90	0.62
969	948	968	UCAGACACUGAGGUGUGUUGU	11	AACAGCACCUUCAGUUCUGA	66	64.57	1.22	34.00	1.93
1009	988	1008	UCUCCAGUGUGGAAGGUGCC	161	GCACUUCAGCACUUGGAGA	328	82.37	2.25	91.47	4.33
1109	1088	1108	UCACUUGUCCAGGUCAGAGGC	162	CUUGACUUGGACAAAGGUGA	329	104.83	2.17	92.43	3.93
1116	1095	1115	UGACCCUCCACCUUGUCCAGGU	163	CUGGACAAAGGUGGAGGUGA	330	104.37	4.53	75.60	5.60
1120	1099	1119	UGUGAGACCCUCCACCUUGUCC	164	ACAAGGUGGAGGUGUCACACA	331	103.97	2.79	63.03	2.76
1122	1101	1121	UAAGUGAGACCCUCCACCUUGU	165	AAGGUGGAGGUGUCACACUUA	332	79.67	7.48	59.93	4.50
1124	1103	1123	UGAAAGUGAGACCCUCCACCUU	166	GGUGGAGGUGUCACACUUA	333	88.50	8.36	79.13	4.19
1125	1104	1124	UGGAAAGUGAGACCCUCCACCU	167	GUGGAGGUGUCACACUUA	334	72.90	5.76	58.17	2.73
1127	1106	1126	UCUGGAAAGUGAGACCCUCCAC	168	GGAGGUGUCACACUUA	335	78.97	4.97	59.13	5.52
1131	1110	1130	UUUUGUGGAAAGUGAGACCCU	12	GGUUCACUUAUCCAGCAAAA	67	59.20	4.22	34.63	2.80
1133	1112	1132	UGUUUGUGGAAAGUGAGACC	169	UCUCACUUAUCCAGCAAAA	336	74.40	0.85	45.40	2.97
1135	1114	1134	UGAGUUUUGUGGAAAGUGAGA	170	UCACUUUCCAGCAAAAACUCA	337	71.80	4.15	47.67	2.29
1143	1122	1142	UAGUUGAGGAGUUUUGCUGGA	171	CAGCAAAACUCCUCAAACUA	338	68.90	5.61	51.60	9.44
1144	1123	1143	UCAGUUGAGGAGUUUUGCUGG	172	AGCAAAACUCCUCAAACUGA	339	75.23	1.55	96.13	9.89
1147	1126	1146	UAUCCAGUUGAGGGAGUUUUGC	173	AAAACUCCUCAAACUGGAUA	340	82.13	2.49	55.67	2.98
1148	1127	1147	UCAUCCAGUUGAGGGAGUUUUG	174	AAACUCCUCAAACUGGAUA	341	90.33	3.39	87.50	9.55
1153	1132	1152	UUUCUUAUCCAGUUGAGGGAG	175	CCUCAAACUGGAUAGAGAAA	342	91.53	7.36	91.20	10.02
1154	1133	1153	UUUCUUAUCCAGUUGAGGGGA	176	CCUCAAACUGGAUAGAGAAA	343	78.40	17.97	43.63	10.47
1155	1134	1154	UGUUUCUUAUCCAGUUGAGGG	13	CUCAAACUGGAUAGAGAAA	68	60.27	5.41	25.60	6.10
1254	1233	1253	UGAUGGCGGCGAGCUCAGCCU	177	GCUGAGUCCCGCCAUUA	344	62.43	12.31	63.10	6.59
1256	1235	1255	UCAGAAUGGCGGCGAGCUCAGC	178	UGAGCUGCCCGCCAUUA	345	84.10	10.41	75.97	5.67
1279	1258	1278	UUUUGCAGGUUCAGCUCGGUG	179	CCGAGCUGAACCGCAAAA	346	73.07	4.71	46.63	1.48

1280	1259	1279	UUUUUUGCAGGUUCAGCUCGGU	180	CGAGCUGAACCCUGCAAAAAA	347	70.83	2.45	45.13	0.97
1281	1260	1280	UAUUUUGCAGGUUCAGCUCGG	181	GAGCUGAACCCUGCAAAAAUA	348	82.30	1.61	44.17	0.09
1282	1261	1281	UAUUUUGCAGGUUCAGCUCG	182	AGCUGAACCCUGCAAAAAUA	349	89.20	4.02	58.83	3.72
1283	1262	1282	UCAUUUUGCAGGUUCAGCUC	183	GCUGAACCCUGCAAAAAUUGA	350	99.90	1.17	46.17	1.05
1285	1264	1284	UCUCAUUUUGCAGGUUCAGC	47	UGAACCCUGCAAAAAUUGAGA	102	54.53	0.87	32.53	0.86
1290	1269	1289	UCAUUGCUCAAUUUUGCAGGU	48	CUGCAAAAAUUGAGCAAUAGA	103	57.07	1.97	37.37	2.52
1329	1308	1328	UAAAAAUGCUGUUCAGCACC	184	GUGCUGAACAGCAUUUUUA	351	84.30	3.38	51.47	4.78
1330	1309	1329	UAAAAAUGCUGUUCAGCACC	15	UGCUGAACAGCAUUUUUA	70	47.43	3.94	31.73	2.39
1331	1310	1330	UAAAAAUGCUGUUCAGCAC	185	GCUGAACAGCAUUUUUA	352	108.93	1.54	58.43	1.52
1332	1311	1331	UAAAAAUGCUGUUCAGCA	16	CUGAACAGCAUUUUUA	71	49.97	2.11	26.43	0.13
1366	1345	1365	UGACUCUGGGGCUUCUCUA	186	AGAGAGGCCACAGAGUCA	353	64.90	1.15	45.37	2.34
1368	1347	1367	UUAGACUCUGGGGCUUCUCU	187	AGAGAGGCCACAGAGUCUAA	354	74.10	4.18	69.40	1.16
1431	1410	1430	UCAGCAACAGGAUUGGGCGU	17	CGCCCAUCCUGUUGCUGA	72	60.70	1.71	32.70	1.44
1433	1412	1432	UCACAGCAACAGGAUUGGGCG	188	CCCADUCCUGUUGCUGUGA	355	85.37	2.84	53.20	2.30
1436	1415	1435	UAUACACAGCAACAGGAUUGG	189	AUUCUUGUUGCUGUUAUA	356	94.97	1.87	63.47	1.88
1439	1418	1438	UAUCAUACACAGCAACAGGAA	190	CCUGUUGCUGUUAUGAUA	357	77.13	4.28	51.20	0.42
1440	1419	1439	UGAUCAUACACAGCAACAGGA	191	CUUUGCUGUUAUGAUAUA	358	68.47	1.18	40.75	2.47
1442	1421	1441	UUUGAUCAUACACAGCAACAG	192	GUUUGCUGUUAUGAUAUA	359	86.10	6.05	57.13	2.84
1443	1422	1442	UUUGAUCAUACACAGCAACAA	193	UUUGCUGUUAUGAUAUA	360	84.27	2.58	70.30	3.35
1466	1445	1465	UCAGGAAGUGCAGGGCAGUGGC	194	CACUGCCUGCACUUCUGA	361	82.73	17.31	77.20	8.36
1513	1492	1512	UCUGGGGCCUGGGCCUUAUUCU	195	CAUGAGGCCAGGGCCCCAGA	362	67.90	17.83	62.13	9.34
1518	1497	1517	UGUGUUCUGGGGCCUUGGCCUC	196	GGCCAGGGCCCCAGAACACA	363	64.67	15.09	58.93	26.02
1520	1499	1519	UCUGUGUUCUGGGGCCUUGGCC	197	CCAGGGCCCCAGAACACAGA	364	83.20	17.66	89.40	0.38
1622	1601	1621	UAAAAGGUGGGGAGACUGGGGU	198	CCCCAGUCUCCACCUUUA	365	91.20	3.89	70.80	4.54
1623	1602	1622	UGAAAAGGUGGGGAGACUGGGG	199	CCCAGUCUCCACCUUUA	366	97.67	2.51	53.73	2.94
1624	1603	1623	UAGAAAAGGUGGGGAGACUGGGG	200	CCAGUCUCCACCUUUA	367	74.27	0.41	43.90	1.15
1625	1604	1624	UAAGAAAAGGUGGGGAGACUGGG	201	CAGUCUCCACCUUUA	368	78.33	0.85	69.07	4.22
1626	1605	1625	UGAAGAAAAGGUGGGGAGACUGG	18	AGUCUCCACCUUUA	73	60.97	1.40	32.47	2.26
1628	1607	1627	UUAGAAGAAAAGGUGGGAGACU	49	UCUCCACCUUUA	104	36.50	3.89	21.50	0.61
1629	1608	1628	UUAGAAGAAAAGGUGGGAGAC	19	CUCCACCUUUA	74	51.50	7.22	33.43	1.55

1630	1609	1629	UAIUJAGAAAGAAAGGUGGAGA	20	UCCACCUUUUUCUUAUA	75	23.13	5.14	25.73	1.37
1631	1610	1630	UCAUJAGAAAGAAAGGUGGAG	50	CCCACCUUUUUCUUAUA	105	35.67	3.07	29.77	3.00
1633	1612	1632	UCUCAUJAGAAAGAAAGGUGG	51	CACCUUUUUCUUAUA	106	60.93	10.87	21.73	8.05
1677	1656	1676	UCACUJAGACCAGGAGAAACG	24	UUUCUCCUUGGUCUUA	79	73.23	7.03	38.53	13.62
1753	1732	1752	UUUCUCUAAAUAAACCCAGCA	26	CUGGGUUUAUUUAGAGAA	81	52.13	9.70	38.17	4.23
1754	1733	1753	UAUUCUCUAAAUAAACCCAGC	202	UGGGUUUAUUUAGAGAA	369	75.33	5.72	49.47	12.17
1775	1754	1774	UGGUUCUUGCCUCCCAACCC	203	GGUGGGGAGGCAAGAACCA	370	100.97	7.89	91.03	4.43
1777	1756	1776	UCUGGUUCUUGCCUCCCAACCC	204	GUGGGAGGCAAGAACCCAGA	371	95.60	4.15	71.97	2.30
1782	1761	1781	UAAACACUGGUUCUUGCCUCCC	205	GAGGCAAGAACCCAGUUUA	372	80.60	5.77	51.50	3.29
1783	1762	1782	UAAAAACUGGUUCUUGCCUCCC	206	AGGCAAGAACCCAGUUUUA	373	40.87	8.59	41.40	0.58
1820	1799	1819	UGUGGUUGGAAUUCUUUUUGG	207	AAAAAGAAUCCAAACCGACA	374	75.87	2.74	66.30	3.80
1831	1810	1830	UCAAACAAGCUGGUCGGUUGGA	208	CAACCGACCGUUGUUUGA	375	73.17	1.76	52.43	1.33
1835	1814	1834	UUUCACAAAACAAGCUGGUCGGU	52	CGACCAAGCUUGUUUGGAAA	107	72.17	3.43	36.83	1.52
1836	1815	1835	UUUCACAAAACAAGCUGGUCGG	53	GACCAAGCUUGUUUGGAAA	108	90.67	4.97	38.03	2.54
1837	1816	1836	UGUUUCACAAAACAAGCUGGUCG	28	ACCAGCUUGUUUGGAAAACA	83	85.03	1.33	38.17	0.22
1839	1818	1838	UUUGUUUCACAAAACAAGCUGGU	209	CAGCUUGUUUGGAAACAAA	376	84.50	1.44	62.73	2.06
1841	1820	1840	UUUUUGUUUCACAAAACAAGCUG	210	GCUUGUUUGGAAACAAA	377	92.90	2.88	79.60	3.32
1842	1821	1841	UUUUUGUUUCACAAAACAAGCU	211	CUUGUUUGGAAACAAA	378	71.10	3.50	40.13	1.70
1843	1822	1842	UUUUUGUUUCACAAAACAAGC	29	UUGUUUGGAAACAAA	84	47.93	0.32	22.73	0.84
1846	1825	1845	UCACUUUUUGUUUCACAAAACA	30	UUUGGAAACAAAAGUGA	85	48.10	3.42	23.53	0.37
1850	1829	1849	UGGAACACUUUUUGUUUCACA	2	UGAAACAAAAGUGUCCA	57	43.70	0.60	24.47	0.69
1855	1834	1854	UAAAAGGGAACACUUUUUGUU	212	CAAAAAGUGUCCCUUUA	379	64.43	1.56	44.30	0.74
1856	1835	1855	UGAAAAGGGAACACUUUUUGU	213	AAAAAGUGUCCCUUUA	380	82.97	5.98	103.40	13.85
1858	1837	1857	UUUGAAAAGGGAACACUUUUUU	3	AAAAGUGUCCCUUUA	58	45.53	2.82	27.73	1.99
1859	1838	1858	UCUUGAAAAGGGAACACUUUUU	31	AAAGUGUCCCUUUA	86	34.30	2.89	26.17	1.47
1862	1841	1861	UCAACUUGAAAAGGGAACACUU	214	GUGUCCCUUUAAGUUA	381	43.67	5.89	45.13	0.23
1864	1843	1863	UCUCAACUUGAAAAGGGAACAC	54	GUUCCCUUUAAGUUGA	109	49.60	9.01	38.97	1.39
1868	1847	1867	UUGUUCUACUUGAAAAGGGA	32	CCUUUCAGUUGAGAACAA	87	57.50	5.99	37.40	4.28
1873	1852	1872	UAUUUUUGUUCUACAUUGAAA	33	UCAAGUUGAGAACAAAUA	88	66.00	8.20	35.50	4.35
1874	1853	1873	UAUUUUUGUUCUACAUUGAA	34	CAAGUUGAGAACAAAUA	89	61.23	1.18	36.83	3.06

30		9	29	UGUAGUACCCAGAAACAACGGCA	42	CCGUUGUUCUGGUUACUACA	97	54.37	1.30	36.77	1.92
32		11	31	UCUGUAGUACCCAGAAACAACGG	237	GUUGUUCUGGUUACUACAGA	404	70.27	3.87	65.67	1.17
155		134	154	UUUUGUACACCCGGUACUUGC	238	AGGUGACCCGGUACAUAA	405	88.03	5.17	90.27	4.80
285		264	284	UUUUCAUCCACAGGGGUAUCU	239	ACAUCUUCUGGAUAAAA	406	80.80	1.27	76.87	8.18
482		461	481	UAUAGAGAGAGCCAGGGUGCC	240	CACCUUGCCUUCUUAUA	407	66.87	1.72	64.07	0.55
524		503	523	UGAUUGCUUAGCUUGUACAGC	241	UGACAGGUUACAGGCAUCA	408	74.73	2.29	64.43	1.90
553		532	552	UCAGUUCUUGUCCUCCAAGGA	242	CUUGGAAGGACAAGAUCUGA	409	71.63	3.75	57.20	2.53
732		711	731	UUUAGAGAGAGCCAGGCCUGCA	243	CAGGCCUUGGCUCUUAUA	410	68.10	1.48	62.80	1.27
770		749	769	UUUCUGUAGAGUCCAGAGAGCG	244	CUCUCUGGACUUCACAGAAA	411	81.80	2.70	76.90	1.33
799		778	798	UCUGUCAAUCUUCUACAGAGCA	9	CUGCUGAGAAGAUUGACAGA	64	58.97	1.57	34.77	1.86
884		863	883	UGUAGGUUGUAGAAAGCCAGGGU	245	CCUGGUUUCAACACCUACA	412	73.17	2.43	59.50	1.50
943		922	942	UCAGAAUCUUGGGGCUUGGCC	246	CCGAGCCCGAGGAGUUCUGA	413	79.20	4.06	77.60	2.76
1057		1036	1056	UCUCUCAGUGAAGGGCACUUGA	247	AAGUGCCUUCACUGAGAGA	414	79.47	3.57	72.80	1.70
1210		1189	1209	UUUAGAUUCUUGCAGCACACAGU	248	UGGUGCUUCAAGGAUCUUA	415	67.40	0.46	44.23	1.96
1212		1191	1211	UCAUAGAUCUUCUGCAGACCA	249	GUUGUGCAAGGAUCUUAUGA	416	87.77	2.26	85.13	5.30
1321		1300	1320	UCUGUUCAGCACCUCCGCCACC	250	UGGGGAGGUGUCUGAACAGA	417	88.33	5.62	76.90	4.37
1324		1303	1323	UAUGGUGUUCAGCACCUCCGCC	251	GGGAGGUGUGAACACAGCAUA	418	79.17	3.54	56.47	2.43
1327		1306	1326	UAAAUGGUGUUCAGCACCUCC	14	AGGUGCUGAACAGCAUUUA	69	44.17	1.60	32.97	3.87
1424		1403	1423	UCAGGAUUGGGGUGUUCAGGGU	252	CCUGAACCGCCCAUUCUGA	419	94.97	2.10	55.43	0.69
1426		1405	1425	UACAGGAUUGGGGUGUUCAGG	253	UGAACCGCCCAUUCUGUUA	420	88.83	2.71	47.57	3.79
1428		1407	1427	UAAAACAGGAUUGGGCGGUUA	254	AACCGCCCAUUCUGUUA	421	77.57	1.97	50.53	3.64
1463		1442	1462	UGAAGUGCAGGCGAGUGGCGCU	255	CGCCACUGCCUGCACUUA	422	103.57	7.18	63.33	5.68
1500		1479	1499	UCUCAUGCUUGUCUCAGCGGCU	256	CCGUGAGCACAGCAUGAGA	423	99.47	6.09	71.27	3.37
1664		1643	1663	UGAGAAACGGCUGCUUUCAGC	21	UGGAAAGCAGCCGUGUUA	76	50.50	3.04	22.20	2.21
1674		1653	1673	UUUAGACCAAGGAGAAACGGCU	22	CCGUUUCUCCUUGGUCUAAA	77	56.37	7.04	25.87	4.58
1675		1654	1674	UCUUAGACCAAGGAGAAACGGC	23	CGUUUCUCCUUGGUCUAAA	78	57.87	7.44	23.97	1.12
1743		1722	1742	UUAAACCCAGCAAAACUGGAGG	257	UCCAGUUUGCUGGGUUUA	424	86.67	3.43	50.50	5.33
1745		1724	1744	UAAUAAACCCAGCAAAACUGGGA	258	CCAGUUUGCUGGGUUUAUA	425	82.47	3.46	44.60	0.95
1747		1726	1746	UAAAUAACCCAGCAAAACUGG	25	AGUUUGCUGGGUUUAUUUA	80	61.57	5.44	32.77	1.81
1749		1728	1748	UCUAAAAUAAACCCAGCAAAACU	259	UUUGCUGGUUUUAUUUAUA	426	79.97	4.91	53.57	2.73

1816	1795	1815	UGUUGGAAUUCUUUUUUGGAACA	260	UUCCAAAAGAAUUCCAACA	427	88.97	3.41	62.63	7.21
1990	1969	1989	UAUCUGGAAAAACUAAGGU	261	CUUAGUUUUUCCACAGAU	428	97.60	3.37	96.33	2.22
2038	2017	2037	UGAAAUUCAGGUGCUUGCAUCU	262	AUGCAAGACCUGAAUUUCA	429	91.87	0.35	75.13	6.86
2042	2021	2041	UACAGAAUUCAGGUGCUUGC	263	AAGCACUGAAUUUCUGUUA	430	99.13	1.05	75.17	5.98
2046	2025	2045	UUUCAAACAGAAAUUCAGGUGC	264	ACCUGAAUUUCUUUGAAA	431	94.60	7.78	89.13	0.43
2048	2027	2047	UCAUCAAACAGAAAUUCAGGU	265	CUGAAUUUCUUUGAAUGA	432	89.00	1.23	65.47	2.32
2070	2049	2069	UGAAAUAAACAGCUAUGGUUCC	266	AACCAUAGCUGGUUUUUA	433	83.43	4.23	73.37	3.96
324	303	323	UGUUUUGCAGCGACUAGCACCA	267	GUGCUAGUCGUGCAAAACA	434	84.73	9.70	56.93	2.45
346	325	345	UCUCAACUUGUCUUCGGUGUCA	268	ACACGAAGACAAGUUGAGA	435	73.47	7.83	44.23	1.79
1351	1330	1350	UCUCUACUCCGCUUCAAAGCUCA	269	AGCUUGAAGCGGAUGAGAGA	436	70.60	3.87	48.60	0.96
1353	1332	1352	UCUCUCUCAUCCGCUUCAAAGCU	270	CUUGAAGCGGAUGAGAGAGA	437	77.33	3.26	59.40	3.72
1652	1631	1651	UCUUUCCAGCUCAAAGUCGACU	271	UCGACUUUGAGCUGGAAAGA	438	82.10	3.30	53.43	0.60
1804	1783	1803	UUUUGGAAACAGUAGUCCCGCG	272	GCGGACUACUGUCCAAAA	439	76.80	3.19	45.23	2.70
1805	1784	1804	UUUUUGGAAACAGUAGUCCCGCG	273	CGGACUACUGUCCAAAA	440	65.37	3.93	52.60	6.47
1806	1785	1805	UUUUUUGGAAACAGUAGUCCCGCG	27	GGGACUACUUGUCCAAAA	82	64.20	2.86	34.63	1.07
1807	1786	1806	UCUUUUUGGAAACAGUAGUCCCG	274	GGACUACUUGUCCAAAAAGA	441	72.83	5.15	42.47	0.92
1809	1788	1808	UUUCUUUUUGGAAACAGUAGUCC	275	ACUACUUGUCCAAAAAGAAA	442	77.40	2.88	49.33	2.26
192	171	191	UACAAGCUGGUCGUUGGAAUU	276	UUCCAACCGACCCAGCUUGUA	443	85.63	3.96	63.67	3.91
543	522	542	UUUCCAAGGAACACCCAGGAUU	277	UCCUGGGUGUCCUUGGAAA	444	102.07	6.17	77.70	2.48
791	770	790	UUCUACGACGAACAUCUAGUU	278	CUGGAUGUUGCUGCUGAGAA	445	96.13	3.27	74.57	3.83

[001] Table 3: Exemplary Sequences of the Present Application with GalNac Conjugations

Guide Strand position 3'	Start	End	Guide strand sequence (5'-3')	SEQ ID NO:	Passenger strand sequence (5'-3')	SEQ ID NO:	PCH Log (Concentration)	PCH Absol ute IC50 (nM)	PHH Log (Concentration)	PHH Absol ute IC50 (nM)
187	166	186	UCUCUCAUUGUGGAGUAGGAGG	4	UCGUCAUCCACAAGAGAGAGA	59				
189	168	188	UUACUCUCAUUGUGGAGUAGGAA	43	GUCAUCCACAAGAGAGAGUAA	98				
415	394	414	UCAUAGCUCACUGGCAUGCCA	6	GCAUGCACAGUGAGCUAUGA	61				
805	784	804	UAUGAACCCUGCAAUUCUCA	45	AGAAGAUUGACAGGUUCAUA	100				
809	788	808	UCUGCAUGAACCCUGCAAUUCUU	46	GAUGACAGGUUCAUGCAGA	101				
1155	1134	1154	UCUUUCUUCAUCCAGUUGAGGG	13	CUCAACUGGAUGAAGAAACA	68				
1285	1264	1284	UCUCAUUUUUUGCAGGUUCAGC	47	UGAACCUUGCAAAAUAUUGAGA	102				
1330	1309	1329	UAAAAAAAUUCUGUUCAGCACC	15	UGCUGAACAGCAUUUUUUUA	70				
1332	1311	1331	UCAAAAAAAUUCUGUUCAGCA	16	CUGAACAGCAUUUUUUUUGA	71	-0.77	0.17	-0.88	0.13
1628	1607	1627	UUAGAAAGAAAGGUGGGAGACU	49	UCUCCACCUUUUCUUCUAA	104				
1629	1608	1628	UUAGAAAGAAAGGUGGGAGAC	19	CUCCACCUUUUCUUCUAAA	74				
1630	1609	1629	UAUUAGAAAGAAAGGUGGGAGA	20	UCCACCUUUUCUUCUAAUA	75	-0.69	0.21	-0.92	0.12
1631	1610	1630	UCAUUAGAAAGAAAGGUGGGAG	50	CCCACCUUUUCUUCUAAUGA	105				
1633	1612	1632	UCUCAUUAAGAAAGGUGGGG	51	CACCUUUUCUUCUAAUGAGA	106				
1843	1822	1842	UUUUUUUGUUUCACAAACAAGC	29	UUUUUUUGUAAAACAAAAAA	84				
1846	1825	1845	UCACUUUUUUUGUUUCACAAACA	30	UUUGUGAAAACAAAAAAGUGA	85	-0.42	0.38	-0.47	0.34
1850	1829	1849	UGGAACACUUUUUUUGUUUCACA	2	UGAAACAAAAAAGUGUCCA	57	-0.43	0.37	-0.51	0.31
1858	1837	1857	UUUGAAAAAGGGAACACUUUUUU	3	AAAAGUUUCCCUUUUUCAAA	58				
1859	1838	1858	UCUUGAAAAAGGGAACACUUUUU	31	AAAGUUUCCCUUUUUCAAAGA	86				
1875	1854	1874	UCAAUUUUUGUUUCUCAAACUUGA	35	AAGUUGAGAAACAAAAAUUGA	90	-0.30	0.50	-0.43	0.37
1881	1860	1880	UAAAAACCAUUUUUGUUUCUCA	55	AGAACAAAAAUUGGGUUUUA	110	-0.37	0.43	-0.42	0.38
1883	1862	1882	UUUAAAAACCAUUUUUGUUUCU	56	AACAAAAAUUGGGUUUUA	111				
1886	1865	1885	UAUUUUAAAAACCAUUUUUUUGU	37	AAAAAUUGGUUUUUA	92				
1894	1873	1893	UAUACUUUAAAAUUUUAACCCCA	40	GGUUUUAAAAUUAAGUAUA	95				
1895	1874	1894	UUUACUUUAAAAUUUUAACCC	41	GUUUUUAAAAUUAAGUAUA	96	-0.39	0.41	-0.62	0.24

[illegible]

Table 4: Exemplary Sequences of the Present Application

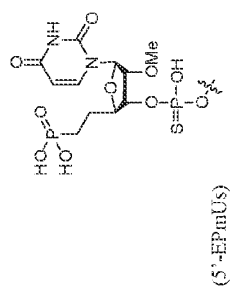
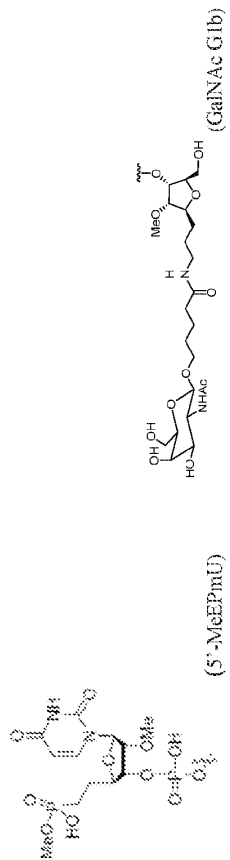
G (5'-3')	[MeEPmUs][fCs][fA][mA][fA][mA][fA][mA][fA][mA][mG][mC][fU][mG][fU][mU][mC][mA][mGs][mCs][mA]	SEQ ID NO: 447
P (5'-3')	[mCs][mUs][mG][mA][fC][mA][fG][fC][fA][fU][mU][mU][mU][mU][mU][mG][mA][Gfb][Gfb][Gfb]	SEQ ID NO: 448
G (5'-3')	[MeEPmUs][fCs][fA][mC][fU][mU][fU][mU][mG][mU][mU][fU][mC][fA][mC][mA][mA][mAs][mCs][mA]	SEQ ID NO: 449
P (5'-3')	[mUs][mUs][mU][mG][mU][fG][mA][fA][fA][fC][fA][mA][mA][mA][mG][mUs][mGs][mA][Gfb][Gfb][Gfb]	SEQ ID NO: 450
G (5'-3')	[MeEPmUs][fGs][fG][mA][fA][mC][mU][fU][mU][mU][mU][mG][fU][mU][mU][mC][mAs][mCs][mA]	SEQ ID NO: 451
P (5'-3')	[mUs][mGs][mA][mA][mA][fC][mA][fA][fA][fA][mA][mG][mU][mU][mCs][mA][Gfb][Gfb][Gfb]	SEQ ID NO: 452
G (5'-3')	[MeEPmUs][fUs][fU][mC][fA][mA][fA][mA][mG][fG][mG][mA][mA][fC][mA][fC][mU][mU][mU][mUs][mU]	SEQ ID NO: 453
P (5'-3')	[mAs][mAs][mA][mA][mG][fU][mG][fU][fU][fC][fC][mC][mU][mU][mU][mC][mAs][mA][Gfb][Gfb][Gfb]	SEQ ID NO: 454
G (5'-3')	[MeEPmUs][fCs][fA][mA][fU][mU][fU][mU][fG][mU][mU][mC][fU][mC][fA][mA][mC][mU][mUs][mGs][mA]	SEQ ID NO: 455
P (5'-3')	[mAs][mAs][mG][mU][mU][fG][mA][fG][fA][fA][fC][mA][mA][mA][mU][mUs][mGs][mA][Gfb][Gfb][Gfb]	SEQ ID NO: 456
G (5'-3')	[MeEPmUs][fAs][fA][mA][fA][mC][fC][mA][fA][mU][mU][mU][fU][mU][fG][mU][mU][mC][mUs][mCs][mA]	SEQ ID NO: 457
P (5'-3')	[mAs][mGs][mA][mA][mC][fA][mA][fA][fA][fA][fU][mU][mG][mG][mG][mU][mU][mUs][mU][mG][fA][Gfb][Gfb][Gfb]	SEQ ID NO: 458

G (5'-3')	[MeEPmUs][fAs][fU][mU][fU][mU][fA][mA][mA][fA][mC][mC][fA][mU][mU][mU][mU][mG][mG][mU]	SEQ ID NO: 465
P (5'-3')	[mAs][mA][mAs][mU][mU][fG][fG][fU][mU][mU][mU][mU][mU][mA][mA][mAs][mU][mU][G1b][G1b]	SEQ ID NO: 453
G (5'-3')	[MeEPmUs][fAs][fU][mA][fC][mU][fU][mU][mU][mA][fA][mU][mU][fU][mA][fA][mC][mCs][mA]	SEQ ID NO: 466
P (5'-3')	[mGs][mGs][mU][mU][fU][mA][fA][fA][fA][fU][mU][mA][mA][mG][mU][mAs][mU][G1b][G1b]	SEQ ID NO: 454
G (5'-3')	[MeEPmUs][fUs][fA][mU][fA][mC][fU][mU][mU][fA][mU][mU][fU][mU][fA][mA][mU][mCs][mC]	SEQ ID NO: 467
P (5'-3')	[mGs][mUs][mU][mU][fA][mA][fA][fA][fU][fU][mA][mA][mG][mU][mU][mU][mU][G1b][G1b]	SEQ ID NO: 455
G (5'-3')	[mUs][fGs][fU][mU][fC][mU][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG]	SEQ ID NO: 468
P (5'-3')	[mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fU][mG][mA][mG][mU][mAs][mCs][mA][G1b][G1b]	SEQ ID NO: 456
G (5'-3')	[EPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG]	SEQ ID NO: 469
P (5'-3')	[mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fU][mG][mA][mU][mG][mA][mU][mAs][mCs][mA][G1b][G1b]	SEQ ID NO: 457
G (5'-3')	[MeEPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG]	SEQ ID NO: 469
P (5'-3')	[mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fU][mG][mA][mU][mG][mA][mU][mAs][mCs][mA][G1b][G1b]	SEQ ID NO: 458
G (5'-3')	[MeEPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG]	SEQ ID NO: 469
P (5'-3')	[mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fU][mG][mA][mU][mG][mA][mU][mAs][mCs][mA][G1b][G1b]	SEQ ID NO: 460

G: guide strand, P: passenger strand

"m" indicates 2'-O-methyl modification, "f" indicates a 2'-F modification, "EPmU" is a phosphate mimic linked to a 5'-terminal uracil (shown below);

"MePmU" is a mono methyl protected phosphate mimic linked to a 5'-terminal uracil (shown below). "s" is a phosphorothioate internucleotide linkage, L96 indicates the GalNAc structure as shown below, and "Gib" is a GalNAc Gib moiety (shown below).



[00587] Additional embodiments of the disclosure include the following:

Embodiment 1. An isolated oligonucleotide comprising a sense strand and an antisense strand, wherein:

the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from :

- a) 9 to 29;
- b) 166 to 196;
- c) 394 to 480;
- d) 744 to 968;
- e) 1110 to 1331;
- f) 1410 to 1676; and
- g) 1726 to 1894,

from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1,

and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

Embodiment 2. The isolated oligonucleotide of Embodiment 1, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

- a) 9 to 29;
- b) 166 to 196;
- c) 394 to 480;
- d) 744 to 968;
- e) 1110 to 1331;
- f) 1410 to 1676; and
- g) 1726 to 1894,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 3. The isolated oligonucleotide of Embodiment 1, wherein the sense strand comprises a nucleotide sequence that is identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

- a) 9 to 29;

- b) 166 to 196;
- c) 394 to 480;
- d) 744 to 968;
- e) 1110 to 1331;
- f) 1410 to 1676; and
- g) 1726 to 1894,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 4. The isolated oligonucleotide of any one of Embodiments 1-3, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 5. The isolated oligonucleotide of Embodiment 4, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 6. The isolated oligonucleotide of Embodiment 4, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 7. The isolated oligonucleotide of any one of Embodiments 1-3, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from:

- a) 166 to 196;
- b) 394 to 480;
- c) 744 to 968;
- d) 1110 to 1331;
- e) 1410 to 1676; and
- f) 1726 to 1894,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 8. The isolated oligonucleotide of Embodiment 7, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from:

- a) 166 to 196;
- b) 394 to 480;
- c) 744 to 968;
- d) 1110 to 1331;
- e) 1410 to 1676; and
- f) 1726 to 1894,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 9. The isolated oligonucleotide of Embodiment 7, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from:

- a) 166 to 196;
- b) 394 to 480;
- c) 744 to 968;
- d) 1110 to 1331;
- e) 1410 to 1676; and
- f) 1726 to 1894,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 10. The isolated oligonucleotide of any one of Embodiments 1-3, wherein the sense strand comprises a sequence that is substantially identical to a region comprising the sequence between any one of the nucleotide positions selected from:

- a) 9 to 29;
- b) 168 to 189;
- c) 784 to 808;
- d) 1264 to 1289;
- e) 1607 to 1630; and
- f) 1814 to 1882,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 11. The isolated oligonucleotide of Embodiment 10, wherein the sense strand comprises a sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising the sequence between any one of the nucleotide positions selected from:

- a) 9 to 29;
- b) 168 to 189;
- c) 784 to 808;
- d) 1264 to 1289;
- e) 1607 to 1630; and
- f) 1814 to 1882,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 12. The isolated oligonucleotide of Embodiment 10, wherein the sense strand comprises a sequence that is identical to a region comprising the sequence between any one of the nucleotide positions selected from:

- a) 9 to 29;
- b) 168 to 189;
- c) 784 to 808;
- d) 1264 to 1289;
- e) 1607 to 1630; and
- f) 1814 to 1882,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

Embodiment 13. The isolated oligonucleotide of any one of Embodiments 1-12, wherein the isolated oligonucleotide is capable of inducing degradation of the AGT mRNA.

Embodiment 14. The isolated oligonucleotide of any one of Embodiments 1-13, wherein the sense strand is a single stranded RNA molecule.

Embodiment 15. The isolated oligonucleotide of any one of Embodiments 1-13, wherein the antisense strand is a single stranded RNA molecule.

Embodiment 16. The isolated oligonucleotide of any one of Embodiments 1-13, wherein both the sense strand and the antisense strand are single stranded RNA molecules.

Embodiment 17. The isolated oligonucleotide of Embodiment 15 or 16, wherein the antisense strand comprises a 3' overhang.

Embodiment 18. The isolated oligonucleotide of Embodiment 17, wherein the 3' overhang comprise at least one nucleotide.

Embodiment 19. The isolated oligonucleotide of Embodiment 18, wherein the 3' overhang comprise two nucleotides.

Embodiment 20. The isolated oligonucleotide of Embodiment 19, wherein the 3' overhang comprises any one of thymidine-thymidine (dTdT), Adenine-Adenine (AA), Cysteine-Cysteine (CC), Guanine-Guanine (GG) or Uracil-Uracil (UU).

Embodiment 21. The isolated oligonucleotide of any one of Embodiments 1-20, wherein the sense strand comprises an RNA sequence of at least 20 nucleotides in length.

Embodiment 22. The isolated oligonucleotide of Embodiment 21, wherein the sense strand comprises an RNA sequence of 20 nucleotides in length.

Embodiment 23. The isolated oligonucleotide of any one of Embodiments 1-22, wherein the antisense strand comprises an RNA sequence of at least 22 nucleotides in length.

Embodiment 24. The isolated oligonucleotide of Embodiment 23, wherein the antisense strand comprises an RNA sequence of 22 nucleotides in length.

Embodiment 25. The isolated oligonucleotide of any one of Embodiments 1-24, wherein the double stranded region is between 19 and 21 nucleotides in length.

Embodiment 26. The isolated oligonucleotide of Embodiment 25, wherein the double stranded region is 20 nucleotides in length.

Embodiment 27. The isolated oligonucleotide of any one of Embodiments 1-26, wherein the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-56.

Embodiment 28. The isolated oligonucleotide of any one of Embodiments 1-27, wherein the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57-111.

Embodiment 29. The isolated oligonucleotide of Embodiment 6, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCCA 3'); or

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCCUUUCAA 3').

Embodiment 30. The isolated oligonucleotide of Embodiment 9, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCUCUCAUUGUGGAUGACGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' UCGUCAUCCACAAUGAGAGA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UCUCACAGGUACUCUCAUUGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' CAAUGAGAGUACCUGUGAGA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UCAUAGCUCACUGUGCAUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' GCAUGCACAGUGAGCUAUGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUAGAGAGAGGCCAGGGUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' GCACCCUGGCCUCUCUCUAA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUGAAGUCCAGAGAGCGUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' CCACGCUCUCUGGACUUCAA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UCUGUCAAUCUUCUCAGCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' CUGCUGAGAAGAUUGACAGA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UGUCCACCCAGAACUCCUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' CCAGGAGUUCUGGGUGGACA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UCAGACACUGAGGUGCUGUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AACAGCACCUCAGUGUCUGA 3');

- ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUUUGCUGGAAAGUGAGACCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' GGUCUCACUUUCCAGCAAAA 3');
- x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UGUUUUCUUAUCCAGUUGAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' CUCAACUGGAUGAAGAAACA 3');
- xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAAUGCUGUUCAGCACCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' AGGUGCUGAACAGCAUUUUA 3');
- xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAUGCUGUUCAGCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUUA 3');
- xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUGA 3');
- xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UCAGCAAACAGGAAUGGGCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' CGCCAUUCCUGUUUGCUGA 3');
- xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAAGAAAAGGUGGGAGACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' AGUCUCCCACCUUUUCUUCA 3');
- xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UUUAGAAGAAAAGGUGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' CUCCCACCUUUUCUUCUAAA 3');
- xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUAGAAGAAAAGGUGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UCCCACCUUUUCUUCUAAUA 3');
- xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UGAGAAACGGCUGCUUCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAAAGCAGCCGUUUCUA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUUAGACCAAGGAGAAACGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' CCGUUUCUCCUUGGUCUAAA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UCUUAGACCAAGGAGAAACGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' CGUUUCUCCUUGGUCUAAGA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UCACUUAGACCAAGGAGAAACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UUUCUCCUUGGUCUAAGUGA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UAAAAUAAACCCAGCAAACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' AGUUUGCUGGGUUUAUUUUA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUCUCUAAAAUAAACCCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' CUGGGUUUAUUUAGAGAAA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' GGGACUACUGUCCAAAAAA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UGUUUCACAAACAAGCUGGUCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 83 (5' ACCAGCUUGUUUGUGAAACA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUUUUUGUUUCACAAACAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UUGUUUGUGAAACAAAAAAA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3');

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UCUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' AAAGUGUCCCCUUUCAAGA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UUGUUCUCAACUUGAAAAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' CCUUUUCAAGUUGAGAACAA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAUUUUUGUUCUCAACUUGAAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCAAGUUGAGAACAAAAUA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAUUUUUGUUCUCAACUUGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' CAAGUUGAGAACAAAAUA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAUUUUUUGUUCUCAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3'); and

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UUUUUAAAACCCAAUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' CAAAAUUGGGUUUUAAAAA 3');

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAAAAUA 3');

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' UAAUUUUAAAACCCAAUUUUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' AAAAUUGGGUUUUAAAAUA 3');

xxxvii) an antisense of nucleic acid sequence according to SEQ ID NO: 39 (5' UUUAAUUUUAAAACCCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' AAUUGGGUUUUAAAAUAAA 3');

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUAAAAGUAUA 3');

xxxix) an antisense of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUAAAAGUAUAA 3'); or

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UCUCAUUAGAAGAAAAGGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' CACCUUUUCUUCUAAUGAGA 3').

Embodiment 31. The isolated oligonucleotide of Embodiment 12, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' UGUAGUACCCAGAACACGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' CCGUUGUUCUGGGUACUACA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' UUACUCUCAUUGUGGAUGACGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' GUCAUCCACAAUGAGAGUAA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UAUGAACCUUGUCAAUCUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' AGAAGAUUGACAGGUUCAUA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' UCUGCAUGAACCUUGUCAAUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' GAUUGACAGGUUCAUGCAGA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' UCUCAAUUUUUGCAGGUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UGAACCUGCAAAAAUUGAGA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' UCAUUGCUCAAUUUUUGCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' CUGCAAAAAUUGAGCAAUGA 3'); or

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCCACCUUUUCUUCUAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' UCAUUAGAAGAAAAGGUGGGAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' CCCACCUUUUCUUCUAAUGA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' UUUUCACAAACAAGCUGGUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' CGACCAGCUUGUUUGUGAAA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' UUUUCACAAACAAGCUGGUCGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' GACCAGCUUGUUUGUGAAAA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' UCUCAACUUGAAAAGGGAACAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' GUUCCCUUUUCAAGUUGAGA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAAUUGGGUUUUA 3'); or

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' UUUAAAACCCAAUUUUUGUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' AACAAAAAUUGGGUUUUA 3').

Embodiment 32. The isolated oligonucleotide of any one of Embodiments 1-31, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% at a dose of 0.02 nM.

Embodiment 33. The isolated oligonucleotide of Embodiment 32, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UCUCACAGGUACUCUCAUUGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' CAAUGAGAGUACCUGUGAGA 3') (42.5);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UCAUAGCUCACUGUGCAUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' GCAUGCACAGUGAGCUAUGA 3') (42.5);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUAGAGAGAGGCCAGGGUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' GCACCCUGGCCUCUCUCUAA 3') (30.4);

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUGAAGUCCAGAGAGCGUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' CCACGCUCUCUGGACUUCUA 3') (37.9);

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UCUGUCAAUCUUCUCAGCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' CUGCUGAGAAGAUUGACAGA 3') (41.3);

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UGUCCACCCAGAACUCCUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' CCAGGAGUUCUGGGUGGACA 3') (49.7);

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UCAGACACUGAGGUGCUGUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AACAGCACCUCAGUGUCUGA 3') (35.4);

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUUUGCUGGAAAGUGAGACCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' GGUCUCACUUCCAGCAAAA 3') (40.8);

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UGUUUUCUUAUCCAGUUGAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' CUCAACUGGAUGAAGAAACA 3') (39.7);

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UCAGCAAACAGGAAUGGGCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' CGCCCAUCCUGUUUGCUGA 3') (39.3);

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAAGAAAAGGUGGGAGACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' AGUCUCCCACCUUUUCUUCA 3') (39);

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UUUAGAAGAAAAGGUGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' CUCCCACCUUUUCUUCUAAA 3') (48.5);

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UGAGAAACGGCUGCUUCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAAAGCAGCCGUUUCUCA 3') (49.5);

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUUAGACCAAGGAGAAACGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' CCGUUUCUCCUUGGUCUAAA 3') (43.6);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UCUUAGACCAAGGAGAAACGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' CGUUUCUCCUUGGUCUAAGA 3') (42.1);

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UCACUUAGACCAAGGAGAAACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UUUCUCCUUGGUCUAAGUGA 3') (26.7);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UAAAAUAAACCCAGCAAACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' AGUUUGCUGGGUUUAUUUUA 3') (38.4);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUCUCUAAAAUAAACCCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' CUGGGUUUAUUUAGAGAAA 3') (47.9);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UUGUUCUCAACUUGAAAAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' CCUUUCAAGUUGAGAACAA 3') (42.5);

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAUUUUUGUUCUCAACUUGAAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCAAGUUGAGAACAAAAUA 3') (34);

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAUUUUUGUUCUCAACUUGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' CAAGUUGAGAACAAAAUUA 3') (38.7);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UUUUUAAAACCCAAUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' CAAAAAUUGGGUUUAAAAA 3') (36.5);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' UAAUUUUAAAAACCCAAUUUUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' AAAAUUGGGUUUUAAAAUUA 3') (27.4);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' UUUAAUUUUAAAAACCCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' AAUUGGGUUUUAAAAUUA 3') (36.1);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUUAAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUAA 3') (43.8);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' UGUAGUACCCAGAACAACGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' CCGUUGUUCUGGGUACUACA 3') (45.6);

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' UCUCAAUUUUUGCAGGUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UGAACCUGCAAAAAUUGAGA 3') (45.4);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' UCAUUGCUCAAUUUUUGCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' CUGCAAAAAUUGAGCAAUGA 3') (42.9);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UCUCAUUAGAAGAAAAGGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' CACCUUUUCUUCUAAUGAGA 3') (39.06); or

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' UUUCACAAACAAGCUGGUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' CGACCAGCUUGUUUGUGAAA 3') (27.8);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' UUUAAAACCCAAUUUUUGUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' AACAAAAAUUGGGUUUUAAA 3') (49.0);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAAUUGGGUUUUA 3') (44.8); or

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' GGGACUACUGUCCAAAAA 3') (35.8).

Embodiment 34. The isolated oligonucleotide of any one of Embodiments 1-31, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% at a dose of 0.02 nM.

Embodiment 35. The isolated oligonucleotide of Embodiment 34, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAGUGUCCA 3') (56.3);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCUUUUCAA 3') (54.5);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCUCUCAUUGUGGAUGACGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' UCGUCAUCCACAAUGAGAGA 3') (63.3);

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAAUGCUGUUCAGCACCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' AGGUGCUGAACAGCAUUUUA 3') (55.8)

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAUGCUGUUCAGCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUA 3') (52.6);

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUGA 3') (50.3);

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUAGAAGAAAAGGUGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UCCCACCUUUUCUUCUAAUA 3') (76.8);

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUUUUUGUUUCACAAACAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UUGUUUGUGAAACAAAAAAA 3') (52);

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3') (51.9);

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UCUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' AAAGUGUCCCCUUUCAAGA 3') (65.7);

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAUUUUUUGUUCUACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAAUUGA 3') (54.9);

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAAAAUA 3') (57.9);

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUUAAGUAUA 3') (61.1);

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' UUACUCUCAUUGUGGAUGACGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' GUCAUCCACAAUGAGAGUAA 3') (55.5);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3') (70.2);

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UAUGAACUGUCAAUUCUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' AGAAGAUUGACAGGUUCAUA 3') (74.3);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' UCUGCAUGAACUGUCAAUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' GAUUGACAGGUUCAUGCAGA 3') (62.6);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCCACCUUUUCUUCUAA 3') (63.5);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' UCAUUAGAAGAAAAGGUGGGAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' CCCACCUUUUCUUCUAAUGA 3') (64.3); or

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' UCUCAACUUGAAAAGGGAACAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' GUUCCCUUUUCAAGUUGAGA 3') (50.4).

Embodiment 36. The isolated oligonucleotide of any one of Embodiments 1-31, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% at a dose of 0.1 nM.

Embodiment 37. The isolated oligonucleotide of Embodiment 36, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCCA 3') (75.5);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCUUUUCAAA 3') (72.3);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCUCUCAUUGUGGAUGACGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' UCGUCAUCCACAAUGAGAGA 3') (78);

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UCUCACAGGUACUCUCAUUGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' CAAUGAGAGUACCUGUGAGA 3') (62.4);

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UCAUAGCUCACUGUGCAUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' GCAUGCACAGUGAGCUAUGA 3') (66.2);

- vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUAGAGAGAGGCCAGGGUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' GCACCCUGGCCUCUCUCUAA 3') (64.9);
- vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUGAAGUCCAGAGAGCGUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' CCACGCUCUCUGGACUCAA 3') (65.7);
- viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UCUGUCAAUCUUCUCAGCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' CUGCUGAGAAGAUUGACAGA 3') (65.2);
- ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UGUCCACCCAGAACUCCUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' CCAGGAGUUCUGGGUGGACA 3') (61.7);
- x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UCAGACACUGAGGUGCUGUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AACAGCACCUCAGUGUCUGA 3') (66);
- xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUUUGCUGGAAAGUGAGACCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' GGUCUCACUUCCAGCAAAA 3') (65.4);
- xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UGUUUCUUAUCCAGUUGAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' CUCAACUGGAUGAAGAAACA 3') (74.4);
- xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAAUGCUGUUCAGCACCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' AGGUGCUGAACAGCAUUUUA 3') (67);
- xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAUGCUGUUCAGCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUUA 3') (68.3);
- xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUGA 3') (73.6);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UCAGCAAACAGGAAUGGGCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' CGCCCAUUCCUGUUUGCUGA 3') (67.3);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAAGAAAAGGUGGGAGACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' AGUCUCCCACCUUUUCUUCA 3') (67.5);

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UUUAGAAGAAAAGGUGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' CUCCCACCUUUUCUUCUAAA 3') (66.6);

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUAGAAGAAAAGGUGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UCCCACCUUUUCUUCUAAUA 3') (74.3);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UGAGAAACGGCUGCUUCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAAAGCAGCCGUUUCUCA 3') (77.8);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUUAGACCAAGGAGAAACGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' CCGUUCUCCUUGGUCUAAA 3') (74.1);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UCUUAGACCAAGGAGAAACGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' CGUUCUCCUUGGUCUAAGA 3') (76);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UAAAAUAAACCCAGCAAACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' AGUUUGCUGGGUUUAUUUUA 3') (67.2);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' GGGACUACUGUCCAAAAAA 3') (65.4);

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UCACUUAGACCAAGGAGAAACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UUUCUCCUUGGUCUAAGUGA 3') (61.5);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUCUCUAAAAUAAACCCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' CUGGGUUUAUUUUAGAGAAA 3') (61.8);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UGUUUCACAAACAAGCUGGUCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 83 (5' ACCAGCUUGUUUGUGAAACA 3') (62);

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUUUUUGUUUCACAAACAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UUGUUUGUGAAACAAAAAAA 3') (77.3);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3') (76.5);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UCUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' AAAGUGUCCCCUUUCAAGA 3') (73.8);

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UUGUUCUCAACUUGAAAAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' CCUUUCAAGUUGAGAACAA 3') (62.6);

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAUUUUUGUUCUCAACUUGAAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCAAGUUGAGAACAAAAUA 3') (64.5);

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAUUUUUGUUCUCAACUUGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' CAAGUUGAGAACAAAAUUA 3') (63.2);

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUCAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3') (75.9);

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UUUUUAAAACCCAAUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' CAAAAAUUGGGUUUAAAAA 3') (68.3);

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAUUGGGUUUUAAAAUA 3') (65.7);

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' UAAUUUAAAACCCAAUUUUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' AAAAUUGGGUUUUAAAAUUA 3') (69.5);

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' UUUAAUUUUAAAACCCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' AAUUGGGUUUUAAAAUUAUA 3') (64.9);

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUUAAGUAUA 3') (69.6);

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUAA 3') (77.6);

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' UGUAGUACCCAGAACAACGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' CCGUUGUUCUGGGUACUACA 3') (63.2);

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' UUACUCUCAUUGUGGAUGACGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' GUCAUCCACAAUGAGAGUAA 3') (73.3);

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3') (84.8);

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UAUGAACUGUCAAUUCUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' AGAAGAUUGACAGGUUCAUA 3') (73);

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' UCUGCAUGAACUGUCAAUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' GAUUGACAGGUUCAUGCAGA 3') (63.6);

XLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' UCUCAAUUUUUUGCAGGUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UGAACCUGCAAAAAUUGAGA 3') (67.5);

XLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' UCAUUGCUCAAUUUUUGCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' CUGCAAAAAUUGAGCAAUGA 3') (62.6);

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCCACCUUUUCUUCUAA 3') (78.5);

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' UCAUUAGAAGAAAAGGUGGGAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' CCCACCUUUUCUUCUAAUGA 3') (70.2);

Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UCUCAAUUAGAAGAAAAGGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' CACCUUUUCUUCUAAUGAGA 3') (78.2);

Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' UUUCACAAACAAGCUGGUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' CGACCAGCUUGUUUGUGAAA 3') (63.2);

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' UUUUCACAAACAAGCUGGUCGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' GACCAGCUUGUUUGUGAAAA 3') (62);

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' UCUCAACUUGAAAAGGGAACAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' GUUCCCUUUUCAAGUUGAGA 3') (61);

Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' UUUAAAACCCAAUUUUUGUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' AACAAAAAUUGGGUUUUAAA 3') (71.3); or

LVii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAAUUGGGUUUUA 3') (74.5).

Embodiment 38. An isolated oligonucleotide comprising a sense strand and an antisense strand, wherein:

the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

- a) 11 to 42;
- b) 144 to 284;
- c) 303 to 405;
- d) 441 to 580;
- e) 690 to 802;
- f) 863 to 883;
- g) 922 to 966;
- h) 1036 to 1056;
- i) 1099 to 1153;
- j) 1189 to 1282;
- k) 1300 to 1367;
- l) 1403 to 1517;
- m) 1601 to 1651;
- n) 1722 to 1890;
- o) 1901 to 1948; and
- p) 2017 to 2095,

from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1,

and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

Embodiment 39. The isolated oligonucleotide of Embodiment 38, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at 20% to 50% at a dose of 0.1 nM.

Embodiment 40. The isolated oligonucleotide of Embodiment 39, wherein the double stranded region comprises:

- i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 237 (5' UCUGUAGUACCCAGAACACGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 404 (5' GUUGUUCUGGGUACUACAGA 3') (34.3);

- ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 128 (5' UCAUUGGCCUUUGCCAGCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 295 (5' CAGCUGGCAAAGGCCAAUGA 3') (39.5);
- iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 145 (5' UGUGCCAAAGACAGCCGUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 312 (5' CAACGGCUGUCUUUGGCACA 3') (39);
- iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 240 (5' UAUAGAGAGAGGCCAGGGUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 407 (5' CACCCUGGCCUCUCUCUAUA 3') (35.9);
- v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 241 (5' UGAUUGCCUGUAGCCUGUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 408 (5' UGACAGGCUACAGGCAAUCA 3') (35.6);
- vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UCAGUUCUUGUCCUCCAAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 409 (5' CUUGGAAGGACAAGAACUGA 3') (42.8);
- vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 243 (5' UUAUAGAGAGCCAGGCCUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 410 (5' CAGGGCCUGGCUCUCUAUAA 3') (37.2);
- viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' UGUAGGUGUUGAAAGCCAGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 412 (5' CCUGGCUUUAACACCUACA 3') (40.5);
- ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 246 (5' UCAGAACUCCUGGGGCUCGGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 413 (5' CCGAGCCCCAGGAGUUCUGA 3') (22.4);
- x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 157 (5' UUUGUCCACCCAGAACUCCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 324 (5' AGGAGUUCUGGGUGGACAAA 3') (32.8);
- xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 160 (5' UGACACUGAGGUGCUGUUGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 327 (5' ACAACAGCACCUCAGUGUCA 3') (34.1);

- xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 247 (5' UCUCUCAGUGAAGGGCACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 414 (5' AAGUGCCCUUCACUGAGAGA 3') (27.2);
- xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAAGUGAGACCCUCCACCUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 332 (5' AAGGUGGAGGGUCUCACUUA 3') (40);
- xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 167 (5' UGGAAAGUGAGACCCUCCACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 334 (5' GUGGAGGGUCUCACUUUCCA 3') (41.8);
- xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UCUGGAAAGUGAGACCCUCCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 335 (5' GGAGGGUCUCACUUUCCAGA 3') (40.8);
- xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAGUUGAGGGAGUUUUGCUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 338 (5' CAGCAAAACUCCCUCAACUA 3') (48.4);
- xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UGAAUGGCGGGCAGCUCAGCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 344 (5' GCUGAGCUGCCCGCCAUUCA 3') (36.9);
- xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 182 (5' UAAUUUUUGCAGGUUCAGCUCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 349 (5' AGCUGAACCUGCAAAAAUUA 3') (41.2);
- xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 251 (5' UAUGCUGUUCAGCACCUCUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 418 (5' GGGAGGUGCUGAACAGCAUA 3') (43.5);
- xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 187 (5' UUAGACUCUGUGGGCUCUCUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 354 (5' AGAGAGCCCACAGAGUCUAA 3') (30.6);
- xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 254 (5' UCAAACAGGAAUGGGCGGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 421 (5' AACCGCCCAUCCUGUUUGA 3') (49.5);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 190 (5' UAUCAUACACAGCAAACAGGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 357 (5' CCUGUUUGCUGUGUAUGAUA 3') (48.8);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 201 (5' UAAGAAAAGGUGGGAGACUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 368 (5' CAGUCUCCCACCUUUUCUUA 3') (30.9);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 259 (5' UCUAAAAUAAACCCAGCAAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 426 (5' UUUGCUGGGUUUAUUUUAGA 3') (46.4);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 273 (5' UUUUUGGAACAGUAGUCCCGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 440 (5' CGGGACUACUGUCCAAAAA 3') (47.4);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' UGUCGGUUGGAAUUCUUUUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' AAAAAGAAUCCAACCGACA 3') (33.7);

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCAAACAAGCUGGUCGGUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' CAACCGACCAGCUUGUUUGA 3') (47.5);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' UCUUUAAUUUUAAAACCCAAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' UUGGGUUUUAAAUAUAAAGA 3') (46.8);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' UAUACAAACCGAAGGCAAUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' CAUUGCCUUCGGUUUGUAUA 3') (39.6);

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 221 (5' UAAUACAAACCGAAGGCAAUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 388 (5' AUUGCCUUCGGUUUGUAUUA 3') (33.2);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' UCACUAAAUACAAACCGAAGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' CUUCGGUUUGUAUUUAGUGA 3') (30.2);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' UAAGACACUAAAUACAAACCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 392 (5' GGUUUGUAUUUAGUGUCUUA 3') (32.9);

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 226 (5' UCAAGACACUAAAUACAAACCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 393 (5' GUUUGUAUUUAGUGUCUUGA 3') (32);

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 120 (5' UGGAAGGGGUGUAUGUACACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 287 (5' GUGUACAUACACCCCUUCCA 3') (20.2);

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 236 (5' UAAGACGUUUUUUACUACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 403 (5' UGUUAGUAAUAAACGUCUUA 3') (23.6); or

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 122 (5' UGGAUGACGAGGUGGAAGGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 289 (5' CCCUCCACCUCGUCAUCCA 3') (25.7);

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 125 (5' UCUCAUUGUGGAUGACGAGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 292 (5' CCUCGUCAUCCACAAUGAGA 3') (22.4);

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 276 (5' UACAAGCUGGUCGGUUGGAAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 443 (5' UUCAACCGACCAGCUUGUA 3') (36.3);

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 127 (5' UCUUUGCCAGCUGCUCACAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 294 (5' CUGUGAGCAGCUGGCAAAGA 3') (35.8);

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 239 (5' UUUUCAUCCACAGGGGAUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 406 (5' ACAUCCCCUGUGGAUGAAAA 3') (23.1);

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 267 (5' UGUUUUGCAGCGACUAGCACCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 434 (5' GUGCUAGUCGCUGCAAAACA 3') (43.1);

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 129 (5' UAAGUUGGCCAGCAUCCCGACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 296 (5' UCGGGAUGCUGGCCAACUUA 3') (25.2);

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAUAUACGGAAGCCCAAGAAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 300 (5' UUCUUGGGCUUCCGUAUAUA 3') (50.0);

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 135 (5' UAUAUAUACGGAAGCCCAAGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 302 (5' CUUGGGCUUCCGUAUAUAUA 3') (33.6);

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 136 (5' UCAUAUAUACGGAAGCCCAAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 303 (5' UUGGGCUUCCGUAUAUAUGA 3') (39.2);

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 138 (5' UCAUGCCAUAUAUACGGAAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 305 (5' CUUCCGUAUAUAUGGCAUGA 3') (22.9);

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 139 (5' UCUGUGCAUGCCAUAUAUACGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 306 (5' GUAUAUAUGGCAUGCACAGA 3') (31.9);

xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 144 (5' UCAAAGACAGCCGUUGGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 311 (5' UCCCCAACGGCUGUCUUUGA 3') (45.5);

xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 277 (5' UUUCCAAGGAACACCCAGGAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 444 (5' UCCUGGGUGUCCUUGGAAA 3') (22.3);

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 149 (5' UGACCUUGUGCGCAUCCAGCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 316 (5' GCUGGAUGCGCACAAGGUCA 3') (41.9);

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 151 (5' UCAAACGGCUGCUUCAGGUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 318 (5' CACCUGAAGCAGCCGUUUGA 3') (34.7);

Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 152 (5' UCACAAACGGCUGCUUCAGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 319 (5' CCUGAAGCAGCCGUUUGUGA 3') (32.6);

Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 153 (5' UUAGAGAGCCAGGCCUGCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 320 (5' UGCAGGGCCUGGCUCUCUAA 3') (33.3);

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 154 (5' UAAGUCCAGAGAGCGUGGGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 321 (5' UCCCACGCUCUCUGGACUUA 3') (29.8);

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 155 (5' UGUGAAGUCCAGAGAGCGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 322 (5' CACGCUCUCUGGACUUCACA 3') (28.3);

Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 244 (5' UUUCUGUGAAGUCCAGAGAGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 411 (5' CUCUCUGGACUUCACAGAAA 3') (23.1);

Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 278 (5' UUCUCAGCAGCAACAUCAGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 445 (5' CUGGAUGUUGCUGCUGAGAA 3') (25.4);

Lviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 158 (5' UCUGUUGUCCACCCAGAACUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 325 (5' AGUUCUGGGUGGACAACAGA 3') (32.2);

Lix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 164 (5' UGUGAGACCCUCCACCUUGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 331 (5' ACAAGGUGGAGGGUCUCACA 3') (35.0);

Lx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 166 (5' UGAAAGUGAGACCCUCCACCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 333 (5' GGUGGAGGGUCUCACUUUCA 3') (20.9);

Lxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 173 (5' UAUCCAGUUGAGGGAGUUUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 340 (5' AAAACUCCCUCAACUGGAUA 3') (44.3);

Lxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 178 (5' UCAGAAUGGCGGGCAGCUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 345 (5' UGAGCUGCCCGCCAUUCUGA 3') (24.0);

Lxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 250 (5' UCUGUUCAGCACCUCACCCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 417 (5' UGGGGGAGGUGCUGAACAGA 3') (23.1);

Lxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 184 (5' UAAAAAUGCUGUUCAGCACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 351 (5' GUGCUGAACAGCAUUUUUUA 3') (48.5);

Lxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 185 (5' UAAAAAUGCUGUUCAGCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 352 (5' GCUGAACAGCAUUUUUUUA 3') (41.6);

Lxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 270 (5' UCUCUCUAUCCGCUUCAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 437 (5' CUUGAAGCGGAUGAGAGAGA 3') (40.6);

Lxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 252 (5' UCAGGAUUGGCGGUUCAGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 419 (5' CCUGAACCGCCCAUCCUGA 3') (44.6);

Lxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 188 (5' UCACAGCAAACAGGAUUGGGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 355 (5' CCCAUUCCUGUUUGCUGUGA 3') (46.8);

Lxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 189 (5' UAUACACAGCAAACAGGAAUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 356 (5' AUUCCUGUUUGCUGUGUAUA 3') (36.5);

Lxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 192 (5' UUUGAUCAUACACAGCAAACAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 359 (5' GUUUGCUGUGUAUGAUGAUA 3') (42.9);

Lxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 193 (5' UUUUGAUCAUACACAGCAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 360 (5' UUUGCUGUGUAUGAUGAUA 3') (29.7);

Lxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 255 (5' UGAAGUGCAGGGCAGUGGCGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 422 (5' CGCCACUGCCCUGCACUUCA 3') (36.7);

Lxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 194 (5' UCAGGAAGUGCAGGGCAGUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 361 (5' CACUGCCCUGCACUUCCUGA 3') (22.8);

Lxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 256 (5' UCUCAUGCUGUGCUCAGCGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 423 (5' CCGCUGAGCACAGCAUGAGA 3') (28.7);

Lxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 195 (5' UCUGGGGCCCUGGCCUCAUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 362 (5' CAUGAGGCCAGGGCCCCAGA 3') (37.9);

Lxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 198 (5' UAAAAGGUGGGAGACUGGGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 365 (5' CCCAGUCUCCCACCUUUUA 3') (29.2);

Lxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 199 (5' UGAAAAGGUGGGAGACUGGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 366 (5' CCCAGUCUCCCACCUUUUA 3') (46.3);

Lxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 271 (5' UCUUUCCAGCUAAAGUCGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 438 (5' UCGACUUUGAGCUGGAAAGA 3') (46.6);

Lxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 257 (5' UUAAACCCAGCAAACUGGGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 424 (5' UCCCAGUUUGCUGGGUUUA 3') (49.5);

Lxxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 204 (5' UCUGGUUCUUGCCUCCCCACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 371 (5' GUGGGGAGGCAAGAACCAGA 3') (28.0);

Lxxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 205 (5' UAAACACUGGUUCUUGCCUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 372 (5' GAGGCAAGAACCAGUGUUUA 3') (48.5);

Lxxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 260 (5' UGUUGGAAUUCUUUUUGGAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 427 (5' UUCCAAAAAGAAUCCAACA 3') (37.4);

Lxxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 209 (5' UUUGUUUCACAAACAAGCUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 376 (5' CAGCUUGUUUGUGAAACAAA 3') (37.3);

Lxxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 210 (5' UUUUUGUUUCACAAACAAGCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 377 (5' GCUUGUUUGUGAAACAAAAA 3') (20.4);

Lxxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 227 (5' UCUUACAUUCAAGACACUAAAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 394 (5' UUAGUGUCUUGAAUGUAAGA 3') (44.3);

Lxxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 229 (5' UGUCAUGUUCUUAUUAAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 396 (5' UUGAAUGUAAGAACAUGACA 3') (22.7);

Lxxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 262 (5' UGAAAUUCAGGUGCUUGCAUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 429 (5' AUGCAAGCACCUGAAUUUCA 3') (24.9);

Lxxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 263 (5' UAACAGAAAUUCAGGUGCUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 430 (5' AAGCACCUGAAUUUCUGUUA 3') (24.8);

Lxxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 265 (5' UCAUUCAAACAGAAAUUCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 432 (5' CUGAAUUUCUGUUUGAAUGA 3') (34.5);

XC) an antisense strand of nucleic acid sequence according to SEQ ID NO: 266 (5' UGAAAUAAACCAGCUAUGGUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 433 (5' AACCAUAGCUGGUUAUUUCA 3') (26.6);

XCi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 196 (5' UGUGUUCUGGGGCCUGGCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 363 (5' GGCCAGGGCCCCAGAACACA 3') (41); or

XCii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 112 (5' UCUUCUGCUGUAGUACCCAGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 279 (5' CUGGGUACUACAGCAGAAGA 3') (37.4).

Embodiment 41. The isolated oligonucleotide of Embodiment 38, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% at a dose of 0.1 nM.

Embodiment 42. The isolated oligonucleotide of Embodiment 41, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UAUACCCUUCUGCUGUAGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 280 (5' UACUACAGCAGAAGGGUAUA 3') (54.0);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 126 (5' UCACAGGUACUCUCAUUGUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 293 (5' CACAAUGAGAGUACCUGUGA 3') (55.2);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 268 (5' UCUCAACUUGUCUUCGGUGUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 435 (5' ACACCGAAGACAAGUUGAGA 3') (55.8);

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 130 (5' UAGAAGUUGGCCAGCAUCCCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 297 (5' GGGAUGCUGGCCAACUUCUA 3') (50.8);

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UGGAAGCCCAAGAAGUUGGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 299 (5' GCCAACUUCUUGGGCUUCCA 3') (57.6);

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAUAUACGGAAGCCCAAGAAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 300 (5' UUCUUGGGCUUCCGUAUAUA 3') (50.0);

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 134 (5' UUAUAUACGGAAGCCCAAGAAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 301 (5' UCUUGGGCUUCCGUAUAUAA 3') (58.8);

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 137 (5' UAUGCCAUUAUACGGAAGCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 304 (5' GCUUCCGUAUAUAUGGCAUA 3') (51.4);

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 156 (5' UGAACCUGUCAAAUCUUCUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 323 (5' UGAGAAGAUUGACAGGUUCA 3') (54.2);

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 169 (5' UGUUUUGCUGGAAAGUGAGACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 336 (5' UCUCACUUUCCAGCAAAACA 3') (54.6);

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 170 (5' UGAGUUUUGCUGGAAAGUGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 337 (5' UCACUUUCCAGCAAAACUCA 3') (52.3);

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UUUUCUUAUCCAGUUGAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 343 (5' CCUCAACUGGAUGAAGAAAA 3') (56.4);

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' UUAAGAUCUUGCAGCACCAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 415 (5' UGGUGCUGCAAGGAUCUUA 3') (55.8);

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UUUUUGCAGGUUCAGCUCGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 346 (5' CCGAGCUGAACCUGCAAAAA 3') (53.4);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 180 (5' UUUUUUGCAGGUUCAGCUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 347 (5' CGAGCUGAACCUGCAAAAA 3') (54.9);

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 181 (5' UAUUUUUGCAGGUUCAGCUCGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 348 (5' GAGCUGAACCUGCAAAAAUA 3') (55.8);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 183 (5' UCAAUUUUUGCAGGUUCAGCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 350 (5' GCUGAACCUGCAAAAAUUGA 3') (53.8);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UCUCUCAUCCGCUUCAAGCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 436 (5' AGCUUGAAGCGGAUGAGAGA 3') (51.4);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 186 (5' UGACUCUGUGGGCUCUCUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 353 (5' AGAGAGAGCCCCACAGAGUCA 3') (54.6);

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 253 (5' UAACAGGAAUGGGCGGUUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 420 (5' UGAACCGCCCAUCCUGUUA 3') (52.4);

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUCAUACACAGCAAACAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 358 (5' CUGUUUGCUGUGUAUGAUA 3') (59.3);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' UAGAAAAGGUGGGAGACUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 367 (5' CCAGUCUCCCACCUUUUCUA 3') (56.1);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' UUUUAAAACCCAAUUUUUGUUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' ACAAAAUUGGGUUUUAAAA 3') (59.0);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 258 (5' UAAUAAACCCAGCAAACUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 425 (5' CCAGUUUGCUGGGUUUAUUA 3') (55.4);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 202 (5' UAUUCUCUAAAAUAAACCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 369 (5' UGGGUUUAUUUAGAGAAUA 3') (50.5);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 206 (5' UUAACACUGGUUCUUGCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' AGGCAAGAACCAGUGUUUAA 3') (58.6);

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 272 (5' UUUUGGAACAGUAGUCCCGCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 439 (5' GCGGGACUACUGUCCAAAA 3') (54.8);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 274 (5' UCUUUUUGGAACAGUAGUCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 441 (5' GGACUACUGUCCAAAAAGA 3') (57.5);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' UUUCUUUUUGGAACAGUAGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 442 (5' ACUACUGUUCACAAAAGAAA 3') (50.7);

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 211 (5' UUUUUUGUUUCACAAACAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' CUUGUUUGUGAAACAAAAA 3') (59.9);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' UAAAAGGGAACACUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' CAAAAAGUGUCCCUUUUA 3') (55.7);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 214 (5' UCAACUUGAAAAGGGAACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' GUGUCCCUUUUCAAGUUGA 3') (54.9);

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' UUUUAAUUUAAAACCCAAUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' AUUGGGUUUAAAAUUAAAA 3') (56.5).

Embodiment 43. The isolated oligonucleotide of any one of Embodiments 38-42, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% at a dose of 0.02 nM.

Embodiment 44. The isolated oligonucleotide of Embodiment 43, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 237 (5' UCUGUAGUACCCAGAACAACGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 404 (5' GUUGUUCUGGGUACUACAGA 3') (29.7);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UAUACCCUUCUGCUGUAGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 280 (5' UACUACAGCAGAAGGGUAUA 3') (32.8);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 126 (5' UCACAGGUACUCUCAUUGUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 293 (5' CACAAUGAGAGUACCUGUGA 3') (35.0);

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 128 (5' UCAUUGGCCUUUGCCAGCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 295 (5' CAGCUGGCAAAGGCCAAUGA 3') (23.9);

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 268 (5' UCUCAACUUGUCUUCGGUGUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 435 (5' ACACCGAAGACAAGUUGAGA 3') (26.5);

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 130 (5' UAGAAGUUGGCCAGCAUCCCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 297 (5' GGGAUGCUGGCCAACUUCUA 3') (24.4);

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 131 (5' UCAAGAAGUUGGCCAGCAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 298 (5' GAUGCUGGCCAACUUCUUGA 3') (22.0);

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UGGAAGCCCAAGAAGUUGGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 299 (5' GCCAACUUCUUGGGCUUCCA 3') (34.0);

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAUUAUCGGAAGCCCAAGAAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 300 (5' UUCUUGGGCUUCCGUUAUAUA 3') (21.8);

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 134 (5' UUAUAUACGGAAGCCCAAGAAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 301 (5' UCUUGGGCUUCCGUUAUAUA 3') (35.0);

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 137 (5' UAUGCCAUAUAUACGGAAGCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 304 (5' GCUUCCGUUAUAUAUGGCAUA 3') (25.8);

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 145 (5' UGUGCCAAAGACAGCCGUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 312 (5' CAACGGCUGUCUUUGGCACA 3') (25.2);

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 240 (5' UAUAGAGAGAGGCCAGGGUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 407 (5' CACCCUGGCCUCUCUCUAUA 3') (33.1);

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 241 (5' UGAUUGCCUGUAGCCUGUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 408 (5' UGACAGGCUACAGGCAAUCA 3') (25.3);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UCAGUUCUUGUCCUCCAAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 409 (5' CUUGGAAGGACAAGAACUGA 3') (28.4);

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 243 (5' UUAUAGAGAGCCAGGCCUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 410 (5' CAGGGCCUGGCUCUCUAUAA 3') (31.9);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 156 (5' UGAACCUGUCAAUUCUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 323 (5' UGAGAAGAUUGACAGGUUCA 3') (31.2);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' UGUAGGUGUUGAAAGCCAGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 412 (5' CCUGGCUUUAACACCUACA 3') (26.8);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 246 (5' UCAGAACUCCUGGGGCUCGGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 413 (5' CCGAGCCCCAGGAGUUCUGA 3') (20.8);

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 160 (5' UGACACUGAGGUGCUGUUGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 327 (5' ACAACAGCACCUCAGUGUCA 3') (21.2);

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 247 (5' UCUCUCAGUGAAGGGCACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 414 (5' AAGUGCCCUUCACUGAGAGA 3') (20.5);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAAGUGAGACCCUCCACCUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 332 (5' AAGGUGGAGGGUCUCACUUA 3') (20.3);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 167 (5' UGGAAAGUGAGACCCUCCACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 334 (5' GUGGAGGGUCUCACUUUCCA 3') (27.1);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UCUGGAAAGUGAGACCCUCCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 335 (5' GGAGGGUCUCACUUUCCAGA 3') (21.0);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 169 (5' UGUUUUGCUGGAAAGUGAGACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 336 (5' UCUCACUUUCCAGCAAAACA 3') (25.6);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 170 (5' UGAGUUUUGCUGGAAAGUGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 337 (5' UCACUUUCCAGCAAAACUCA 3') (28.2);

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAGUUGAGGGAGUUUUGCUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 338 (5' CAGCAAAACUCCCUCAACUA 3') (31.1);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 172 (5' UCAGUUGAGGGAGUUUUGCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 339 (5' AGCAAAACUCCCUCAACUGA 3') (24.8);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UUUUCUUCAUCCAGUUGAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 343 (5' CCUCAACUGGAUGAAGAAAA 3') (21.6);

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' UUAAGAUCUUGCAGCACCAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 415 (5' UGGUGCUGCAAGGAUCUUA 3') (32.6);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UGAAUGGCGGGCAGCUCAGCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 344 (5' GCUGAGCUGCCCGCCAUUA 3') (37.6);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UUUUUGCAGGUUCAGCUCGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 346 (5' CCGAGCUGAACCUGCAAAAA 3') (26.9);

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 180 (5' UUUUUGCAGGUUCAGCUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 347 (5' CGAGCUGAACCUGCAAAAA 3') (29.2);

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 270 (5' UCUCUCUCAUCCGCUUCAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 437 (5' CUUGAAGCGGAUGAGAGAGA 3') (22.7);

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 187 (5' UUAGACUCUGUGGGCUCUCUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 354 (5' AGAGAGCCCACAGAGUCUAA 3') (25.9);

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 254 (5' UCAAACAGGAAUGGGCGGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 421 (5' AACCGCCCAUCCUGUUUGA 3') (22.4);

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 190 (5' UAUCAUACACAGCAAACAGGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 357 (5' CCUGUUUGCUGUGUAUGAUA 3') (22.9);

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUCAUACACAGCAAACAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 358 (5' CUGUUUGCUGUGUAUGAUA 3') (31.5);

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 195 (5' UCUGGGGCCCUGGGCCUAUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 362 (5' CAUGAGGCCAGGGCCCCAGA 3') (32.1);

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 196 (5' UGUGUUCUGGGGCCCUGGCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 363 (5' GGCCAGGGCCCCAGAACACA 3') (35.3);

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' UAGAAAAGGUGGGAGACUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 367 (5' CCAGUCUCCCACCUUUUCUA 3') (25.7);

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 201 (5' UAAGAAAAGGUGGGAGACUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 368 (5' CAGUCUCCCACCUUUUCUUA 3') (21.7);

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 259 (5' UCUAAAAUAAACCCAGCAAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 426 (5' UUUGCUGGGUUUAUUUUAGA 3') (20.0);

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 202 (5' UAUUCUCUAAAAUAAACCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 369 (5' UGGGUUUUUUUAGAGAAUA 3') (24.7);

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 272 (5' UUUUGGAACAGUAGUCCCGCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 439 (5' GCGGGACUACUGUCCAAAA 3') (23.2);

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 273 (5' UUUUUGGAACAGUAGUCCCGCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 440 (5' CGGGACUACUGUCCAAAA 3') (34.6);

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 274 (5' UCUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 441 (5' GGACUACUGUCCAAAAAGA 3') (27.2);

xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' UUUCUUUUUGGAACAGUAGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 442 (5' ACUACUGUCCAAAAAGAAA 3') (22.6);

xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' UGUCGGUUGGAAUUCUUUUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' AAAAAGAAUCCAACCGACA 3') (24.1);

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCAAACAAGCUGGUCGGUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' CAACCGACCAGCUUGUUUGA 3') (26.8);

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 211 (5' UUUUUUGUUUCACAAACAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' CUUGUUUGUGAAACAAAAAA 3') (28.9);

Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' UAAAAGGGAACACUUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' CAAAAAGUGUCCCUUUUA 3') (35.6);

Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' UUUUAAAACCCAAUUUUUGUUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' ACAAAAUUGGGUUUUAAAA 3') (32.3);

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' UCUUUAUUUUUAAAACCCAAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' UUGGGUUUUUAAAUAAGA 3') (31.1);

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' UAUACAAACCGAAGGCAAUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' CAUUGCCUUCGGUUUGUAUA 3') (37.1);

Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 221 (5' UAAUACAAACCGAAGGCAAUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 388 (5' AUUGCCUUCGGUUUGUAUUA 3') (30.5);

Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 223 (5' UCUAAAUACAAACCGAAGGCAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 390 (5' GCCUUCGGUUUGUAUUUAGA 3') (26.6);

Lviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' UCACUAAAUACAAACCGAAGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' CUUCGGUUUGUAUUUAGUGA 3') (28.4);

Lix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' UAAGACACUAAAUACAAACCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 392 (5' GGUUUGUAUUUAGUGUCUUA 3') (44.1);

Lx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 226 (5' UCAAGACACUAAAUACAAACCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 393 (5' GUUUGUAUUUAGUGUCUUGA 3') (26.0);

Lxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 235 (5' UGAGAAAUAACCAGCUAUGGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 402 (5' CCAUAGCUGGUUAUUUCUCA 3') (20.5);

Lxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 236 (5' UAAGACGUUUAUUACUAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 403 (5' UGUUAGUAAUAAACGUCUUA 3') (34.5);

Lxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 251 (5' UAUGCUGUUCAGCACCUCCCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 418 (5' GGGAGGUGCUGAACAGCAUA 3') (20.8);

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UCUCUCAUCCGCUUCAAGCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 436 (5' AGCUUGAAGCGGAUGAGAGA 3') (29.4); or

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 186 (5' UGACUCUGUGGGCUCUCUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 353 (5' AGAGAGAGCCCCACAGAGUCA 3') (35.1).

Embodiment 45. The isolated oligonucleotide of any one of Embodiments 38-42, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% at a dose of 0.02 nM.

Embodiment 46. The isolated oligonucleotide of Embodiment 45, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 157 (5' UUUGUCCACCCAGAACUCCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 324 (5' AGGAGUUCUGGGUGGACAAA 3') (53.4);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 206 (5' UUAAACACUGGUUCUUGCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' AGGCAAGAACCAGUGUUUAA 3') (59.1);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 214 (5' UCAACUUGAAAAGGGAACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' GUGUCCCCUUUCAAGUUGA 3') (56.3); or

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' UUUUAAUUUUAAAACCCAAUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' AUUGGGUUUUAAAUAUAAA 3') (52.9).

Embodiment 47. The isolated oligonucleotide of any one of Embodiments 1-46, wherein the sense strand or the antisense strand or both comprise one or more modified nucleotide(s).

Embodiment 48. The isolated oligonucleotide of Embodiment 47, wherein the one or more modified nucleotide(s) increases the stability or potency or both of the isolated oligonucleotide.

Embodiment 49. A vector encoding the isolated oligonucleotide of any one of Embodiments 1-48.

Embodiment 50. The vector of Embodiment 49, wherein the vector is a plasmid.

- Embodiment 51. A delivery system comprising the isolated oligonucleotide of any one of Embodiments 1-48 or the vector of any one of Embodiments 49-50.
- Embodiment 52. The delivery system of Embodiment 51, wherein the delivery system is any one of a liposome, a nanoparticle, a polymer based delivery system, or a ligand-conjugate delivery system.
- Embodiment 53. The delivery system of Embodiment 52, wherein the ligand-conjugate delivery system comprises one or more of an antibody, a peptide, a lipid, a sugar moiety or a combination thereof.
- Embodiment 54. A pharmaceutical composition comprising the isolated oligonucleotide of any one of Embodiments 1-48, the vector of any one of Embodiments 49-50, the delivery system of any one of Embodiments 51-53, and a pharmaceutically acceptable carrier, diluent or excipient.
- Embodiment 55. A kit comprising the isolated oligonucleotide of any one of Embodiments 1-48, the vector of any one of Embodiments 49-50, the delivery system of any one of Embodiments 51-53, or the pharmaceutical composition of Embodiment 54.
- Embodiment 56. The kit of Embodiment 55, further comprising instructions for administering the isolated oligonucleotide, the vector, the delivery system or the pharmaceutical composition to a subject.
- Embodiment 57. A method of inhibiting or downregulating the expression or level of AGT in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of the isolated oligonucleotide of any one of Embodiments 1-48, the vector of any one of Embodiments 49-50, the delivery system of any one of Embodiments 51-53, or the pharmaceutical composition of Embodiment 54.
- Embodiment 58. The method of Embodiment 57, wherein the isolated oligonucleotide, the vector, the delivery system or the pharmaceutical composition is administered parenterally.
- Embodiment 59. The method of Embodiment 58, wherein the parenteral administration is intravenous, subcutaneous, intraperitoneal or intramuscular.
- Embodiment 60. The method of any one of Embodiments 58-59, wherein the subject is a human.

Embodiment 61. The method of any one of Embodiments 58-60, wherein the subject has hypertension, coronary artery disease, heart failure, diabetes, chronic kidney disease, myocardial infarction.

Embodiment 62. The method of any one of Embodiments 58-61, wherein the method comprises administering the isolated oligonucleotide, the vector, the delivery system, or the pharmaceutical composition, in combination with at least a second therapeutic agent.

Embodiment 63. The method of Embodiment 62, wherein the second therapeutic agent is an antibody, a small molecule drug, a peptide, a nucleic acid molecule or a combination thereof.

Embodiment 64. The method of Embodiment 62, wherein the second therapeutic agent is an isolated oligonucleotide of any one of Embodiments 1-48.

Embodiment 65. A method of inhibiting or downregulating the expression or level of AGT in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of a first and at least a second oligonucleotides of any one of Embodiments 1-48, wherein the first and at least second oligonucleotides comprise different sequences.

Embodiment 66. The method of Embodiment 65, wherein the first and at least second oligonucleotides are administered simultaneously.

Embodiment 67. The method of Embodiment 65, wherein the first and at least second oligonucleotides are administered sequentially.

Embodiment 68. A method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of the isolated oligonucleotide of any one of Embodiments 1-48, the vector of any one of Embodiments 49-50, the delivery system of any one of Embodiments 51-53, or the pharmaceutical composition of Embodiment 54.

Embodiment 69. The method of Embodiment 68, wherein the subject is a human.

CLAIMS

What is claimed is:

1. An isolated oligonucleotide comprising a sense strand and an antisense strand, wherein:
the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from :

- a) 9 to 29;
- b) 166 to 196;
- c) 394 to 480;
- d) 744 to 968;
- e) 1110 to 1331;
- f) 1410 to 1676; and
- g) 1726 to 1894,

from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1,

and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

2. The isolated oligonucleotide of claim 1, wherein the sense strand comprises a nucleotide sequence that is identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

- a) 9 to 29;
- b) 166 to 196;
- c) 394 to 480;
- d) 744 to 968;
- e) 1110 to 1331;
- f) 1410 to 1676; and
- g) 1726 to 1894,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

3. The isolated oligonucleotide of any one of claims 1-2, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide

positions from 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

4. The isolated oligonucleotide of claim 3, wherein the sense strand comprises a nucleotide sequence that is identical to a region between nucleotide positions 1829 to 1857, from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

5. The isolated oligonucleotide of any one of claims 1-2, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from:

- a) 166 to 196;
- b) 394 to 480;
- c) 744 to 968;
- d) 1110 to 1331;
- e) 1410 to 1676; and
- f) 1726 to 1894,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

6. The isolated oligonucleotide of claim 5, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from:

- a) 166 to 196;
- b) 394 to 480;
- c) 744 to 968;
- d) 1110 to 1331;
- e) 1410 to 1676; and
- f) 1726 to 1894,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

7. The isolated oligonucleotide of any one of claims 1-2, wherein the sense strand comprises a sequence that is substantially identical to a region comprising the sequence between any one of the nucleotide positions selected from:

- a) 9 to 29;
- b) 168 to 189;
- c) 784 to 808;
- d) 1264 to 1289;
- e) 1607 to 1630; and
- f) 1814 to 1882,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

8. The isolated oligonucleotide of claim 7, wherein the sense strand comprises a sequence that is identical to a region comprising the sequence between any one of the nucleotide positions selected from:

- a) 9 to 29;
- b) 168 to 189;
- c) 784 to 808;
- d) 1264 to 1289;
- e) 1607 to 1630; and
- f) 1814 to 1882,

from the 5' end of an AGT mRNA sequence according to SEQ ID NO: 1.

9. The isolated oligonucleotide of any one of claims 1-8, wherein the antisense strand comprises a 3' overhang.

10. The isolated oligonucleotide of any one of claims 1-9, wherein the sense strand comprises an RNA sequence of at least 20 nucleotides in length.

11. The isolated oligonucleotide of any one of claims 1-10, wherein the antisense strand comprises an RNA sequence of at least 22 nucleotides in length.

12. The isolated oligonucleotide of any one of claims 1-11, wherein the double stranded region is between 19 and 21 nucleotides in length.

13. The isolated oligonucleotide of claim 12, wherein the double stranded region is 20 nucleotides in length.
14. The isolated oligonucleotide of any one of claims 1-13, wherein the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-56.
15. The isolated oligonucleotide of any one of claims 1-14, wherein the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 57-111.
16. The isolated oligonucleotide of claim 4, wherein the double stranded region comprises:
- i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3'); or
 - ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCUUUUCAA 3').
17. The isolated oligonucleotide of claim 6, wherein the double stranded region comprises:
- i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCUCUCAUUGUGGAUGACGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' UCGUCAUCCACAAUGAGAGA 3');
 - ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UCUCACAGGUACUCUCAUUGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' CAAUGAGAGUACCUGUGAGA 3');
 - iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UCAUAGCUCACUGUGCAUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' GCAUGCACAGUGAGCUAUGA 3');
 - iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUAGAGAGAGGCCAGGGUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' GCACCCUGGCCUCUCUCUAA 3');

- v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUGAAGUCCAGAGAGCGUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' CCACGCUCUCUGGACUUCAA 3');
- vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UCUGUCAAUUCUUCAGCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' CUGCUGAGAAGAUUGACAGA 3');
- vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UGUCCACCCAGAACUCCUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' CCAGGAGUUCUGGGUGGACA 3');
- viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UCAGACACUGAGGUGCUGUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AACAGCACCUCAGUGUCUGA 3');
- ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUUUGCUGGAAAGUGAGACCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' GGUCUCACUUUCCAGCAAAA 3');
- x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UGUUUCUUAUCCAGUUGAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' CUCAACUGGAUGAAGAAACA 3');
- xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAAUGCUGUUCAGCACCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' AGGUGCUGAACAGCAUUUUA 3');
- xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAUGCUGUUCAGCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUUA 3');
- xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUUGA 3');
- xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UCAGCAAACAGGAAUGGGCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' CGCCCAUCCUGUUUGCUGA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAAGAAAAGGUGGGAGACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' AGUCUCCCACCUUUUCUUCA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UUUAGAAGAAAAGGUGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' CUCCCACCUUUUCUUCUAAA 3');

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUAGAAGAAAAGGUGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UCCCACCUUUUCUUCUAAUA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UGAGAAACGGCUGCUUCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAAAGCAGCCGUUUCUCA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUUAGACCAAGGAGAAACGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' CCGUUCUCCUUGGUCUAAA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UCUUAGACCAAGGAGAAACGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' CGUUCUCCUUGGUCUAAGA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UCACUUAGACCAAGGAGAAACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UUUCUCCUUGGUCUAAGUGA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UAAAAUAAACCCAGCAAACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' AGUUUGCUGGGUUUAUUUUA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUCUCUAAAAUAAACCCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' CUGGGUUUAUUUAGAGAAA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' GGGACUACUGUCCAAAAAA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UGUUUCACAAACAAGCUGGUCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 83 (5' ACCAGCUUGUUUGUGAAACA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUUUUUGUUUCACAAACAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UUGUUUGUGAAACAAAAAAA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3');

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UCUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' AAAGUGUCCCCUUUCAAGA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UUGUUCUCAACUUGAAAAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' CCUUUCAAGUUGAGAACAA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAUUUUUGUUCUCAACUUGAAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCAAGUUGAGAACAAAAUA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAUUUUUGUUCUCAACUUGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' CAAGUUGAGAACAAAAUUA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUCAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3'); and

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UUUUUAAAACCCAAUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' CAAAAUUGGGUUUUAAAAA 3');

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAAAAUA 3');

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' UAAUUUUAAAACCCAAUUUUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' AAAAUUGGGUUUUAAAAUUA 3')

xxxvii) an antisense of nucleic acid sequence according to SEQ ID NO: 39 (5' UUUAAUUUUAAAACCCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' AAUUGGGUUUUAAAAUUA 3')

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUUAAGUAUA 3');

xxxix) an antisense of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUA 3'); or

xl) an antisense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UCUCAUUAGAAGAAAAGGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' CACCUUUUCUUCUAAUGAGA 3').

18. The isolated oligonucleotide of claim 8, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' UGUAGUACCCAGAACACGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' CCGUUGUUCUGGGUACUACA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' UUACUCUCAUUGUGGAUGACGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' GUCAUCCACAAUGAGAGUAA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UAUGAACCUUGUCAAUCUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' AGAAGAUUGACAGGUUCAUA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' UCUGCAUGAACCUGUCAAUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' GAUUGACAGGUUCAUGCAGA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' UCUCAAUUUUUGCAGGUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UGAACCUGCAAAAAUUGAGA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' UCAUUGCUCAAUUUUUGCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' CUGCAAAAAUUGAGCAAUGA 3'); or

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCACCUUUUCUUCUAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' UCAUUAGAAGAAAAGGUGGGAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' CCCACCUUUUCUUCUAAUGA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' UUUCACAAACAAGCUGGUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' CGACCAGCUUGUUUGUGAAA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' UUUUCACAAACAAGCUGGUCGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' GACCAGCUUGUUUGUGAAAA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' UCUCAACUUGAAAAGGGAACAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' GUUCCCUUUUCAAGUUGAGA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAUUGGGUUUUA 3'); or

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' UUUAAAACCCAAUUUUUGUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' AACAAAAUUGGGUUUUA 3').

19. The isolated oligonucleotide of any one of claims 1-18, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% at a dose of 0.02 nM.
20. The isolated oligonucleotide of claim 19, wherein the double stranded region comprises:
- i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UCUCACAGGUACUCUCAUUGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' CAAUGAGAGUACCUGUGAGA 3') (42.5);
 - ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UCAUAGCUCACUGUGCAUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' GCAUGCACAGUGAGCUAUGA 3') (42.5);
 - iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUAGAGAGAGGCCAGGGUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' GCACCCUGGCCUCUCUCUAA 3') (30.4);
 - iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUGAAGUCCAGAGAGCGUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' CCACGCUCUCUGGACUUCUA 3') (37.9);
 - v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UCUGUCAAUCUUCUCAGCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' CUGCUGAGAAGAUUGACAGA 3') (41.3);
 - vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UGUCCACCCAGAACUCCUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' CCAGGAGUUCUGGGUGGACA 3') (49.7);
 - vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UCAGACACUGAGGUGCUGUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AACAGCACCUCAGUGUCUGA 3') (35.4);
 - viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUUUGCUGGAAAGUGAGACCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' GGUCUCACUUUCCAGCAAAA 3') (40.8);
 - ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UGUUUUCUUAUCCAGUUGAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' CUCAACUGGAUGAAGAAACA 3') (39.7);

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UCAGCAAACAGGAAUGGGCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' CGCCCAUCCUGUUUGCUGA 3') (39.3);

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAAGAAAAGGUGGGAGACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' AGUCUCCCACCUUUUCUUCA 3') (39);

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UUUAGAAGAAAAGGUGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' CUCCCACCUUUUCUUCUAAA 3') (48.5);

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UGAGAAACGGCUGCUUCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAAAGCAGCCGUUCUCA 3') (49.5);

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUUAGACCAAGGAGAAACGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' CCGUUUCUCCUUGGUCUAAA 3') (43.6);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UCUUAGACCAAGGAGAAACGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' CGUUUCUCCUUGGUCUAAGA 3') (42.1);

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UCACUUAGACCAAGGAGAAACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UUUCUCCUUGGUCUAAGUGA 3') (26.7);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UAAAAUAAACCCAGCAAACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' AGUUUGCUGGGUUUAUUUUA 3') (38.4);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUCUCUAAAAUAAACCCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' CUGGGUUUAUUUUAGAGAAA 3') (47.9);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UUGUUCUAAACUUGAAAAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' CCUUUUAAGUUGAGAACAA 3') (42.5);

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAUUUUUGUUCUCAACUUGAAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCAAGUUGAGAACAAAAUA 3') (34);

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAUUUUUGUUCUCAACUUGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' CAAGUUGAGAACAAAAUUA 3') (38.7);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UUUUUAAAACCCAAUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' CAAAAUUGGGUUUUAAAAA 3') (36.5);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' UAAUUUUAAAACCCAAUUUUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' AAAAUUGGGUUUUAAAAUUA 3') (27.4);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' UUUAAUUUUAAAACCCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' AAUUGGGUUUUAAAAUUA 3') (36.1);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUAAUUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUAA 3') (43.8);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' UGUAGUACCCAGAACAACGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' CCGUUGUUCUGGGUACUACA 3') (45.6);

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' UCUCAAUUUUUGCAGGUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UGAACCUGCAAAAUUGAGA 3') (45.4);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' UCAUUGCUCAAUUUUUGCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' CUGCAAAAUUGAGCAAUGA 3') (42.9);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UCUCAUAGAAGAAAAGGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' CACCUUUUCUUCUAAUGAGA 3') (39.06); or

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' UUUCACAAACAAGCUGGUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' CGACCAGCUUGUUUGUGAAA 3') (27.8);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' UUUAAAACCCAAUUUUUGUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' AACAAAAAUUGGGUUUAAA 3') (49.0);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAAUUGGGUUUUA 3') (44.8); or

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' GGGACUACUGUCCAAAAAA 3') (35.8).

21. The isolated oligonucleotide of any one of claims 1-20, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% at a dose of 0.02 nM.

22. The isolated oligonucleotide of claim 21, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3') (56.3);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCUUUUCAA 3') (54.5);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCUCUCAUUGUGGAUGACGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' UCGUCAUCCACAAUGAGAGA 3') (63.3);

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAAUGCUGUUCAGCACCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' AGGUGCUGAACAGCAUUUA 3') (55.8);

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAAAAUGCUGUUCAGCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUUA 3') (52.6);

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUUGA 3') (50.3);

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUAGAAGAAAAGGUGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UCCCACCUUUUCUUCUAAUA 3') (76.8);

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUUUUUGUUUCACAAACAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UUGUUUGUGAAACAAAAAAA 3') (52);

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3') (51.9);

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UCUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' AAAGUGUCCCCUUUUAAGA 3') (65.7);

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAAUUGA 3') (54.9);

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAUUUA 3') (57.9);

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUAAUUUUAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUUAAAGUAUA 3') (61.1);

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' UUACUCUCAUUGUGGAUGACGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' GUCAUCCACAAUGAGAGUAA 3') (55.5);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3') (70.2);

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UAUGAACUGUCAAUUCUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' AGAAGAUUGACAGGUUCAUA 3') (74.3);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' UCUGCAUGAACUGUCAAUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' GAUUGACAGGUUCAUGCAGA 3') (62.6);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCACCUUUUCUUCUAA 3') (63.5);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' UCAUUAGAAGAAAAGGUGGGAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' CCCACCUUUUCUUCUAAUGA 3') (64.3); or

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' UCUCAACUUGAAAAGGGAACAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' GUUCCCUUUUCAAGUUGAGA 3') (50.4).

23. The isolated oligonucleotide of any one of claims 1-18, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% at a dose of 0.1 nM.

24. The isolated oligonucleotide of claim 23, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UGGAACACUUUUUUGUUUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' UGAAACAAAAAAGUGUCCA 3') (75.5);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAAAGUGUCCCUUUUCAAA 3') (72.3);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCUCUCAUUGUGGAUGACGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' UCGUCAUCCACAAUGAGAGA 3') (78);

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UCUCACAGGUACUCUCAUUGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' CAAUGAGAGUACCUGUGAGA 3') (62.4);

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UCAUAGCUCACUGUGCAUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' GCAUGCACAGUGAGCUAUGA 3') (66.2);

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUAGAGAGAGGCCAGGGUGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' GCACCCUGGCCUCUCUCUAA 3') (64.9);

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUGAAGUCCAGAGAGCGUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' CCACGCUCUCUGGACUUCAA 3') (65.7);

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UCUGUCAAUUCUUCUCAGCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' CUGCUGAGAAGAUUGACAGA 3') (65.2);

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UGUCCACCCAGAACUCCUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' CCAGGAGUUCUGGGUGGACA 3') (61.7);

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UCAGACACUGAGGUGCUGUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AACAGCACCUCAGUGUCUGA 3') (66);

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUUUGCUGGAAAGUGAGACCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' GGUCUCACUUCCAGCAAAA 3') (65.4);

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UGUUUCUUCAUCCAGUUGAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' CUCAACUGGAUGAAGAAACA 3') (74.4);

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAAAUGCUGUUCAGCACCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' AGGUGCUGAACAGCAUUUUA 3') (67);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAAAAAAAAAUGCUGUUCAGCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UGCUGAACAGCAUUUUUUUA 3') (68.3);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UCAAAAAAAAAAUGCUGUUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' CUGAACAGCAUUUUUUUUGA 3') (73.6);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UCAGCAAACAGGAAUGGGCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' CGCCCAUUCCUGUUUGCUGA 3') (67.3);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAAGAAAAGGUGGGAGACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' AGUCUCCCACCUUUUCUUCA 3') (67.5);

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UUUAGAAGAAAAGGUGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' CUCCCACCUUUUCUUCUAAA 3') (66.6);

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUAGAAGAAAAGGUGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UCCCACCUUUUCUUCUAAUA 3') (74.3);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UGAGAAACGGCUGCUUCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAAAGCAGCCGUUUCUCA 3') (77.8);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUUAGACCAAGGAGAAACGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' CCGUUCUCCUUGGUCUAAA 3') (74.1);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UCUUAGACCAAGGAGAAACGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' CGUUUCUCCUUGGUCUAAGA 3') (76);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UAAAAUAAACCCAGCAAACUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' AGUUUGCUGGGUUUAUUUUA 3') (67.2);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUUUUGGAACAGUAGUCCCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' GGGACUACUGUCCAAAAA 3') (65.4)

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UCACUUAGACCAAGGAGAAACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UUUCUCCUUGGUCUAAGUGA 3') (61.5);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUCUCUAAAAUAAACCCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' CUGGGUUUAUUUAGAGAAA 3') (61.8);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UGUUUCACAAACAAGCUGGUCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 83 (5' ACCAGCUUGUUUGUGAAACA 3') (62);

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUUUUUGUUUCACAAACAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UUGUUUGUGAAACAAAAAAA 3') (77.3);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UCACUUUUUUGUUUCACAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUGAAACAAAAAAGUGA 3') (76.5);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UCUUGAAAAGGGAACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' AAAGUGUCCCCUUUCAAGA 3') (73.8);

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UUGUUCUCAACUUGAAAAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' CCUUUCAAGUUGAGAACAA 3') (62.6);

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAUUUUUGUUCUCAACUUGAAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCAAGUUGAGAACAAAAUA 3') (64.5);

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAUUUUUGUUCUCAACUUGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' CAAGUUGAGAACAAAAUUA 3') (63.2);

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAAUUUUUGUUCUCAACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' AAGUUGAGAACAAAAUUGA 3') (75.9);

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UUUUUAAAACCCAAUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' CAAAAUUGGGUUUUAAAAA 3') (68.3);

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' UAUUUUUAAAACCCAAUUUUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' AAAAAUUGGGUUUUAAAAUA 3') (65.7);

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' UAAUUUUAAAACCCAAUUUUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' AAAAUUGGGUUUUAAAAUUA 3') (69.5);

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' UUUAAUUUUAAAACCCAAUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' AAUUGGGUUUUAAAAUUA 3') (64.9);

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 40 (5' UAUACUUUUAAUUUUAAAACCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' GGUUUUAAAAUUAAGUAUA 3') (69.6);

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' UUAUACUUUUAAUUUUAAAACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' GUUUUAAAAUUAAGUAUA 3') (77.6);

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' UGUAGUACCCAGAACACGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' CCGUUGUUCUGGGUACUACA 3') (63.2);

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' UUACUCUCAUUGUGGAUGACGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' GUCAUCCACAAUGAGAGUAA 3') (73.3);

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUACUCUCAUUGUGGAUGACG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UCAUCCACAAUGAGAGUACA 3') (84.8);

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UAUGAACCUGUCAAUUCUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' AGAAGAUUGACAGGUUCAUA 3') (73);

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' UCUGCAUGAACCUGUCAAUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' GAUUGACAGGUUCAUGCAGA 3') (63.6);

xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' UCUCAAUUUUUGCAGGUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UGAACCUGCAAAAAUUGAGA 3') (67.5);

xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' UCAUUGCUCAAUUUUUGCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' CUGCAAAAAUUGAGCAAUGA 3') (62.6);

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' UUAGAAGAAAAGGUGGGAGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUCCACCUUUUCUUCUAA 3') (78.5);

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' UCAUUAGAAGAAAAGGUGGGAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' CCCACCUUUUCUUCUAAUGA 3') (70.2);

Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UCUCAUUAGAAGAAAAGGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' CACCUUUUCUUCUAAUGAGA 3') (78.2);

Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' UUUCACAAACAAGCUGGUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' CGACCAGCUUGUUUGUGAAA 3') (63.2);

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' UUUUCACAAACAAGCUGGUCGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' GACCAGCUUGUUUGUGAAA 3') (62);

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' UCUCAACUUGAAAAGGGAACAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' GUUCCCUUUUCAAGUUGAGA 3') (61);

Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' UUUAAAACCCAAUUUUUGUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' AACAAAAAUUGGGUUUUA 3') (71.3); or

Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' UAAAACCCAAUUUUUGUUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' AGAACAAAAAUUGGGUUUA 3') (74.5).

25. An isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

- a) 11 to 42;
- b) 144 to 284;
- c) 303 to 405;
- d) 441 to 580;
- e) 690 to 802;
- f) 863 to 883;
- g) 922 to 966;
- h) 1036 to 1056;
- i) 1099 to 1153;
- j) 1189 to 1282;
- k) 1300 to 1367;
- l) 1403 to 1517;
- m) 1601 to 1651;
- n) 1722 to 1890;
- o) 1901 to 1948; and
- p) 2017 to 2095,

from the 5' end of an angiotensinogen (AGT) mRNA sequence according to SEQ ID NO: 1,

and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

26. The isolated oligonucleotide of claim 25, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at 20% to 50% at a dose of 0.1 nM.

27. The isolated oligonucleotide of claim 26, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 237 (5' UCUGUAGUACCCAGAACACGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 404 (5' GUUGUUCUGGGUACUACAGA 3') (34.3);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 128 (5' UCAUUGGCCUUUGCCAGCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 295 (5' CAGCUGGCAAAGGCCAAUGA 3') (39.5);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 145 (5' UGUGCCAAAGACAGCCGUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 312 (5' CAACGGCUGUCUUUGGCACA 3') (39);

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 240 (5' UAUAGAGAGAGGCCAGGGUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 407 (5' CACCCUGGCCUCUCUCUAUA 3') (35.9);

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 241 (5' UGAUUGCCUGUAGCCUGUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 408 (5' UGACAGGCUACAGGCAAUCA 3') (35.6);

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UCAGUUCUUGUCCUCCAAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 409 (5' CUUGGAAGGACAAGAACUGA 3') (42.8);

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 243 (5' UUAUAGAGAGCCAGGCCUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 410 (5' CAGGGCCUGGCUCUCUAUAA 3') (37.2);

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' UGUAGGUGUUGAAAGCCAGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 412 (5' CCUGGCUUUAACACCUACA 3') (40.5);

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 246 (5' UCAGAACUCCUGGGGCUCGGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 413 (5' CCGAGCCCCAGGAGUUCUGA 3') (22.4);

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 157 (5' UUUGUCCACCCAGAACUCCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 324 (5' AGGAGUUCUGGGUGGACAAA 3') (32.8);

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 160 (5' UGACACUGAGGUGCUGUUGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 327 (5' ACAACAGCACCUCAGUGUCA 3') (34.1);

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 247 (5' UCUCUCAGUGAAGGGCACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 414 (5' AAGUGCCCUUCACUGAGAGA 3') (27.2);

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAAGUGAGACCCUCCACCUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 332 (5' AAGGUGGAGGGUCUCACUUA 3') (40);

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 167 (5' UGGAAAGUGAGACCCUCCACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 334 (5' GUGGAGGGUCUCACUUUCCA 3') (41.8);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UCUGGAAAGUGAGACCCUCCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 335 (5' GGAGGGUCUCACUUUCCAGA 3') (40.8);

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAGUUGAGGGAGUUUUGCUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 338 (5' CAGCAAAACUCCCUCAACUA 3') (48.4);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UGAAUGGCGGGCAGCUCAGCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 344 (5' GCUGAGCUGCCCGCCAUUA 3') (36.9);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 182 (5' UAAUUUUUGCAGGUUCAGCUCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 349 (5' AGCUGAACCUGCAAAAAUUA 3') (41.2);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 251 (5' UAUGCUGUUCAGCACCUCUCCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 418 (5' GGGAGGUGCUGAACAGCAUA 3') (43.5);

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 187 (5' UUAGACUCUGUGGGCUCUCUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 354 (5' AGAGAGCCCACAGAGUCUAA 3') (30.6);

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 254 (5' UCAAACAGGAAUGGGCGGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 421 (5' AACCGCCCAUUCUGUUUGA 3') (49.5);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 190 (5' UAUCAUACACAGCAAACAGGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 357 (5' CCUGUUUGCUGUGUAUGAUA 3') (48.8);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 201 (5' UAAGAAAAGGUGGGAGACUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 368 (5' CAGUCUCCCACCUUUUCUUA 3') (30.9);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 259 (5' UCUAAAAUAAACCCAGCAAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 426 (5' UUUGCUGGGUUUAUUUUAGA 3') (46.4);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 273 (5' UUUUUGGAACAGUAGUCCCGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 440 (5' CGGGACUACUGUCCAAAAA 3') (47.4);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' UGUCGGUUGGAAUUCUUUUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' AAAAAGAAUCCAACCGACA 3') (33.7);

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCAAACAAGCUGGUCGGUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' CAACCGACCAGCUUGUUUGA 3') (47.5);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' UCUUUAUUUUAAAACCCAAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' UUGGGUUUUAAAAUUAAAGA 3') (46.8);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' UAUACAAACCGAAGGCAAUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' CAUUGCCUUCGGUUUGUAUA 3') (39.6);

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 221 (5' UAAUACAAACCGAAGGCAAUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 388 (5' AUUGCCUUCGGUUUGUAUUA 3') (33.2);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' UCACUAAAUACAAACCGAAGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' CUUCGGUUUGUAUUUAGUGA 3') (30.2);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' UAAGACACUAAAUACAAACCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 392 (5' GGUUUGUAUUUAGUGUCUUA 3') (32.9);

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 226 (5' UCAAGACACUAAAUACAAACCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 393 (5' GUUUGUAUUUAGUGUCUUGA 3') (32);

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 120 (5' UGGAAGGGGUGUAUGUACACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 287 (5' GUGUACAUACACCCCUUCCA 3') (20.2);

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 236 (5' UAAGACGUUUUUUACUACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 403 (5' UGUUAGUAAUAAACGUCUUA 3') (23.6); or

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 122 (5' UGGAUGACGAGGUGGAAGGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 289 (5' CCCUCCACCUCGUCAUCCA 3') (25.7);

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 125 (5' UCUCAUUGUGGAUGACGAGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 292 (5' CCUCGUCAUCCACAAUGAGA 3') (22.4);

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 276 (5' UACAAGCUGGUCGGUUGGAAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 443 (5' UUCCAACCGACCAGCUUGUA 3') (36.3);

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 127 (5' UCUUUGCCAGCUGCUCACAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 294 (5' CUGUGAGCAGCUGGCAAAGA 3') (35.8);

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 239 (5' UUUUCAUCCACAGGGGAUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 406 (5' ACAUCCCCUGUGGAUGAAAA 3') (23.1);

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 267 (5' UGUUUUGCAGCGACUAGCACCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 434 (5' GUGCUAGUCGCUGCAAAACA 3') (43.1);

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 129 (5' UAAGUUGGCCAGCAUCCCGACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 296 (5' UCGGGAUGCUGGCCAACUUA 3') (25.2);

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAUUAUCGGAAGCCCAAGAAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 300 (5' UUCUUGGGCUUCCGUAUAUA 3') (50.0);

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 135 (5' UAUUAUACGGAAGCCCAAGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 302 (5' CUUGGGCUUCCGUAUAUAUA 3') (33.6);

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 136 (5' UCAUAUAUACGGAAGCCCAAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 303 (5' UUGGGCUUCCGUAUAUAUGA 3') (39.2);

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 138 (5' UCAUGCCAUAUAUACGGAAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 305 (5' CUUCCGUAUAUAUGGCAUGA 3') (22.9);

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 139 (5' UCUGUGCAUGCCAUAUAUACGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 306 (5' GUAUAUAUGGCAUGCACAGA 3') (31.9);

xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 144 (5' UCAAAGACAGCCGUUGGGGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 311 (5' UCCCCAACGGCUGUCUUUGA 3') (45.5);

xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 277 (5' UUUCCAAGGAACACCCAGGAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 444 (5' UCCUGGGUGUCCUUGGAAA 3') (22.3);

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 149 (5' UGACCUUGUGCGCAUCCAGCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 316 (5' GCUGGAUGCGCACAAGGUCA 3') (41.9);

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 151 (5' UCAAACGGCUGCUUCAGGUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 318 (5' CACCUGAAGCAGCCGUUUGA 3') (34.7);

Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 152 (5' UCACAAACGGCUGCUUCAGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 319 (5' CCUGAAGCAGCCGUUUGUGA 3') (32.6);

Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 153 (5' UUAGAGAGCCAGGCCUGCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 320 (5' UGCAGGGCCUGGCUCUCUAA 3') (33.3);

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 154 (5' UAAGUCCAGAGAGCGUGGGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 321 (5' UCCCACGCUCUCUGGACUUA 3') (29.8);

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 155 (5' UGUGAAGUCCAGAGAGCGUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 322 (5' CACGCUCUCUGGACUUCACA 3') (28.3);

Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 244 (5' UUUCUGUGAAGUCCAGAGAGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 411 (5' CUCUCUGGACUUCACAGAAA 3') (23.1);

Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 278 (5' UUCUCAGCAGCAACAUCAGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 445 (5' CUGGAUGUUGCUGCUGAGAA 3') (25.4);

Lviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 158 (5' UCUGUUGUCCACCCAGAACUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 325 (5' AGUUCUGGGUGGACAACAGA 3') (32.2);

Lix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 164 (5' UGUGAGACCCUCCACCUUGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 331 (5' ACAAGGUGGAGGGUCUCACA 3') (35.0);

Lx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 166 (5' UGAAAGUGAGACCCUCCACCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 333 (5' GGUGGAGGGUCUCACUUUCA 3') (20.9);

Lxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 173 (5' UAUCAGUUGAGGGAGUUUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 340 (5' AAAACUCCCUCAACUGGAUA 3') (44.3);

Lxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 178 (5' UCAGAAUGGCGGGCAGCUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 345 (5' UGAGCUGCCCGCCAUUCUGA 3') (24.0);

Lxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 250 (5' UCUGUUCAGCACCUCUUUUUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 417 (5' UGGGGGAGGUGCUGAACAGA 3') (23.1);

Lxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 184 (5' UAAAAAUGCUGUUCAGCACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 351 (5' GUGCUGAACAGCAUUUUUUA 3') (48.5);

Lxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 185 (5' UAAAAAUGCUGUUCAGCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 352 (5' GCUGAACAGCAUUUUUUA 3') (41.6);

Lxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 270 (5' UCUCUCUAUCCGCUUCAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 437 (5' CUUGAAGCGGAUGAGAGAGA 3') (40.6);

Lxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 252 (5' UCAGGAAUGGGCGGUUCAGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 419 (5' CCUGAACCGCCCAUCCUGA 3') (44.6);

Lxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 188 (5' UCACAGCAAACAGGAAUGGGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 355 (5' CCCAUUCCUGUUUGCUGUGA 3') (46.8);

Lxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 189 (5' UAUACACAGCAAACAGGAAUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 356 (5' AUUCCUGUUUGCUGUGUAUA 3') (36.5);

Lxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 192 (5' UUUGAUCAUACACAGCAAACAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 359 (5' GUUUGCUGUGUAUGAUCAAA 3') (42.9);

Lxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 193 (5' UUUUGAUCAUACACAGCAAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 360 (5' UUUGCUGUGUAUGAUCAAAA 3') (29.7);

Lxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 255 (5' UGAAGUGCAGGGCAGUGGCGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 422 (5' CGCCACUGCCCUGCACUUCA 3') (36.7);

Lxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 194 (5' UCAGGAAGUGCAGGGCAGUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 361 (5' CACUGCCCUGCACUUCCUGA 3') (22.8);

Lxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 256 (5' UCUCAUGCUGUGCUCAGCGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 423 (5' CCGCUGAGCACAGCAUGAGA 3') (28.7);

Lxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 195 (5' UCUGGGGCCCUGGCCUCAUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 362 (5' CAUGAGGCCAGGGCCCCAGA 3') (37.9);

Lxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 198 (5' UAAAAGGUGGGAGACUGGGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 365 (5' CCCAGUCUCCCACCUUUUA 3') (29.2);

Lxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 199 (5' UGAAAAGGUGGGAGACUGGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 366 (5' CCCAGUCUCCCACCUUUUCA 3') (46.3);

Lxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 271 (5' UCUUCCAGCUCAAAGUCGACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 438 (5' UCGACUUUGAGCUGGAAAGA 3') (46.6);

Lxxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 257 (5' UUAAACCCAGCAAACUGGGAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 424 (5' UCCCAGUUUGCUGGGUUUAA 3') (49.5);

Lxxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 204 (5' UCUGGUUCUUGCCUCCCCACCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 371 (5' GUGGGGAGGCAAGAACCAGA 3') (28.0);

Lxxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 205 (5' UAAACACUGGUUCUUGCCUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 372 (5' GAGGCAAGAACCAGUGUUUA 3') (48.5);

Lxxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 260 (5' UGUUGGAAUUCUUUUUGGAACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 427 (5' UUCCAAAAAGAAUCCAACA 3') (37.4);

Lxxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 209 (5' UUUGUUUCACAAACAAGCUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 376 (5' CAGCUUGUUUGUGAAACAAA 3') (37.3);

Lxxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 210 (5' UUUUUGUUUCACAAACAAGCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 377 (5' GCUUGUUUGUGAAACAAAAA 3') (20.4);

Lxxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 227 (5' UCUUACAUUAAGACACUAAAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 394 (5' UUAGUGUCUUGAAUGUAAGA 3') (44.3);

Lxxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 229 (5' UGUCAUGUUCUUAUUAUUAAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 396 (5' UUGAAUGUAAGAACAUGACA 3') (22.7);

Lxxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 262 (5' UGAAAUUCAGGUGCUUGCAUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 429 (5' AUGCAAGCACCUGAAUUUCA 3') (24.9);

Lxxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 263 (5' UAACAGAAAUUCAGGUGCUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 430 (5' AAGCACCUGAAUUCUGUUA 3') (24.8);

Lxxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 265 (5' UCAUCAAACAGAAAUCAGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 432 (5' CUGAAUUUCUGUUUGAAUGA 3') (34.5);

XC) an antisense strand of nucleic acid sequence according to SEQ ID NO: 266 (5' UGAAAUAACCAGCUAUGGUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 433 (5' AACCAUAGCUGGUUAUUUCA 3') (26.6);

XCi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 196 (5' UGUGUUCUGGGGCCUGGCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 363 (5' GGCCAGGGCCCCAGAACACA 3') (41); or

XCii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 112 (5' UCUUCUGCUGUAGUACCCAGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 279 (5' CUGGGUACUACAGCAGAAGA 3') (37.4).

28. The isolated oligonucleotide of claim 25, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% at a dose of 0.1 nM.

29. The isolated oligonucleotide of claim 28, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UAUACCCUUCUGCUGUAGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 280 (5' UACUACAGCAGAAGGGUAUA 3') (54.0);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 126 (5' UCACAGGUACUCUCAUUGUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 293 (5' CACAAUGAGAGUACCUGUGA 3') (55.2);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 268 (5' UCUCAACUUGUCUUCGGUGUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 435 (5' ACACCGAAGACAAGUUGAGA 3') (55.8);

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 130 (5' UAGAAGUUGGCCAGCAUCCCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 297 (5' GGGAUGCUGGCCAACUUCUA 3') (50.8);

- v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UGGAAGCCCAAGAAGUUGGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 299 (5' GCCAACUUCUUGGGCUUCCA 3') (57.6);
- vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAUUAUCGGAAGCCCAAGAAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 300 (5' UUCUUGGGCUUCCGUAUAUA 3') (50.0);
- vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 134 (5' UUAUAUACGGAAGCCCAAGAAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 301 (5' UCUUGGGCUUCCGUAUAUAA 3') (58.8);
- viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 137 (5' UAUGCCAUUAUACGGAAGCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 304 (5' GCUUCCGUAUAUAUGGCAUA 3') (51.4);
- ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 156 (5' UGAACCUGUCAAUUCUUCUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 323 (5' UGAGAAGAUUGACAGGUUCA 3') (54.2);
- x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 169 (5' UGUUUUGCUGGAAAGUGAGACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 336 (5' UCUCACUUUCCAGCAAAACA 3') (54.6);
- xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 170 (5' UGAGUUUUGCUGGAAAGUGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 337 (5' UCACUUUCCAGCAAAACUCA 3') (52.3);
- xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UUUUCUUCAUCCAGUUGAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 343 (5' CCUCAACUGGAUGAAGAAAA 3') (56.4);
- xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' UUAAGAUCUUGCAGCACCAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 415 (5' UGGUGCUGCAAGGAUCUUA 3') (55.8);
- xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UUUUUGCAGGUUCAGCUCGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 346 (5' CCGAGCUGAACCUGCAAAAA 3') (53.4);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 180 (5' UUUUUUGCAGGUUCAGCUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 347 (5' CGAGCUGAACCUGCAAAAAA 3') (54.9);

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 181 (5' UAUUUUUGCAGGUUCAGCUCGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 348 (5' GAGCUGAACCUGCAAAAAUA 3') (55.8);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 183 (5' UCAAUUUUUGCAGGUUCAGCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 350 (5' GCUGAACCUGCAAAAAUUGA 3') (53.8);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UCUCUCAUCCGCUUCAAGCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 436 (5' AGCUUGAAGCGGAUGAGAGA 3') (51.4);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 186 (5' UGACUCUGUGGGCUCUCUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 353 (5' AGAGAGAGCCCACAGAGUCA 3') (54.6);

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 253 (5' UAACAGGAAUGGGCGGUUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 420 (5' UGAACCGCCCAUCCUGUUA 3') (52.4);

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUCAUACACAGCAAACAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 358 (5' CUGUUUGCUGUGUAUGAUA 3') (59.3);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' UAGAAAAGGUGGGAGACUGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 367 (5' CCAGUCUCCCACCUUUCUA 3') (56.1);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' UUUUAAAACCCAAUUUUUGUUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' ACAAAAUUGGGUUUAAAA 3') (59.0);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 258 (5' UAAUAAACCCAGCAAACUGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 425 (5' CCAGUUUGCUGGGUUUAUA 3') (55.4);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 202 (5' UAUUCUCUAAAAUAAACCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 369 (5' UGGGUUUUUUUUAGAGAAUA 3') (50.5);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 206 (5' UUAAACACUGGUUCUUGCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' AGGCAAGAACCAGUGUUUAA 3') (58.6);

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 272 (5' UUUUGGAACAGUAGUCCCGCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 439 (5' GCGGGACUACUGUCCAAAA 3') (54.8);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 274 (5' UCUUUUUGGAACAGUAGUCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 441 (5' GGACUACUGUCCAAAAAGA 3') (57.5);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' UUUCUUUUUGGAACAGUAGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 442 (5' ACUACUGUCCAAAAAGAAA 3') (50.7);

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 211 (5' UUUUUUGUUUCACAAACAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' CUUGUUUGUGAAACAAAAAA 3') (59.9);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' UAAAAGGGAACACUUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' CAAAAAGUGUCCCUUUUA 3') (55.7);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 214 (5' UCAACUUGAAAAGGGAACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' GUGUCCCUUUUCAAGUUGA 3') (54.9);

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' UUUUAAUUUAAAACCCAAUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' AUUGGUUUUAAAAUAAAA 3') (56.5).

30. The isolated oligonucleotide of any one of claims 25-29, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by 20% to 50% at a dose of 0.02 nM.

31. The isolated oligonucleotide of claim 30, wherein the double stranded region comprises:
- i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 237 (5' UCUGUAGUACCCAGAACACGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 404 (5' GUUGUUCUGGGUACUACAGA 3') (29.7);
 - ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UAUACCCUUCUGCUGUAGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 280 (5' UACUACAGCAGAAGGGUAUA 3') (32.8);
 - iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 126 (5' UCACAGGUACUCUCAUUGUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 293 (5' CACAAUGAGAGUACCUGUGA 3') (35.0);
 - iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 128 (5' UCAUUGGCCUUGCCAGCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 295 (5' CAGCUGGCAAAGGCCAAUGA 3') (23.9);
 - v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 268 (5' UCUCAACUUGUCUUCGGUGUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 435 (5' ACACCGAAGACAAGUUGAGA 3') (26.5);
 - vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 130 (5' UAGAAGUUGGCCAGCAUCCCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 297 (5' GGGAUGCUGGCCAACUUCUA 3') (24.4);
 - vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 131 (5' UCAAGAAGUUGGCCAGCAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 298 (5' GAUGCUGGCCAACUUCUUGA 3') (22.0);
 - viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UGGAAGCCCAAGAAGUUGGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 299 (5' GCCAACUUCUUGGGCUUCCA 3') (34.0);
 - ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAUAUACGGAAGCCCAAGAAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 300 (5' UUCUUGGGCUUCCGUUAUAUA 3') (21.8);
 - x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 134 (5' UUAUAUACGGAAGCCCAAGAAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 301 (5' UCUUGGGCUUCCGUUAUAUA 3') (35.0);

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 137 (5' UAUGCCAUUAUACGGAAGCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 304 (5' GCUUCCGUAUAUAUGGCAUA 3') (25.8);

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 145 (5' UGUGCCAAAGACAGCCGUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 312 (5' CAACGGCUGUCUUUGGCACA 3') (25.2);

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 240 (5' UAUAGAGAGAGGCCAGGGUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 407 (5' CACCCUGGCCUCUCUCUAUA 3') (33.1);

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 241 (5' UGAUUGCCUGUAGCCUGUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 408 (5' UGACAGGCUACAGGCAAUCA 3') (25.3);

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UCAGUUCUUGUCCUCCAAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 409 (5' CUUGGAAGGACAAGAACUGA 3') (28.4);

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 243 (5' UUAUAGAGAGCCAGGCCUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 410 (5' CAGGGCCUGGCUCUCUAUAA 3') (31.9);

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 156 (5' UGAACCUGUCAAUUCUUCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 323 (5' UGAGAAGAUUGACAGGUUCA 3') (31.2);

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' UGUAGGUGUUGAAAGCCAGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 412 (5' CCUGGCUUUAACACCUACA 3') (26.8);

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 246 (5' UCAGAACUCCUGGGGCUCGGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 413 (5' CCGAGCCCCAGGAGUUCUGA 3') (20.8);

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 160 (5' UGACACUGAGGUGCUGUUGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 327 (5' ACAACAGCACCUCAGUGUCA 3') (21.2);

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 247 (5' UCUCUCAGUGAAGGGCACUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 414 (5' AAGUGCCCUUCACUGAGAGA 3') (20.5);

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAAGUGAGACCCUCCACCUUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 332 (5' AAGGUGGAGGGUCUCACUUA 3') (20.3);

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 167 (5' UGGAAAGUGAGACCCUCCACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 334 (5' GUGGAGGGUCUCACUUUCCA 3') (27.1);

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UCUGGAAAGUGAGACCCUCCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 335 (5' GGAGGGUCUCACUUUCCAGA 3') (21.0);

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 169 (5' UGUUUUGCUGGAAAGUGAGACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 336 (5' UCUCACUUUCCAGCAAAACA 3') (25.6);

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 170 (5' UGAGUUUUGCUGGAAAGUGAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 337 (5' UCACUUUCCAGCAAAACUCA 3') (28.2);

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAGUUGAGGGAGUUUUGCUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 338 (5' CAGCAAAACUCCCUCAACUA 3') (31.1);

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 172 (5' UCAGUUGAGGGAGUUUUGCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 339 (5' AGCAAAACUCCCUCAACUGA 3') (24.8);

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UUUUCUUCAUCCAGUUGAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 343 (5' CCUCAACUGGAUGAAGAAAA 3') (21.6);

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' UUAAGAUCUUGCAGCACCAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 415 (5' UGGUGCUGCAAGGAUCUUA 3') (32.6);

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UGAAUGGCGGGCAGCUCAGCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 344 (5' GCUGAGCUGCCCCGCCAUUCA 3') (37.6);

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UUUUUGCAGGUUCAGCUCGGUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 346 (5' CCGAGCUGAACCUGCAAAAA 3') (26.9);

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 180 (5' UUUUUGCAGGUUCAGCUCGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 347 (5' CGAGCUGAACCUGCAAAAA 3') (29.2);

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 270 (5' UCUCUCUCAUCCGCUUCAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 437 (5' CUUGAAGCGGAUGAGAGAGA 3') (22.7);

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 187 (5' UUAGACUCUGUGGGCUCUCUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 354 (5' AGAGAGCCCACAGAGUCUAA 3') (25.9);

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 254 (5' UCAAACAGGAAUGGGCGGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 421 (5' AACCGCCCAUCCUGUUUGA 3') (22.4);

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 190 (5' UAUCAUACACAGCAAACAGGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 357 (5' CCUGUUUGCUGUGUAUGAUA 3') (22.9);

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUCAUACACAGCAAACAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 358 (5' CUGUUUGCUGUGUAUGAUA 3') (31.5);

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 195 (5' UCUGGGGCCCUGGCCUCAUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 362 (5' CAUGAGGCCAGGGCCCCAGA 3') (32.1);

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 196 (5' UGUGUUCUGGGGCCCUGGCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 363 (5' GGCCAGGGCCCCAGAACACA 3') (35.3);

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' UAGAAAAGGUGGGAGACUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 367 (5' CCAGUCUCCCACCUUUUCUA 3') (25.7);

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 201 (5' UAAGAAAAGGUGGGAGACUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 368 (5' CAGUCUCCCACCUUUUCUUA 3') (21.7);

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 259 (5' UCUAAAAUAAACCCAGCAAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 426 (5' UUUGCUGGGUUUAUUUUAGA 3') (20.0);

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 202 (5' UAUUCUCUAAAAUAAACCCAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 369 (5' UGGGUUUAUUUUAGAGAAUA 3') (24.7);

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 272 (5' UUUUGGAACAGUAGUCCCGCGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 439 (5' GCGGGACUACUGUCCAAAA 3') (23.2);

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 273 (5' UUUUUGGAACAGUAGUCCCGCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 440 (5' CGGGACUACUGUCCAAAA 3') (34.6);

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 274 (5' UCUUUUUGGAACAGUAGUCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 441 (5' GGACUACUGUCCAAAAAGA 3') (27.2);

xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' UUUCUUUUGGAACAGUAGUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 442 (5' ACUACUGUCCAAAAAGAAA 3') (22.6);

xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' UGUCGGUUGGAAUUCUUUUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' AAAAAGAAUCCAACCGACA 3') (24.1);

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCAAACAAGCUGGUCGGUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' CAACCGACCAGCUUGUUUGA 3') (26.8);

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 211 (5' UUUUUUGUUUCACAAACAAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' CUUGUUUGUGAAACAAAAA 3') (28.9);

Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' UAAAAGGGAACACUUUUUUGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' CAAAAAAGUGUCCCCUUUA 3') (35.6);

Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' UUUUAAAACCCAAUUUUUGUUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' AAAAAAUUGGGUUUUAAAA 3') (32.3);

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' UCUUUAUUUUAAAACCCAAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' UUGGGUUUUAAAAUUAAGA 3') (31.1);

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' UAUACAAACCGAAGGCAAUGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' CAUUGCCUUCGGUUUGUAUA 3') (37.1);

Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 221 (5' UAAUACAAACCGAAGGCAAUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 388 (5' AUUGCCUUCGGUUUGUAUUA 3') (30.5);

Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 223 (5' UCUAAAUACAAACCGAAGGCAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 390 (5' GCCUUCGGUUUGUAUUUAGA 3') (26.6);

Lviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' UCACUAAAUACAAACCGAAGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' CUUCGGUUUGUAUUUAGUGA 3') (28.4);

Lix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' UAAGACACUAAAUACAAACCGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 392 (5' GGUUUGUAUUUAGUGUCUUA 3') (44.1);

Lx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 226 (5' UCAAGACACUAAAUACAAACCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 393 (5' GUUUGUAUUUAGUGUCUUGA 3') (26.0);

Lxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 235 (5' UGAGAAAUAACCAGCUAUGGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 402 (5' CCAUAGCUGGUUAAUUCUCA 3') (20.5);

Lxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 236 (5' UAAGACGUUUAUUACUAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 403 (5' UGUUAGUAAUAAACGUCUUA 3') (34.5);

Lxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 251 (5' UAUGCUGUUCAGCACCUCUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 418 (5' GGGAGGUGCUGAACAGCAUA 3') (20.8);

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UCUCUCAUCCGCUUCAAGCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 436 (5' AGCUUGAAGCGGAUGAGAGA 3') (29.4); or

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 186 (5' UGACUCUGUGGGCUCUCUCUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 353 (5' AGAGAGAGCCCACAGAGUCA 3') (35.1).

32. The isolated oligonucleotide of any one of claims 25-29, wherein the isolated oligonucleotide attenuates expression of the AGT mRNA by at least 50% at a dose of 0.02 nM.

33. The isolated oligonucleotide of claim 32, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 157 (5' UUUGUCCACCCAGAACUCCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 324 (5' AGGAGUUCUGGGUGGACAAA 3') (53.4);

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 206 (5' UUAACACUGGUUCUUGCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' AGGCAAGAACCAGUGUUUAA 3') (59.1);

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 214 (5' UCAACUUGAAAAGGGAACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' GUGUUCCCUUUUCAAGUUGA 3') (56.3); or

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' UUUUAAUUUUAAAACCCAAUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' AUUGGGUUUUAAAAUAAAA 3') (52.9).

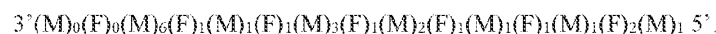
34. The isolated oligonucleotide of any one of claims 1-33, wherein the sense strand or the antisense strand or both comprise one or more modified nucleotide(s).

35. The isolated oligonucleotide of claim 34, wherein the antisense strand comprises a mono methyl protected phosphate mimic (5'-MeEP).

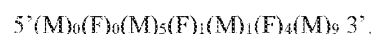
36. The isolated oligonucleotide of any one of claims 1-35, wherein in the sense strand or the antisense strand or both, a terminal or internal nucleotide is linked to a targeting ligand.

37. The isolated oligonucleotide of claim 36, wherein the targeting ligand comprises at least one GalNAc G1b moiety.

38. The isolated oligonucleotide of any one of claims 1-37, wherein the antisense strand comprises nucleotides modified with 2'-F modification, and nucleotides modified with 2'-O-methyl modification, according to the formula:



39. The isolated oligonucleotide of any one of claims 1-38, wherein the sense strand comprises nucleotides modified with 2'-F modification, and nucleotides modified with 2'-O-methyl modification, according to the formula:



40. The isolated oligonucleotide of any one of claims 1-39, wherein the antisense strand comprises any one of:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 447 (5' [MeEPmUs][fCs][fA][mA][fA][mA][fA][mA][mA][fA][mU][mG][mC][fU][mG][fU][mU][mC][mA][mGs][mCs][mA] 3');

- ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 448 (5' [MeEPmUs][fCs][fA][mC][fU][mU][fU][mU][mU][fU][mG][mU][mU][fU][mC][fA][mC][mA][mA][mAs][mCs][mA] 3');
- iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 449 (5' [MeEPmUs][fGs][fG][mA][fA][mC][fA][mC][mU][fU][mU][mU][mU][fU][mG][fU][mU][mU][mC][mAs][mCs][mA] 3');
- iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 450 (5' [MeEPmUs][fUs][fU][mG][fA][mA][fA][mA][mG][fG][mG][mA][mA][fC][mA][fC][mU][mU][mU][mUs][mUs][mU] 3');
- v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 451 (5' [MeEPmUs][fCs][fA][mA][fU][mU][fU][mU][mU][fG][mU][mU][mC][fU][mC][fA][mA][mC][mU][mUs][mGs][mA] 3');
- vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 452 (5' [MeEPmUs][fAs][fA][mA][fA][mC][fC][mC][mA][fA][mU][mU][mU][fU][mU][fG][mU][mU][mC][mUs][mCs][mA] 3');
- vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 453 (5' [MeEPmUs][fAs][fU][mU][fU][mU][fA][mA][mA][fA][mC][mC][mC][fA][mA][fU][mU][mU][mU][mUs][mGs][mU] 3');
- viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 454 (5' [MeEPmUs][fAs][fU][mA][fC][mU][fU][mU][mA][fA][mU][mU][mU][fU][mA][fA][mA][mA][mC][mCs][mCs][mA] 3');
- ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 455 (5' [MeEPmUs][fUs][fA][mU][fA][mC][fU][mU][mU][fA][mA][mU][mU][fU][mU][fA][mA][mA][mA][mCs][mCs][mC] 3');
- x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 456 (5' [mUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG] 3');
- xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 457 (5' [EPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG] 3'); or

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 458 (5' [MeEPmUs][fGs][fU][mA][fC][mU][fC][mU][mC][fA][mU][mU][mG][fU][mG][fG][mA][mU][mG][mAs][mCs][mG] 3'),

wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, "MeEP" is a mono methyl protected phosphate mimic.

41. The isolated oligonucleotide of any one of claims 1-40, wherein the sense strand comprises any one of:

i) a sense strand of nucleic acid sequence according to SEQ ID NO: 460 (5' [mCs][mUs][mG][mA][mA][fC][mA][fG][fC][fA][fU][mU][mU][mU][mU][mU][mU][mUs][mGs][mA][G1b][G1b][G1b] 3');

ii) a sense strand of nucleic acid sequence according to SEQ ID NO: 461 (5' [mUs][mUs][mU][mG][mU][fG][mA][fA][fA][fC][fA][mA][mA][mA][mA][mG][mUs][mGs][mA][G1b][G1b][G1b] 3');

iii) a sense strand of nucleic acid sequence according to SEQ ID NO: 462 (5' [mUs][mGs][mA][mA][mA][fC][mA][fA][fA][fA][fA][mA][mG][mU][mG][mU][mCs][mCs][mA][G1b][G1b][G1b] 3');

iv) a sense strand of nucleic acid sequence according to SEQ ID NO: 463 (5' [mAs][mAs][mA][mA][mG][fU][mG][fU][fU][fC][fC][mC][mU][mU][mU][mU][mC][mAs][mAs][mA][G1b][G1b][G1b] 3');

v) a sense strand of nucleic acid sequence according to SEQ ID NO: 464 (5' [mAs][mAs][mG][mU][mU][fG][mA][fG][fA][fA][fC][mA][mA][mA][mA][mA][mU][mUs][mGs][mA][G1b][G1b][G1b] 3');

vi) a sense strand of nucleic acid sequence according to SEQ ID NO: 465 (5' [mAs][mGs][mA][mA][mC][fA][mA][fA][fA][fA][fU][mU][mG][mG][mG][mU][mU][mUs][mUs][mA][G1b][G1b][G1b] 3');

vii) a sense strand of nucleic acid sequence according to SEQ ID NO: 466 (5' [mAs][mAs][mA][mA][mA][fU][mU][fG][fG][fG][fU][mU][mU][mU][mA][mA][mA][mAs][mUs][mA][G1b][G1b][G1b] 3');

viii) a sense strand of nucleic acid sequence according to SEQ ID NO: 467 (5' [mGs][mGs][mU][mU][mU][fU][mA][fA][fA][fA][fU][mU][mA][mA][mG][mU][mAs][mUs][mA][G1b][G1b][G1b] 3');

ix) a sense strand of nucleic acid sequence according to SEQ ID NO: 468 (5' [mGs][mUs][mU][mU][mU][fA][mA][fA][fA][fU][fU][mA][mA][mA][mG][mU][mA][mUs][mAs][mA][G1b][G1b][G1b] 3'); or

x) a sense strand of nucleic acid sequence according to SEQ ID NO: 469 (5' [mUs][mCs][mA][mU][mC][fC][mA][fC][fA][fA][fU][mG][mA][mG][mA][mG][mU][mAs][mCs][mA][G1b][G1b][G1b] 3').

wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, and "G1b" is a GalNac G1b moiety.

42. A vector encoding the isolated oligonucleotide of any one of claims 1-41.

43. A delivery system comprising the isolated oligonucleotide of any one of claims 1-41 or the vector of claim 42.

44. A pharmaceutical composition comprising the isolated oligonucleotide of any one of claims 1-41, the vector of claim 42, and a pharmaceutically acceptable carrier, diluent or excipient.

45. A kit comprising the isolated oligonucleotide of any one of claims 1-41, the vector of claim 42, or the pharmaceutical composition of claim 44.

46. A method of inhibiting or downregulating the expression or level of AGT in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of the isolated oligonucleotide of any one of claims 1-41, the vector of claim 42, or the pharmaceutical composition of claim 44.

47. A method of inhibiting or downregulating the expression or level of AGT in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of a first and at least a second isolated oligonucleotide of any one of claims 1-41, wherein the first and at least the second oligonucleotide comprises different sequences.

48. A method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of AGT or a disease or disorder where AGT plays a role in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of the isolated oligonucleotide of any one of claims 1-41, the vector of claim 42, or the pharmaceutical composition of claim 44.