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(54) **Titre : COMPOSITIONS ET PROCEDES D'INHIBITION DE LA CETOHEXOKINASE (KHK)**
(54) **Title: COMPOSITIONS AND METHODS FOR INHIBITING KETOHEXOKINASE (KHK)**

(57) **Abrégé/Abstract:**

Oligonucleotides are provided herein that inhibit KHK expression. Also provided are compositions including the same and uses thereof, particularly uses relating to treating diseases, disorders and/or conditions associated with KHK expression.

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(57) Abstract: Oligonucleotides are provided herein that inhibit KHK expression. Also provided are compositions including the same and uses thereof, particularly uses relating to treating diseases, disorders and/or conditions associated with KHK expression.



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LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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CONTENANT LES PAGES 1 À 233

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COMPOSITIONS AND METHODS FOR INHIBITING KETOHEXOKINASE (KHK)

BACKGROUND

[0001] Kethexokinese (KHK) is an important enzyme in fructose metabolism. KHK catalyzes the conversion of D-fructose to fructose-1-phosphate. Under conditions of elevated fructose consumption, a major part of fructose-1 phosphate contributes to fatty-acid and triglyceride synthesis among other things. In the liver, uncontrolled regulation of this process can lead to diseases such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Similarly, fructose metabolism converts fructose to glucose in the liver. Increased levels of glucose can lead to glucose intolerance (i.e., pre-diabetes, type-2 diabetes, and impaired fasting glucose). Excess glucose is converted to fatty acids and triglycerides and heightens the risk of developing cardiovascular disease (e.g., hypertension). Decreasing the amount of KHK in the liver is likely to reduce the development of, or symptoms of these diseases. Strategies for targeting the *KHK* gene to prevent such diseases are needed. RNAi agents targeting the *KHK* gene have been disclosed e.g., in WO 2015/123264 and WO 2020/060986.

SUMMARY OF DISCLOSURE

[0002] The disclosure is based in part on the discovery that oligonucleotides (e.g., RNAi oligonucleotides) reduce KHK expression in the liver. Specifically, target sequences within *KHK* mRNA were identified and oligonucleotides that bind to these target sequences and inhibit *KHK* mRNA expression were generated. As demonstrated herein, the oligonucleotides inhibited murine *KHK* expression, and/or monkey and human *KHK* expression in the liver. Without being bound by theory, the oligonucleotides described herein are useful for treating a disease, disorder or condition associated with *KHK* expression (e.g., Non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH)). In some embodiments, the oligonucleotides described herein are useful for treating a disease, disorder or condition associated with mutations in the *KHK* gene.

[0003] Accordingly, in some aspects, the present disclosure provides a double stranded RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising an antisense strand and a sense strand, wherein the antisense strand and the sense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387 and wherein the region of complementarity is at least 15 contiguous nucleotides in length, or a pharmaceutically acceptable salt thereof. In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising an antisense strand and a sense strand, wherein the antisense strand and the sense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, wherein the region of complementarity is at least 15 contiguous nucleotides in length, and wherein *KHK* expression is reduced by at least 50%.

[0004] In any of the foregoing or related aspects, the sense strand comprises a sequence set forth in any one of SEQ ID NOs: 4-387.

[0005] In any of the foregoing or related aspects, the anti-sense strand comprises a sequence set forth in any one of SEQ ID NOs: 388-771.

[0006] In other aspects, the disclosure provides a double stranded RNAi oligonucleotide for inhibiting expression of *KHK*, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a duplex

region, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO: 4-387 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequences of SEQ ID NO: 388-771, or a pharmaceutically acceptable salt thereof. In other aspects, the disclosure provides a double stranded RNAi oligonucleotide for inhibiting expression of *KHK*, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a duplex region, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO:4-387 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequences of SEQ ID NO: 388-771, and wherein *KHK* expression is reduced by at least 50%, or a pharmaceutically acceptable salt thereof.

[0007] In any of the foregoing or related aspects, the sense strand is 15 to 50 nucleotides in length. In some aspects, the sense strand is 18 to 36 nucleotides in length. In other aspects, the sense strand is 15 to 30 nucleotides in length. In some aspects, the antisense strand is 15-30 nucleotides in length. In some aspects, the antisense strand is 22 nucleotides in length.

[0008] In any of the foregoing or related aspects, the antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length. In any of the foregoing or related aspects, the antisense strand and the sense strand form a duple region of at least 20 nucleotides in length. In any of the foregoing or related aspects, the antisense strand and the sense strand form a duplex region of 20 nucleotides in length. In some aspects, the antisense strand is 22 nucleotides in length and the antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length. In some aspects, the antisense strand is 22 nucleotides in length and the antisense strand and the sense strand form a duplex region of at least 20 nucleotides in length. In some aspects, the antisense strand is 22 nucleotides in length and the antisense strand and the sense strand form a duplex region of 20 nucleotides in length.

[0009] In any of the foregoing or related aspects, the antisense strand comprises a region of complementarity of at least 19 contiguous nucleotides in length, optionally at least 20 nucleotides in length.

[0010] In any of the foregoing or related aspects, the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

[0011] In some aspects, the disclosure provides an RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length, or a pharmaceutically acceptable salt thereof.

[0012] In yet other aspects, the disclosure provides an RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387,

and wherein the region of complementarity is at least 15 contiguous nucleotides in length, or a pharmaceutically acceptable salt thereof.

[0013] In other aspects, the disclosure provides an RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length, or a pharmaceutically acceptable salt thereof.

[0014] In other aspects, the disclosure provides an RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length, or a pharmaceutically acceptable salt thereof.

[0015] In yet other aspects, the disclosure provides an RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length, or a pharmaceutically acceptable salt thereof.

[0016] In some aspects, the disclosure provides an RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length, or a pharmaceutically acceptable salt thereof.

[0017] In other aspects, the disclosure provides an RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length, or a pharmaceutically acceptable salt thereof.

[0018] In yet other aspects, the disclosure provides an RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region of at least 19 nucleotides in length,

optionally 20 nucleotides in length, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length, or a pharmaceutically acceptable salt thereof.

[0019] In some aspects, the disclosure provides a RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising:

(i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is selected from SEQ ID NOs: 948-953; and

(ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand,

wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand. In some aspects, the RNAi oligonucleotide comprises a stem-loop at the 3' terminus, wherein the stem loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

[0020] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide comprising a stem loop set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length. In some aspects, L is a triloop or a tetraloop. In any of the foregoing or related aspects, L is a tetraloop. In some aspects, the tetraloop comprises the sequence 5'-GAAA-3'. In any of the foregoing or related aspects, S1 and S2 are 1-10 nucleotides in length and have the same length. In some aspects, S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length. In some aspects, S1 and S2 are 6 nucleotides in length. In any of the foregoing or related aspects, the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 871).

[0021] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide comprising a nicked tetraloop structure. In some aspects, the RNAi oligonucleotide comprises a nick between the 3' terminus of the sense strand and the 5' terminus of the antisense strand. In some aspects, the antisense and sense strands are not covalently linked.

[0022] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the antisense strand comprises a 3' overhang of one or more nucleotides in length. In some aspects, the 3' overhang comprises purine nucleotides. In some aspects, the 3' overhang is 2 nucleotides in length. In some aspects, the 3' overhang is selected from AA, GG, AG and GA. In some aspects, the 3' overhang is GG or AA. In some aspects, the 3' overhang is GG.

[0023] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide comprising at least one modified nucleotide. In some aspects, the modified nucleotide comprises a 2'-modification. In some aspects, the 2'-modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-

2'-fluoro- β -d-arabinonucleic acid. In some aspects, the 2'-modification is 2'-fluoro. In some aspects, the 2'-modification is 2'-O-methyl. In some aspects, the 2'-modification is 2'-fluoro and 2'-O-methyl.

[0024] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide comprising at least one modified nucleotide, wherein about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise a 2'-fluoro modification. In some aspects, about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprise a 2'-fluoro modification. In some aspects, about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the oligonucleotide comprise a 2'-fluoro modification. In some aspects, the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3', wherein positions 8-11 comprise a 2'-fluoro modification. In some aspects, the antisense strand comprises 22 nucleotides with positions 1-22 from 5' to 3', wherein positions 2, 3, 4, 5, 7, 10 and 14 comprise a 2'-fluoro modification. In some aspects, the remaining nucleotides of the sense and/or antisense strand comprise a 2'-O-methyl modification.

[0025] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein all of the nucleotides are modified. In some aspects, positions 8, 9, 10 and 11 (from 5' to 3') of the sense strand are modified. In some aspects, positions 3, 8, 9, 10, 12, 13 and 17 (from 5' to 3') of the sense strand are modified. In some aspects, positions 2, 3, 4, 5, 7, 10 and 14 (from 5' to 3') of the antisense strand are modified. In some aspects, positions 2-5, 7, 8, 10, 14, 16 and 19 (from 5' to 3') of the antisense strand are modified. In some aspects, positions 8, 9, 10 and 11 (from 5' to 3') of the sense strand and positions 2, 3, 4, 5, 7, 10 and 14 (from 5' to 3') of the antisense strand are modified. In some aspects, positions 3, 8, 9, 10, 12, 13 and 17 (from 5' to 3') of the sense strand and positions 2-5, 7, 8, 10, 14, 16 and 19 (from 5' to 3') of the antisense strand are modified. In some aspects, the modification is a 2'-fluoro modification.

[0026] In any of the foregoing or related aspects, the oligonucleotide comprises at least one modified internucleotide linkage. In some aspects, the at least one modified internucleotide linkage is a phosphorothioate linkage. In some aspects, the antisense strand comprises a phosphorothioate linkage (i) between positions 1 and 2, and between positions 2 and 3; or (ii) between positions 1 and 2, between positions 2 and 3, and between positions 3 and 4, wherein positions are numbered 1-4 from 5' to 3'. In some aspects, the antisense strand is 22 nucleotides in length and comprises a phosphorothioate linkage between positions 20 and 21 and between positions 21 and 22, wherein positions are numbered 1-22 from 5' to 3'.

[0027] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog. In some aspects, the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonyl phosphonate, optionally wherein the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.

[0028] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide comprising an antisense strand comprising a phosphorylated nucleotide at the 5' terminus, wherein the phosphorylated nucleotide is selected from uridine and adenosine. In some aspects, the phosphorylated nucleotide is uridine.

[0029] In any of the foregoing or related aspects, the oligonucleotide reduces or inhibits *KHK* expression *in vivo*. In any of the foregoing or related aspects, the oligonucleotide is a Dicer substrate. In some aspects, the oligonucleotide

is a Dicer substrate that, upon endogenous Dicer processing, yields double-stranded nucleic acids of 19-23 nucleotides in length capable of reducing *KHK* expression in a mammalian cell.

[0030] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands. In some aspects, each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid. In some aspects, the stem loop comprises one or more targeting ligands conjugated to one or more nucleotides of the stem loop. In some aspects, one or more targeting ligands is conjugated to one or more nucleotides of the loop. In some aspects, the loop comprises 4 nucleotides numbered 1-4 from 5' to 3', wherein nucleotides at positions 2, 3 and 4 each comprise one or more targeting ligands, wherein the targeting ligands are the same or different.

[0031] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety. In some aspects, the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety. In some aspects, up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

[0032] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide comprising an antisense strand comprising a region of complementarity, wherein the region of complementarity is fully complementary to the *KHK* mRNA target sequence at nucleotide positions 2-8 of the antisense strand, wherein nucleotide positions are numbered 5' to 3'. In some aspects, the region of complementarity is fully complementary to the *KHK* mRNA target sequence at nucleotide positions 2-11 of the antisense strand, wherein nucleotide positions are numbered 5' to 3'.

[0033] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 872-878 and 886-911.

[0034] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 879-884 and 912-938.

[0035] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the antisense strand comprises a nucleotide sequence selected from SEQ ID NOs: 913, 917, 918, 920, 923 and 936. In some aspects, the sense strand comprises a nucleotide sequence selected from SEQ ID NOs: 942-947. In some aspects, the sense strand comprises a nucleotide sequence selected from SEQ ID NOs: 887, 891, 892, 894, 897 and 909.

[0036] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 886 and 912, respectively;
- (b) SEQ ID NOs: 887 and 913, respectively;
- (c) SEQ ID NOs: 910 and 937, respectively;
- (d) SEQ ID NOs: 888 and 914, respectively;
- (e) SEQ ID NOs: 889 and 915, respectively;
- (f) SEQ ID NOs: 890 and 916, respectively;
- (g) SEQ ID NOs: 891 and 917, respectively;
- (h) SEQ ID NOs: 877 and 884, respectively;

- (i) SEQ ID NOs: 878 and 930, respectively;
- (j) SEQ ID NOs: 876 and 883, respectively;
- (k) SEQ ID NOs: 875 and 882, respectively;
- (l) SEQ ID NOs: 892 and 918, respectively;
- 5 (m) SEQ ID NOs: 893 and 919, respectively;
- (n) SEQ ID NOs: 894 and 920, respectively;
- (o) SEQ ID NOs: 904 and 931, respectively;
- (p) SEQ ID NOs: 895 and 921, respectively;
- (q) SEQ ID NOs: 905 and 932, respectively;
- 10 (r) SEQ ID NOs: 896 and 922, respectively;
- (s) SEQ ID NOs: 911 and 938, respectively;
- (t) SEQ ID NOs: 906 and 933, respectively;
- (u) SEQ ID NOs: 897 and 923, respectively;
- (v) SEQ ID NOs: 907 and 934, respectively;
- 15 (w) SEQ ID NOs: 908 and 935, respectively;
- (x) SEQ ID NOs: 903 and 929, respectively;
- (y) SEQ ID NOs: 901 and 927, respectively;
- (z) SEQ ID NOs: 874 and 881, respectively;
- (aa) SEQ ID NOs: 902 and 928, respectively;
- 20 (bb) SEQ ID NOs: 873 and 880, respectively;
- (cc) SEQ ID NOs: 872 and 879, respectively;
- (dd) SEQ ID NOs: 898 and 924, respectively;
- (ee) SEQ ID NOs: 899 and 925, respectively;
- (gg) SEQ ID NOs: 900 and 926, respectively; and
- 25 (hh) SEQ ID NOs: 909 and 936, respectively.

[0037] In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 887 and 913, respectively;
- (b) SEQ ID NOs: 891 and 917, respectively;
- 30 (c) SEQ ID NOs: 892 and 918, respectively;
- (d) SEQ ID NOs: 894 and 920, respectively;
- (e) SEQ ID NOs: 897 and 923, respectively; and
- (f) SEQ ID NOs: 909 and 936, respectively.

[0038] In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands
 35 comprise the nucleotide sequences set forth in SEQ ID NOs: 909 and 936, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 894 and 920, respectively. In yet other aspects, the disclosure provides an RNAi oligonucleotide

wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 897 and 923, respectively. In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 892 and 918, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 891 and 917, respectively. In yet further aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 887 and 913, respectively.

[0039] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the oligonucleotide as described herein achieves at least 50% knockdown of *KHK* mRNA. In some aspects, an oligonucleotide described herein achieves at least 50% knockdown of *KHK* mRNA *in vitro*. In some aspects, an oligonucleotide described herein achieves at least 50% knockdown of *KHK* mRNA *in vivo*. In some aspects, an oligonucleotide described herein achieves at least 50% knockdown of *KHK* mRNA *in vitro* and *in vivo*. In some aspects, an oligonucleotide described herein that achieves at least 50% knockdown of *KHK* mRNA comprises a sense strand and an antisense strand, wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 886 and 912, respectively;
- (b) SEQ ID NOs: 887 and 913, respectively;
- (c) SEQ ID NOs: 910 and 937, respectively;
- (d) SEQ ID NOs: 890 and 916, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively;
- (f) SEQ ID NOs: 892 and 918, respectively;
- (g) SEQ ID NOs: 893 and 919, respectively;
- (h) SEQ ID NOs: 894 and 920, respectively;
- (i) SEQ ID NOs: 911 and 938, respectively;
- (j) SEQ ID NOs: 899 and 925, respectively;
- (k) SEQ ID NOs: 900 and 926, respectively;
- (l) SEQ ID NOs: 909 and 936, respectively; and
- (m) SEQ ID NOs: 897 and 923, respectively.

[0040] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the sense strand and the antisense strand are modified, wherein the antisense strand and the sense strand comprise one or more 2'-fluoro and 2'-O-methyl modified nucleotides and at least one phosphorothioate linkage, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog.

[0041] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 774-804.

[0042] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 819- 849.

[0043] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 774 and 819, respectively;
- (b) SEQ ID NOs: 775 and 820, respectively;
- 5 (c) SEQ ID NOs: 776 and 821, respectively;
- (d) SEQ ID NOs: 777 and 822, respectively;
- (e) SEQ ID NOs: 778 and 823, respectively;
- (f) SEQ ID NOs: 779 and 824, respectively;
- (g) SEQ ID NOs: 780 and 825, respectively;
- 10 (h) SEQ ID NOs: 781 and 826, respectively;
- (i) SEQ ID NOs: 782 and 827, respectively;
- (j) SEQ ID NOs: 783 and 828, respectively;
- (k) SEQ ID NOs: 784 and 829, respectively;
- (l) SEQ ID NOs: 785 and 830, respectively;
- 15 (m) SEQ ID NOs: 786 and 831, respectively;
- (n) SEQ ID NOs: 787 and 832, respectively;
- (o) SEQ ID NOs: 788 and 833, respectively;
- (p) SEQ ID NOs: 789 and 834, respectively;
- (q) SEQ ID NOs: 790 and 835, respectively;
- 20 (r) SEQ ID NOs: 791 and 836, respectively;
- (s) SEQ ID NOs: 792 and 837, respectively;
- (t) SEQ ID NOs: 793 and 838, respectively;
- (u) SEQ ID NOs: 794 and 839, respectively;
- (v) SEQ ID NOs: 795 and 840, respectively;
- 25 (w) SEQ ID NOs: 796 and 841, respectively;
- (x) SEQ ID NOs: 797 and 842, respectively;
- (y) SEQ ID NOs: 798 and 843, respectively;
- (z) SEQ ID NOs: 799 and 844, respectively;
- (aa) SEQ ID NOs: 800 and 845, respectively;
- 30 (bb) SEQ ID NOs: 801 and 846, respectively;
- (cc) SEQ ID NOs: 802 and 847, respectively;
- (dd) SEQ ID NOs: 803 and 848, respectively; and
- (ee) SEQ ID NOs: 804 and 849, respectively.

[0044] In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands
35 comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 775 and 820, respectively;
- (b) SEQ ID NOs: 779 and 824, respectively;

- (c) SEQ ID NOs: 780 and 825, respectively;
- (d) SEQ ID NOs: 782 and 827, respectively;
- (e) SEQ ID NOs: 785 and 830, respectively; and
- (f) SEQ ID NOs: 804 and 849, respectively.

5 **[0045]** In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 804 and 849, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 782 and 827, respectively. In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 775 and 820,
10 respectively. In yet other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 779 and 824, respectively. In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 780 and 825, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs:
15 785 and 830, respectively.

[0046] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 805-818.

[0047] In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 850-863.

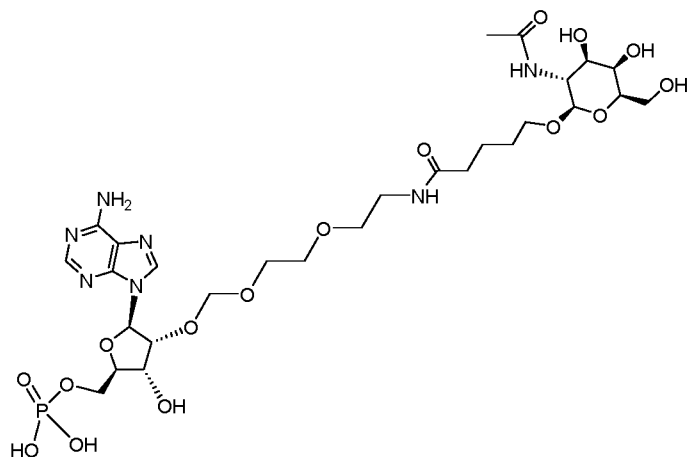
20 **[0048]** In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 805 and 850, respectively;
- (b) SEQ ID NOs: 806 and 851, respectively;
- (c) SEQ ID NOs: 807 and 852, respectively;
- 25 (d) SEQ ID NOs: 808 and 853, respectively;
- (e) SEQ ID NOs: 809 and 854, respectively;
- (f) SEQ ID NOs: 810 and 855, respectively;
- (g) SEQ ID NOs: 811 and 856, respectively;
- (h) SEQ ID NOs: 812 and 857, respectively;
- 30 (i) SEQ ID NOs: 813 and 858, respectively;
- (j) SEQ ID NOs: 814 and 859, respectively;
- (k) SEQ ID NOs: 815 and 860, respectively;
- (l) SEQ ID NOs: 816 and 861, respectively;
- (m) SEQ ID NOs: 817 and 862, respectively and;
- 35 (n) SEQ ID NOs: 818 and 863, respectively.

[0049] In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences

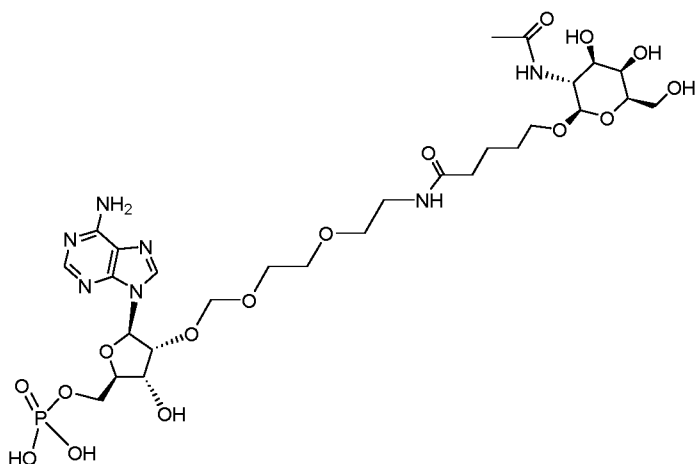
set forth in SEQ ID NOs: 805 and 850, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 809 and 854, respectively. In yet other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 810 and 855, respectively. In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 812 and 857, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 815 and 860, respectively. In yet other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 818 and 863, respectively.

[0050] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNAi comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mG-S-mA-mA-mG-mA-mG-mA-fA-fG-fC-fA-mG-mA-mU-mC-mC-mU-mG-mU-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 775), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fA-S-fC-fA-fG-mG-fA-mU-mC-fU-mG-mC-mU-fU-mC-mU-mC-mU-mU-mC-S-mG-S-mG-3' (SEQ ID NO: 820), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



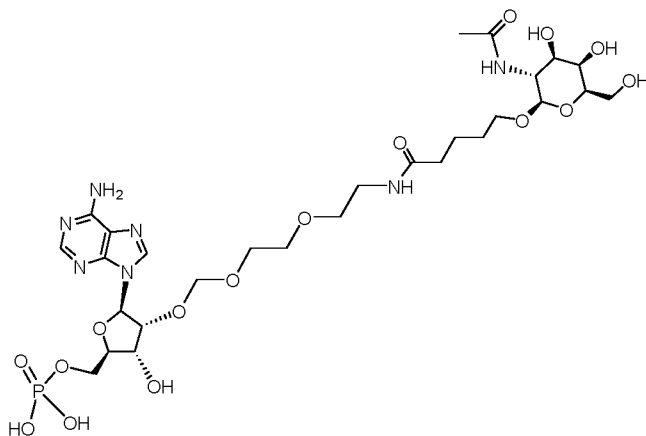
, or a pharmaceutically acceptable salt thereof.

[0051] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mC-S-mA-mG-mA-mU-mG-mU-fG-fU-fC-fU-mG-mC-mU-mA-mC-mA-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 779), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fU-S-fC-S-fU-fG-mU-fA-mG-mC-fA-mG-mA-mC-fA-mC-mA-mU-mC-mU-mG-S-mG-S-mG-3' (SEQ ID NO: 824), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



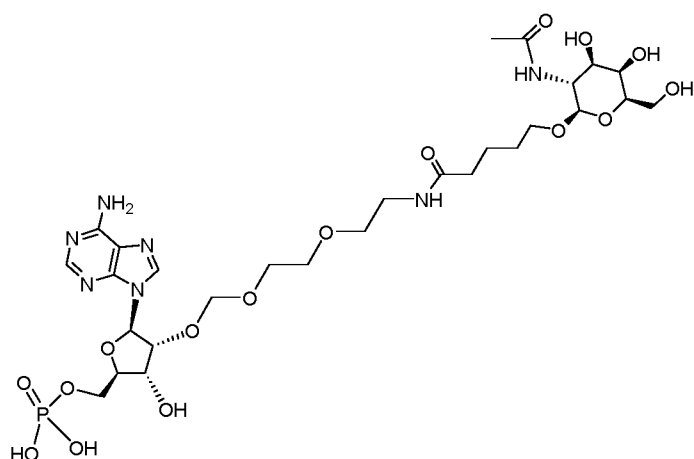
, or a pharmaceutically acceptable salt thereof.

[0052] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mG-S-mA-mC-mU-mU-mU-mG-fA-fG-fA-fA-mG-mU-mU-mG-mA-mU-mC-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 780), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fG-S-fA-S-fU-fC-mA-fA-mC-mC-fU-mU-mC-mU-fC-mA-mA-mA-mG-mU-mC-S-mG-S-mG-3' (SEQ ID NO: 825), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



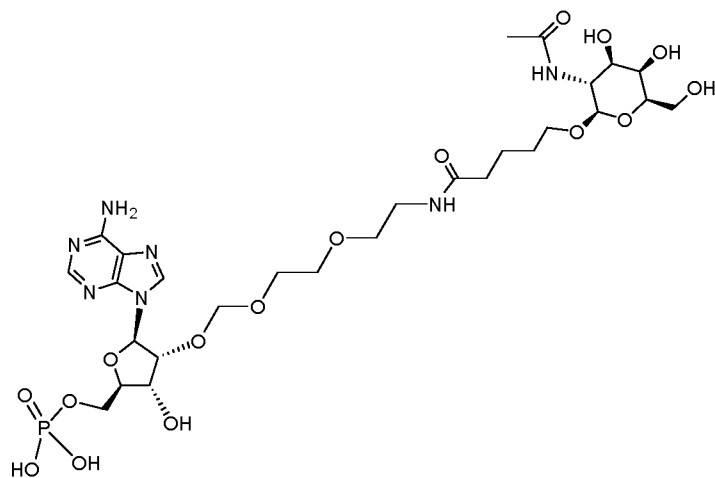
, or a pharmaceutically acceptable salt thereof.

[0053] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mU-S-mG-mU-mU-mU-mG-mU-fC-fA-fG-fC-mA-mA-mA-mG-mA-mU-mG-mU-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 785), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fA-S-fC-fA-fU-mC-fU-mU-mU-fG-mC-mU-mG-fA-mC-mA-mA-mA-mC-mA-S-mG-S-mG-3' (SEQ ID NO: 830), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



, or a pharmaceutically acceptable salt thereof.

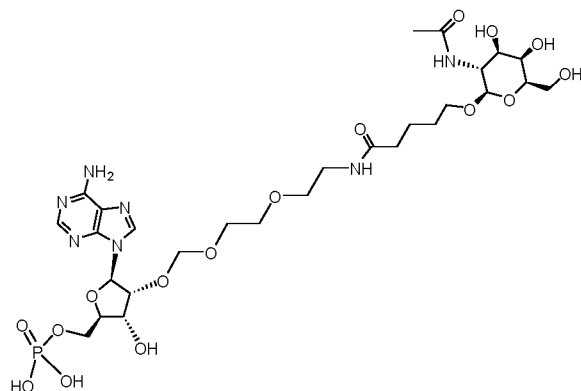
[0054] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mG-S-mC-mA-mG-mG-mA-mA-fG-fC-fA-fC-mU-mG-mA-mG-mA-mU-mU-mC-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 804), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fG-S-fA-S-fA-fU-mC-fU-mC-mA-fG-mU-mG-mC-fU-mU-mC-mC-mU-mG-mC-S-mG-S-mG-3' (SEQ ID NO: 849), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



, or a pharmaceutically acceptable salt thereof.

[0055] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mU-S-mU-mU-mG-mA-mG-mA-fA-fG-fG-fU-mU-mG-mA-mU-mC-mU-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 782), and wherein the antisense strand comprises the sequence and all of the

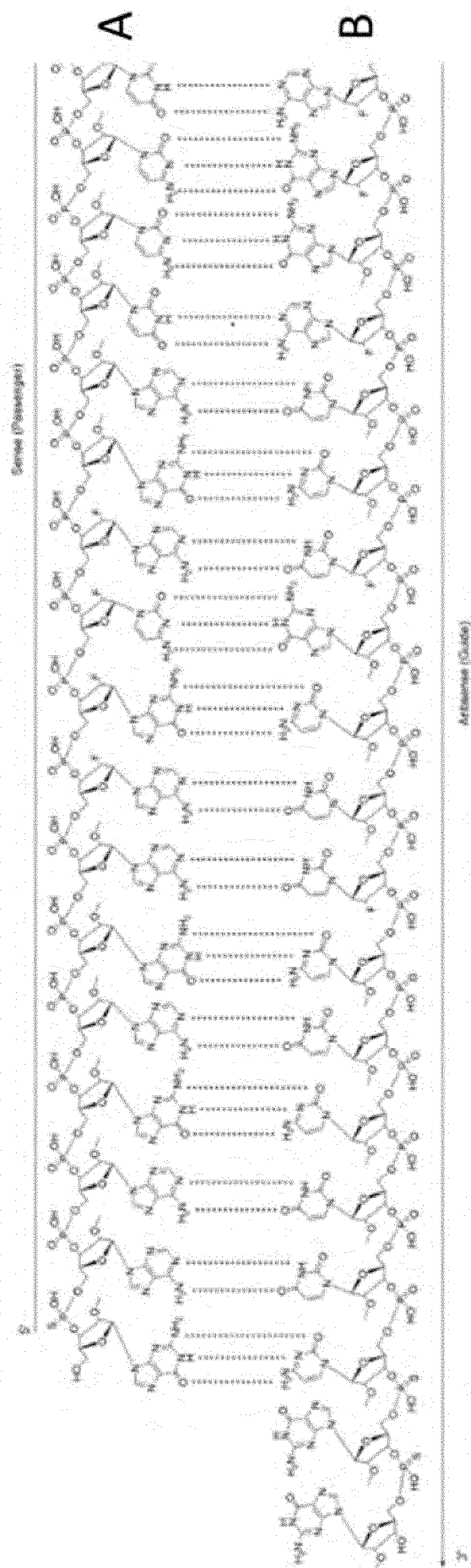
modifications of 5' [MePhosphonate-4O-mU]-S-fU-S-fC-S-fA-fG-mA-fU-mC-mA-fA-mC-mC-mU-fU-mC-mU-mC-mA-mA-mA-S-mG-S-mG-3' (SEQ ID NO: 827), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



, or a pharmaceutically acceptable salt thereof.

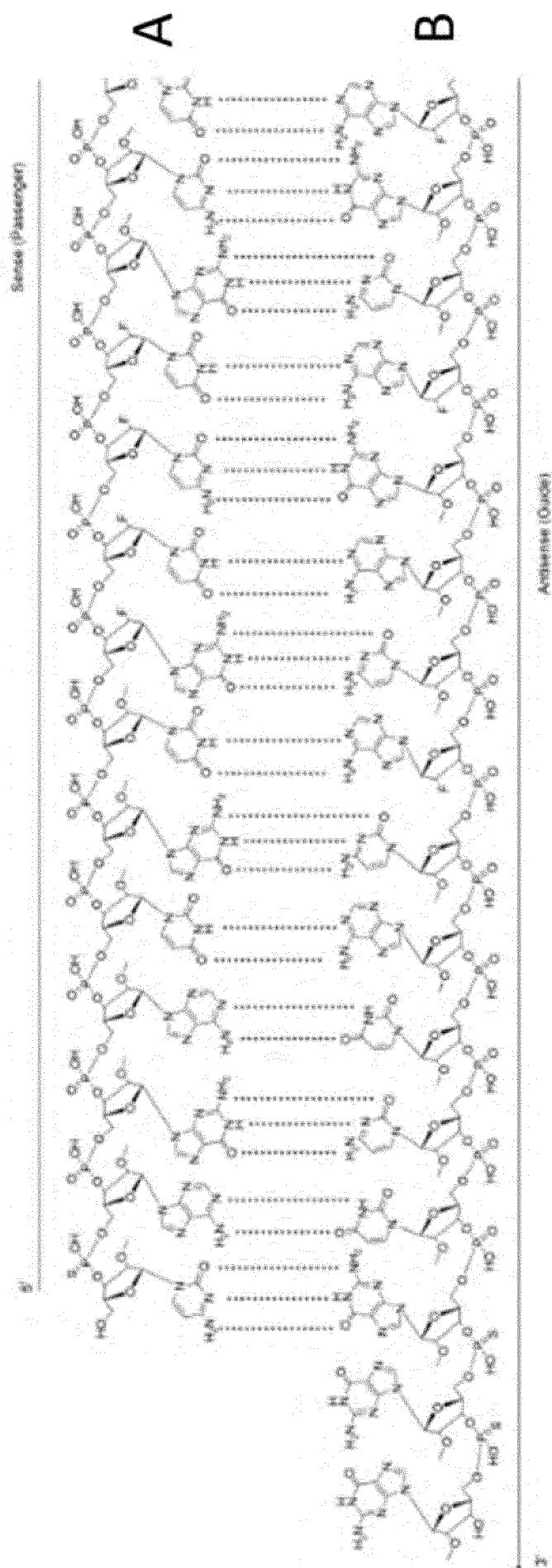
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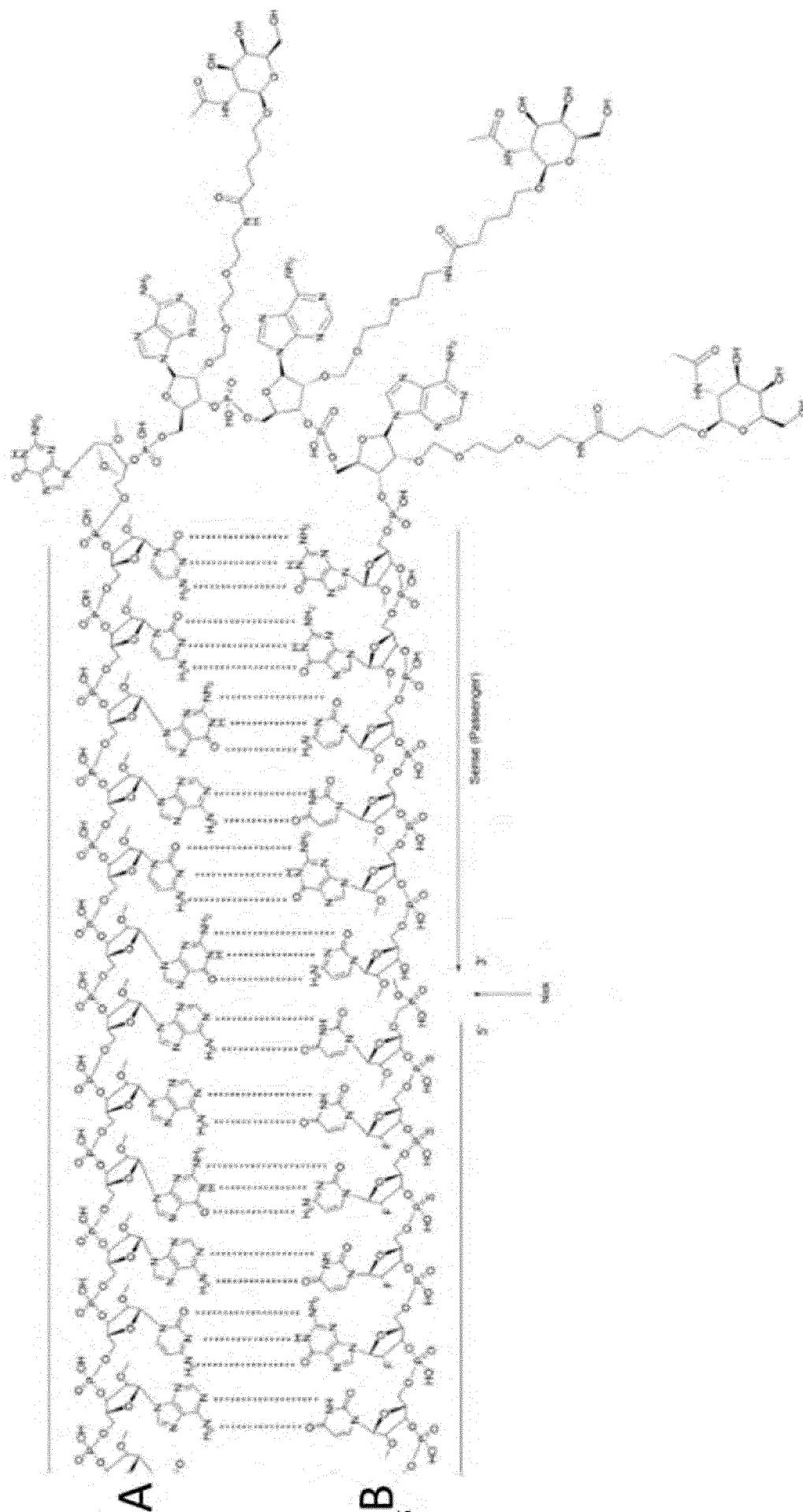
[0056] In yet other aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand comprising SEQ ID NO: 775 and an antisense strand comprising SEQ ID NO: 820, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein said dsRNA is in the form of a conjugate having the structure of:



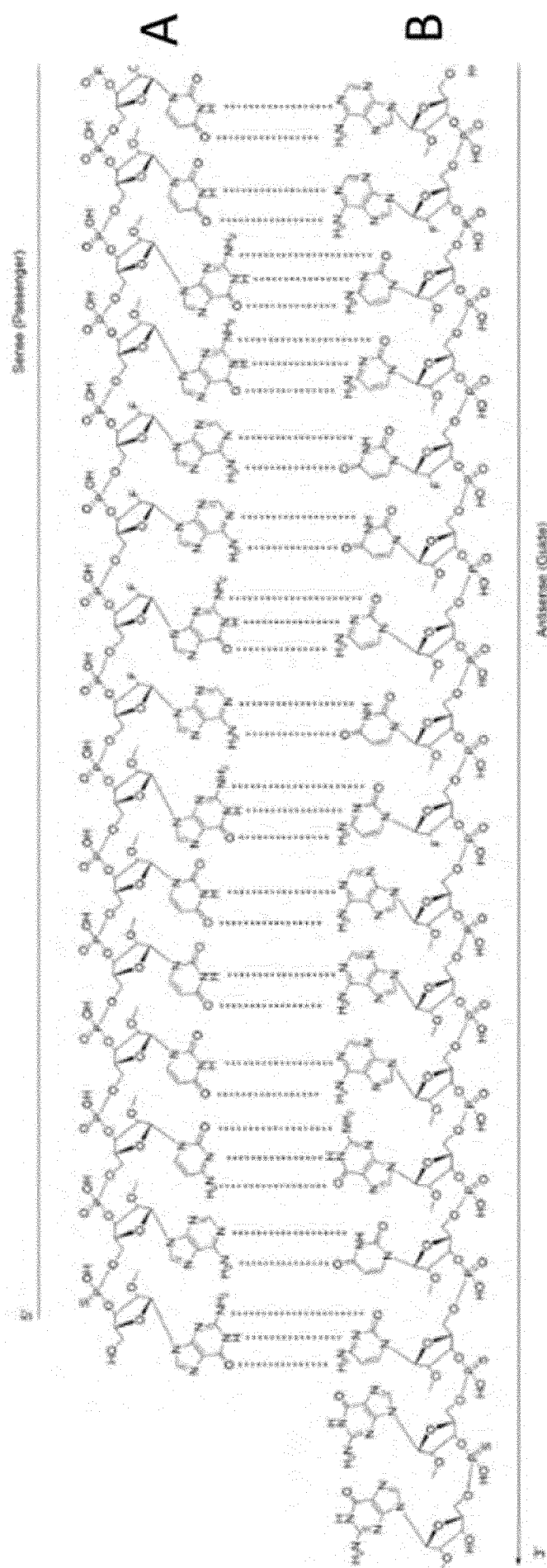


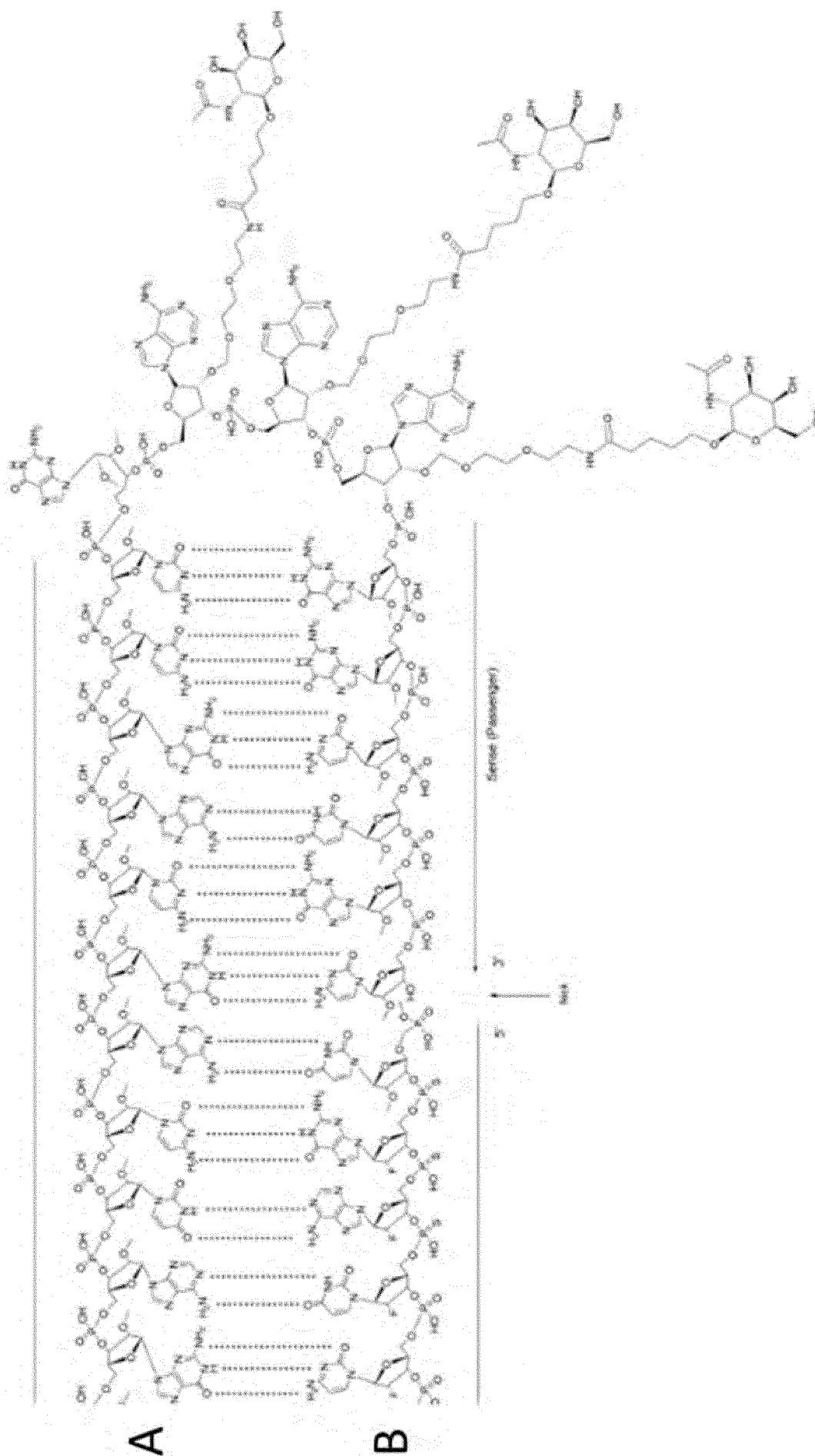
[0057] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand comprising SEQ ID NO: 779 and an antisense strand comprising SEQ ID NO: 824, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein said dsRNA is in the form of a conjugate having the structure of:





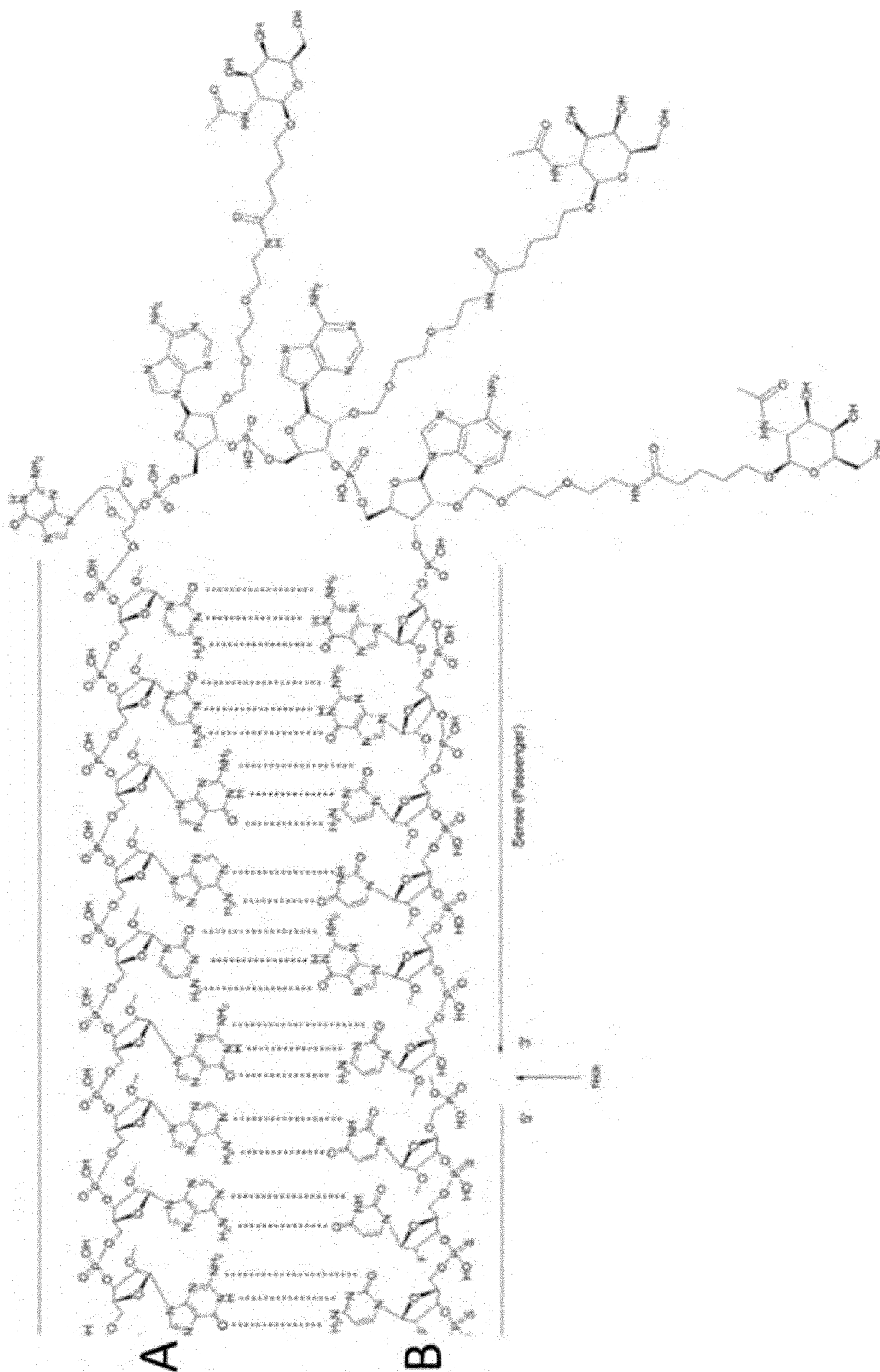
[0058] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand comprising SEQ ID NO: 780 and an antisense strand comprising SEQ ID NO: 825, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein said dsRNA is in the form of a conjugate having the structure of:



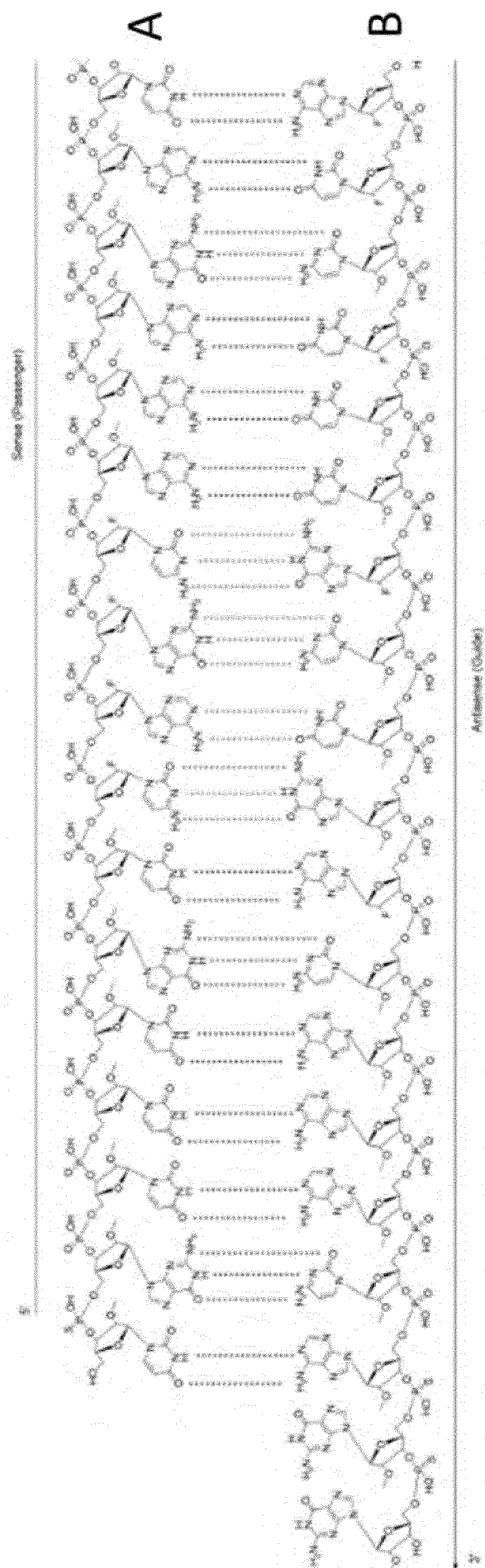


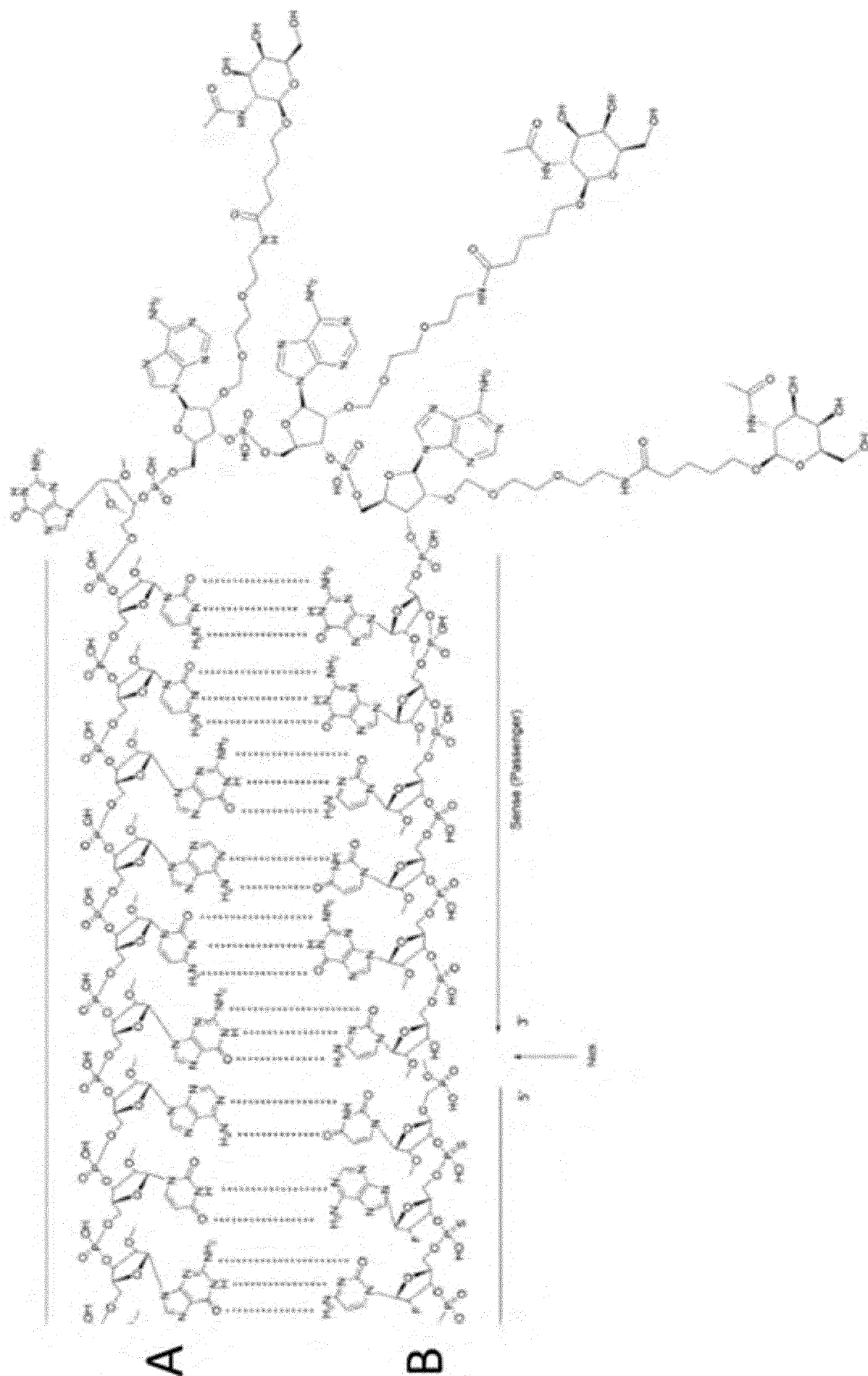
[0059] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand comprising SEQ ID NO: 782 and an antisense strand comprising SEQ ID NO: 827, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein said dsRNA is in the form of a conjugate having the structure of:



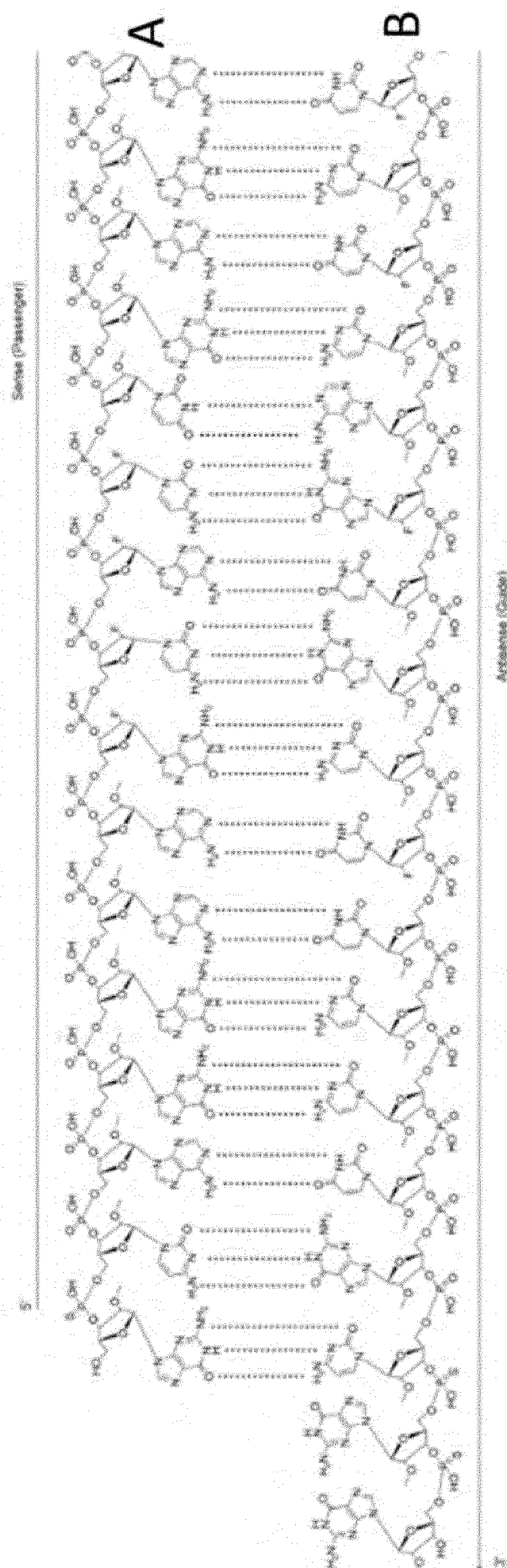


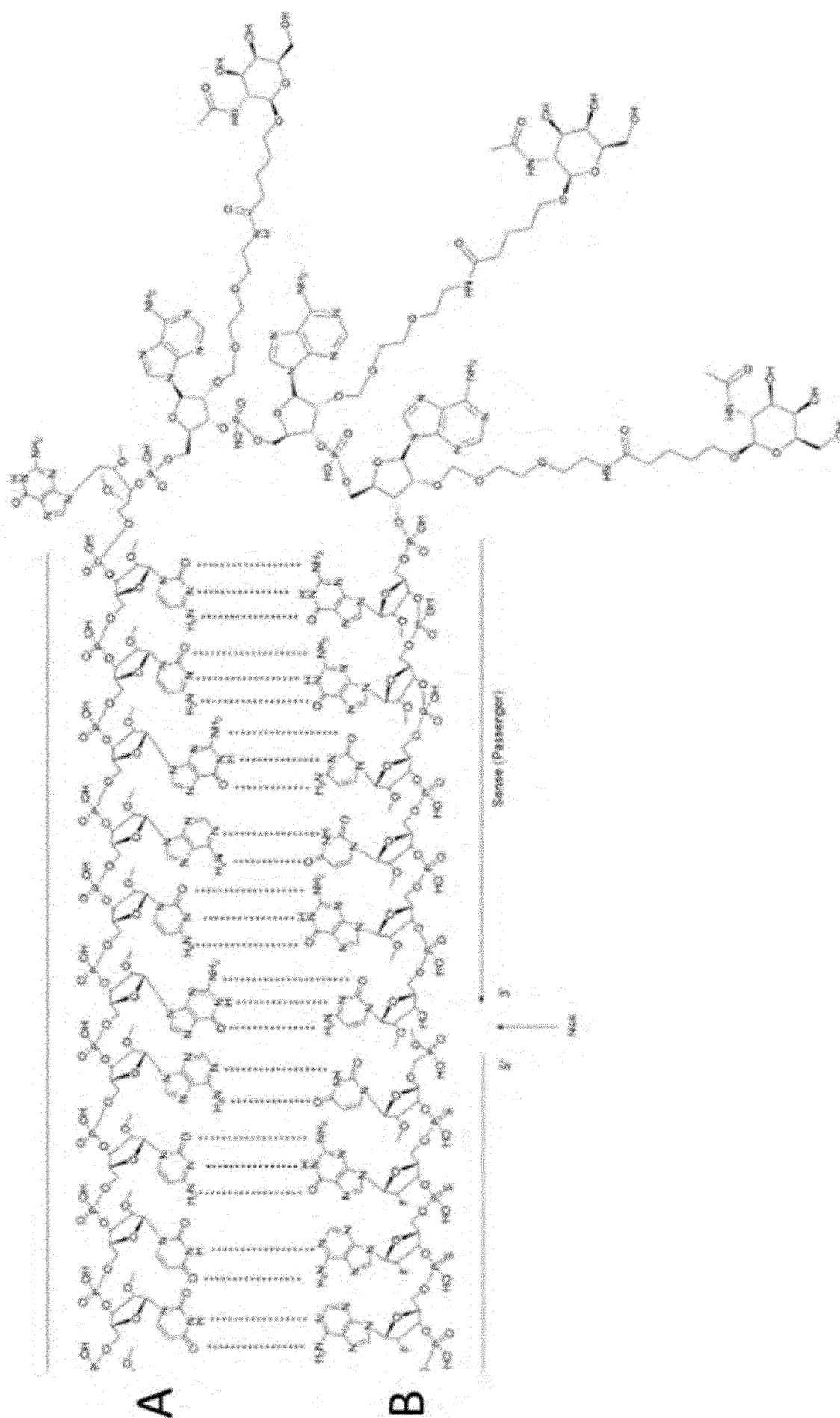
[0060] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand comprising SEQ ID NO: 785 and an antisense strand comprising SEQ ID NO: 830, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein said dsRNA is in the form of a conjugate having the structure of:





[0061] In some aspects, the present disclosure provides a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *KHK*, wherein said dsRNA comprises a sense strand comprising SEQ ID NO: 804 and an antisense strand comprising SEQ ID NO: 849, the antisense strand comprising a region of complementarity to a *KHK* RNA transcript, e.g. *KHK* mRNA, wherein said dsRNA is in the form of a conjugate having the structure of:





[0062] In some aspects, the present disclosure provides a method for treating a subject having a disease, disorder or condition associated with *KHK* expression, the method comprising administering to the subject a therapeutically effective amount of any RNAi oligonucleotide or pharmaceutical composition described herein, thereby treating the subject.

[0063] In some aspects, the disclosure provides a pharmaceutically acceptable salt of any of the oligonucleotides described herein. In some aspects, the present disclosure provides a pharmaceutical composition comprising any RNAi oligonucleotide described herein, and a pharmaceutically acceptable carrier, salt, delivery agent or excipient. In some aspects, the present disclosure provides a pharmaceutical composition comprising any RNAi oligonucleotide described herein, and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant. Likewise, the oligonucleotides herein may be provided in the form of their free acids.

[0064] In some aspects, the disclosure provides a method for modulating *KHK* expression in a target cell expressing *KHK*, the method comprising administering an RNAi oligonucleotide or pharmaceutical composition described herein in an effective amount to the target cell.

[0065] In some aspects, the present disclosure provides a method of delivering an oligonucleotide to a subject, the method comprising administering a pharmaceutical composition described herein.

[0066] In some aspects, the present disclosure provides a method for reducing *KHK* expression in a cell, a population of cells or a subject, the method comprising the step of:

- i. contacting the cell or the population of cells with any RNAi oligonucleotide or pharmaceutical composition described herein; or
- ii. administering to the subject any RNAi oligonucleotide or pharmaceutical composition described herein.

[0067] In any of the foregoing or related aspects, the method of reducing *KHK* expression comprises reducing an amount or level of *KHK* mRNA, an amount or level of *KHK* protein, or both.

[0068] In any of the foregoing or related aspects, the subject has a disease, disorder or condition associated with *KHK* expression. In some aspects, the disease, disorder, or condition associated with *KHK* expression is non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

[0069] In any of the foregoing or related aspects, the RNAi oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.

[0070] In some aspects, the present disclosure provides a method for treating a subject having a disease, disorder or condition associated with *KHK* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, or a pharmaceutically acceptable salt thereof, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 886 and 912, respectively;
- (b) SEQ ID NOs: 887 and 913, respectively;
- (c) SEQ ID NOs: 910 and 937, respectively;
- (d) SEQ ID NOs: 888 and 914, respectively;

- (e) SEQ ID NOs: 889 and 915, respectively;
- (f) SEQ ID NOs: 890 and 916, respectively;
- (g) SEQ ID NOs: 891 and 917, respectively;
- (h) SEQ ID NOs: 877 and 884, respectively;
- 5 (i) SEQ ID NOs: 878 and 930, respectively;
- (j) SEQ ID NOs: 876 and 883, respectively;
- (k) SEQ ID NOs: 875 and 882, respectively;
- (l) SEQ ID NOs: 892 and 918, respectively;
- (m) SEQ ID NOs: 893 and 919, respectively;
- 10 (n) SEQ ID NOs: 894 and 920, respectively;
- (o) SEQ ID NOs: 904 and 931, respectively;
- (p) SEQ ID NOs: 895 and 921, respectively;
- (q) SEQ ID NOs: 905 and 932, respectively;
- (r) SEQ ID NOs: 896 and 922, respectively;
- 15 (s) SEQ ID NOs: 911 and 938, respectively;
- (t) SEQ ID NOs: 906 and 933, respectively;
- (u) SEQ ID NOs: 897 and 923, respectively;
- (v) SEQ ID NOs: 907 and 934, respectively;
- (w) SEQ ID NOs: 908 and 935, respectively;
- 20 (x) SEQ ID NOs: 903 and 929, respectively;
- (y) SEQ ID NOs: 901 and 927, respectively;
- (z) SEQ ID NOs: 874 and 881, respectively;
- (aa) SEQ ID NOs: 902 and 928, respectively;
- (bb) SEQ ID NOs: 873 and 880, respectively;
- 25 (cc) SEQ ID NOs: 872 and 879, respectively;
- (dd) SEQ ID NOs: 898 and 924, respectively;
- (ee) SEQ ID NOs: 899 and 925, respectively;
- (ff) SEQ ID NOs: 900 and 926, respectively; and
- (gg) SEQ ID NOs: 909 and 936, respectively.

30 **[0071]** In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 887 and 913, respectively;
- (b) SEQ ID NOs: 891 and 917, respectively;
- (c) SEQ ID NOs: 892 and 918, respectively;
- 35 (d) SEQ ID NOs: 894 and 920, respectively;
- (e) SEQ ID NOs: 897 and 923, respectively; and
- (f) SEQ ID NOs: 909 and 936, respectively.

[0072] In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 887 and 913, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 891 and 917, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 892 and 918, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 894 and 920, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 897 and 923, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 909 and 936, respectively.

[0073] In some aspects, the present disclosure provides a method for treating a subject having a disease, disorder or condition associated with *KHK* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, or a pharmaceutically acceptable salt thereof, wherein the sense strand and antisense strands are selected from the group consisting of:

- (a) SEQ ID NOs: 774 and 819, respectively;
- (b) SEQ ID NOs: 775 and 820, respectively;
- (c) SEQ ID NOs: 776 and 821, respectively;
- (d) SEQ ID NOs: 777 and 822, respectively;
- (e) SEQ ID NOs: 778 and 823, respectively;
- (f) SEQ ID NOs: 779 and 824, respectively;
- (g) SEQ ID NOs: 780 and 825, respectively;
- (h) SEQ ID NOs: 781 and 826, respectively;
- (i) SEQ ID NOs: 782 and 827, respectively;
- (j) SEQ ID NOs: 783 and 828, respectively;
- (k) SEQ ID NOs: 784 and 829, respectively;
- (l) SEQ ID NOs: 785 and 830, respectively;
- (m) SEQ ID NOs: 786 and 831, respectively;
- (n) SEQ ID NOs: 787 and 832, respectively;
- (o) SEQ ID NOs: 788 and 833, respectively;
- (p) SEQ ID NOs: 789 and 834, respectively;
- (q) SEQ ID NOs: 790 and 835, respectively;
- (r) SEQ ID NOs: 791 and 836, respectively;
- (s) SEQ ID NOs: 792 and 837, respectively;
- (t) SEQ ID NOs: 793 and 838, respectively;
- (u) SEQ ID NOs: 794 and 839, respectively;
- (v) SEQ ID NOs: 795 and 840, respectively;

- (w) SEQ ID NOs: 796 and 841, respectively;
- (x) SEQ ID NOs: 797 and 842, respectively;
- (y) SEQ ID NOs: 798 and 843, respectively;
- (z) SEQ ID NOs: 799 and 844, respectively;
- 5 (aa) SEQ ID NOs: 800 and 845, respectively;
- (bb) SEQ ID NOs: 801 and 846, respectively;
- (cc) SEQ ID NOs: 802 and 847, respectively;
- (dd) SEQ ID NOs: 803 and 848, respectively; and
- (ee) SEQ ID NOs: 804 and 849, respectively.

10 **[0074]** In any of the foregoing or related aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 775 and 820, respectively;
- (b) SEQ ID NOs: 779 and 824, respectively;
- (c) SEQ ID NOs: 780 and 825, respectively;
- 15 (d) SEQ ID NOs: 782 and 827, respectively;
- (e) SEQ ID NOs: 785 and 830, respectively; and
- (f) SEQ ID NOs: 804 and 849, respectively.

[0075] In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 775 and 820, respectively. In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 779 and 824, respectively. In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 780 and 825, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 782 and 827, respectively. In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 785 and 830, respectively. In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 804 and 849, respectively.

30 **[0076]** In some aspects, the present disclosure provides a method for treating a subject having a disease, disorder or condition associated with *KHK* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, or a pharmaceutically acceptable salt thereof, wherein the sense strand and antisense strands are selected from the group consisting of:

- (a) SEQ ID NOs: 805 and 850, respectively;
- (b) SEQ ID NOs: 806 and 851, respectively;
- 35 (c) SEQ ID NOs: 807 and 852, respectively;
- (d) SEQ ID NOs: 808 and 853, respectively;
- (e) SEQ ID NOs: 809 and 854, respectively;

- (f) SEQ ID NOs: 810 and 855, respectively;
- (g) SEQ ID NOs: 811 and 856, respectively;
- (h) SEQ ID NOs: 812 and 857, respectively;
- (i) SEQ ID NOs: 813 and 858, respectively;
- 5 (j) SEQ ID NOs: 814 and 859, respectively;
- (k) SEQ ID NOs: 815 and 860, respectively;
- (l) SEQ ID NOs: 816 and 861, respectively;
- (m) SEQ ID NOs: 817 and 862, respectively and;
- (n) SEQ ID NOs: 818 and 863, respectively.

10 **[0077]** In some aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 805 and 850, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 809 and 854, respectively. In yet other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 810 and 855, respectively. In further aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 812 and 857, respectively. In other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 815 and 860, respectively. In yet other aspects, the disclosure provides an RNAi oligonucleotide wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 20 818 and 863, respectively.

[0078] In any of the foregoing or related aspects, the disease, disorder, or condition associated with *KHK* expression is non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

[0079] In any of the foregoing or related aspects, a RNAi oligonucleotide described herein is administered at a concentration of 0.01 mg/kg-5 mg/kg.

25 **[0080]** In some aspects, the disclosure provides use of any RNAi oligonucleotide or pharmaceutical composition described herein, in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with *KHK* expression, optionally for the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

30 **[0081]** In some aspects, the disclosure provides any RNAi oligonucleotide or pharmaceutical composition described herein, for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with *KHK* expression, optionally for the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

[0082] In some aspects, the disclosure provides a kit comprising any RNAi oligonucleotide described herein, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a 35 subject having a disease, disorder or condition associated with *KHK* expression.

[0083] In some aspects, the disease, disorder, or condition associated with *KHK* expression is non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

[0084] In some aspects, the disclosure provides an oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising a nucleotide sequence of 15-50 nucleotides in length, wherein the nucleotide sequence comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length, or a pharmaceutically acceptable salt thereof. In some aspects, the oligonucleotide is single stranded. In some aspects, the oligonucleotide is an antisense oligonucleotide. In some aspects, the nucleotide sequence is 15-30 nucleotides in length. In some aspects, the nucleotide sequence is 20-25 nucleotides in length. In some aspects, the nucleotide sequence is 22 nucleotides in length. In some aspects, the region of complementarity is 19 contiguous nucleotides in length. In some aspects, the region of complementarity is 20 contiguous nucleotides in length. In some aspects, the nucleotide sequence comprises at least one modification. In some aspects, the nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 879-885 and 912-938. In some aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 920. In other aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 923. In yet other aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 918. In further aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 917. In yet further aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 913. In yet further aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 936. In some aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 894. In other aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 897. In yet other aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 892. In further aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 891. In yet further aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 887. In yet further aspects, the nucleotide sequence comprises the nucleotide sequence set forth in SEQ ID NO: 909.

[0085] In some aspects, the disclosure provides a cell comprising an oligonucleotide described herein.

[0086] In some aspects, the disclosure provides a pharmaceutical composition comprising an oligonucleotide disclosed herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, delivery agent or excipient.

[0087] In some aspects, the disclosure provides a method for treating a subject having a disease, disorder or condition associated with *KHK* expression, the method comprising administering to the subject a therapeutically effective amount of an oligonucleotide or pharmaceutical composition described herein.

[0088] In some aspects, the disclosure provides a method of delivering an oligonucleotide to a subject, the method comprising administering a pharmaceutical composition described herein to the subject.

[0089] In some aspects, the disclosure provides a method for reducing *KHK* expression in a cell, a population of cells or a subject, the method comprising the step of:

i. contacting the cell or the population of cells with an oligonucleotide or a pharmaceutical composition described herein; or

ii. administering to the subject an oligonucleotide or a pharmaceutical composition described herein. In some aspects, reducing *KHK* expression comprises reducing an amount or level of *KHK* mRNA, an amount or level of *KHK* protein, or both.

[0090] In any of the foregoing or related aspects, the subject has a disease, disorder or condition associated with *KHK* expression. In some aspects, the disease, disorder, or condition associated with *KHK* expression is non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

[0091] In any of the foregoing or related aspects, the oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.

[0092] In some aspects, the disclosure provides use of an oligonucleotide or pharmaceutical composition described herein, in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with *KHK* expression, optionally for the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). In other aspects, the disclosure provides an oligonucleotide or pharmaceutical composition described herein for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with *KHK* expression, optionally for the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

[0093] In some aspects, the disclosure provides a kit comprising an oligonucleotide described herein, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with *KHK* expression.

[0094] In any of the foregoing or related aspects, the disease, disorder, or condition associated with *KHK* expression is non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

[0095] In some aspects, the disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of *KHK*, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a duplex region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a nucleotide sequence selected from SEQ ID NOs: 4-387, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a nucleotide sequence selected from SEQ ID NOs: 388-771.

[0096] In some aspects, the disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of *KHK*, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a duplex region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a nucleotide sequence selected from SEQ ID NOs: 872-878 and 886-911, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a nucleotide sequence selected from SEQ ID NOs: 879-885 and 912-938.

BRIEF DESCRIPTION OF THE DRAWINGS

[0097] FIG. 1 provides a graph depicting the percent (%) mRNA remaining in Hep3B cells (expressing endogenous human *KHK*) after 24-hour treatment with 1nM of DsiRNA targeting various regions of the *KHK* gene. 384 DsiRNAs were designed and screened. Three primer pairs were used that recognized the *KHK*-A isoform (*KHK*-F763,

NM_000221.2), *KHK-C* (KHK-825, NM_006488.3) and *KHK-All* (both isoforms) (KHK-F495, KHK-F1026, NM_006488.3). Expression was normalized between samples using HPRT and SFRS9 housekeeping genes.

[0098] FIG. 2A and FIG. 2B provide schematics of the Low-2'-Fluoro modification pattern (Low-2'-Fluoro (3PS) and Low-2'-Fluoro (2PS), respectively) applied to *KHK* mRNA targeting sequences to generate GalNAc-*KHK* constructs.

5 The sense strand includes a tetraloop structure of nucleotides 26-31 of the 36-nucleotide strand. The anti-sense strand is complementary and includes a 2-nucleotide overhang.

[0099] FIG. 3 provides a graph depicting the percent (%) remaining *KHK* mRNA in *KHK-A* and *KHK-C* HDI (hydrodynamic injection) mice treated with human/non-human primate (NHP) -conserved GalNAc-*KHK* constructs. 3 days after subcutaneous dosing of 2mg/kg of GalNAc-*KHK* constructs formulated in PBS, plasmids encoding either
10 *KHK-A* and *KHK-C* were injected into mice *via* HDI and the percent (%) of *KHK* mRNA was measured 1 day later in liver samples relative to mice treated with PBS. mRNA was measured from livers using primers recognizing *KHK-All* (up-right triangle), *KHK-C* (upside-down triangle), and *KHK-A* (hexagon). The notation "Hs, 1mm Mf" represents a human specific sequence that is one base mismatch different from monkey sequence.

[0100] FIG. 4A provides a schematic of the Med-2'-Fluoro modification pattern applied to *KHK* targeting sequence to generate GalNAc-*KHK* constructs. The sense strand includes a tetraloop structure of nucleotides 26-31 of the 36-nucleotide strand. The anti-sense strand is complementary and includes a 2-nucleotide overhang.

[0101] FIGs. 4B-4C provide graphs depicting the percent (%) *KHK* mRNA remaining after treating mice with GalNAc-*KHK* constructs having the Med-2'-Fluoro modification pattern. 3 days after subcutaneous dosing of 2mg/kg of GalNAc-*KHK* constructs formulated in PBS, plasmid encoding *KHK-C* was injected into mice *via* HDI and the
20 percent (%) of *KHK* mRNA was measured 1 day later in liver samples relative to mice treated with PBS. mRNA was measured using primers identifying both *KHK-A* and *KHK-C* isoforms (i.e., *KHK-All*) (**FIG. 4B**) and primers identifying only the *KHK-C* isoform (**FIG. 4C**). Multiple GalNAc-*KHK* constructs were combined in a "mixed" group at 2mg/kg for a total 10mg/kg treatment (KHK-0861, -0865, -0882, -0883, -0885) as a positive knock-down control. The notation "Hs, 1mm Mf" and the like represents a human specific sequence that is one base mismatch different from monkey
25 sequence.

[0102] FIG. 4D provides a graph depicting the percent (%) *KHK* mRNA remaining after treating mice with different GalNAc-*KHK* constructs having the Med-2'-Fluoro modification pattern. 3 days after subcutaneous dosing of 2mg/kg of GalNAc-*KHK* constructs formulated in PBS, plasmids encoding *KHK-C* were injected into mice *via* HDI and the percent (%) of *KHK* mRNA was measured 1 day later in liver samples relative to mice treated with PBS. mRNA was
30 measured using primers (MmKHK-ALL-5-6, Forward: GCTCTTCCAGTTGTTAGCTATGGT (SEQ ID NO: 939), Reverse: CAGGTGCTTGGCCACATCTT (SEQ ID NO:940), Probe: AGGTGGTGTGTCAGC (SEQ ID NO: 941)) identifying only mouse KHK. Remaining mRNA was normalized to a PBS control. Multiple GalNAc-*KHK* constructs were combined in a "mixed" group as a positive knock-down control.

[0103] FIG. 4E provides a graph depicting the difference in percent (%) *KHK* mRNA remaining after treatment with GalNAc-*KHK* constructs with different modification patterns (Low-2'F (**FIG. 2A and FIG. 2B**) and Med-2'F (**FIG. 4A**)).
35 Remaining mRNA was normalized to a PBS control. Multiple GalNAc-*KHK* constructs were combined in a "mixed" group as a positive knock-down control.

[0104] FIG. 5 provides a graph depicting the difference in percent (%) *KHK* mRNA remaining after treating mice with GalNAc-*KHK* constructs. 3 days after subcutaneous dosing of 2mg/kg of GalNAc-*KHK* constructs formulated in PBS, plasmid encoding *KHK-C* (NM_006488) (pCMV6-*KHK-C*, Cat#: RC223488, OriGene) was injected into mice via HDI and the percent (%) of *KHK* mRNA remaining was measured 1 day later in liver samples relative to mice treated with PBS. Results include mRNA measured from primers for *KHK-All* (up-right triangle), and *KHK-C* (upside-down triangle). Grey arrow shows 30mg/kg treatment of *KHK-885* has more than 98% knockdown.

[0105] FIGs. 6A-6B provide graphs depicting the percent (%) *KHK* mRNA remaining after treating *KHK-C* plasmid HDI mice (as described in **FIG. 5**) with different GalNAc-*KHK* constructs. mRNA was measured using primers identifying both *KHK-A* and *KHK-C* isoforms (*KHK-All*; **FIG. 6A**) and primers identifying only the *KHK-C* isoform (**FIG. 6B**).

[0106] FIG. 6C provides a graph depicting the percent (%) *KHK* mRNA remaining in the liver after treating *KHK-C* plasmid HDI mice (as described in **FIG. 5**) with different GalNAc-*KHK* constructs. mRNA was measured using primers identifying only mouse *KHK*.

[0107] FIGs. 7A-7C provide graphs depicting the percent (%) *KHK* mRNA remaining in liver biopsies from non-human primates (NHP) 28 days (**FIG. 7A**), 56 days (**FIG. 7B**), and 84 days (**FIG. 7C**) after a single dose of specified GalNAc-constructs. NHP were subcutaneously injected with 6 mg/kg of GalNAc-*KHK* on Study Day 0. The percent indicated is the average reduction in *KHK*-mRNA compared to a PBS control.

[0108] FIG. 7D provides a line graph demonstrating the changes in *KHK* mRNA in liver biopsies taken at various time points from NHP (as treated in **FIGs. 7A-7C**) after a single dose of GalNAc-*KHK* constructs.

[0109] FIGs. 8A-8C provide graphs depicting the percent (%) *KHK* protein remaining in liver biopsies from non-human primates (NHP) 28 days (**FIG. 8A**), 56 days (**FIG. 8B**), and 84 days (**FIG. 8C**) after treatment. NHP were treated as in **FIGs. 7A-7C**. The percent indicated is the average reduction in *KHK*-protein compared to a PBS control.

[0110] FIG. 8D provides a line graph demonstrating the changes in *KHK* protein in liver biopsies taken at various time points from NHP (as treated in **FIGs. 7A-7C**) after a single dose of GalNAc-*KHK* constructs.

[0111] FIGs. 9A-9C provide correlation graphs demonstrating the relationship between remaining *KHK* mRNA expression and remaining *KHK* protein expression in liver biopsies from NHP treated with a single dose of GalNAc-*KHK* constructs. Correlation among all constructs is compared at days 28 (**FIG. 9A**), 56 (**FIG. 9B**), and 84 (**FIG. 9C**) after dosing. Individual dots represent individual biopsies.

DETAILED DESCRIPTION

[0112] According to some aspects, the disclosure provides oligonucleotides that reduce *KHK* expression in the liver. In some embodiments, the oligonucleotides provided herein are useful to treat diseases associated with *KHK* expression in the liver. In some respects, the disclosure provides methods of treating a disease associated with *KHK* expression by reducing *KHK* gene expression in cells (e.g., cells of the liver).

Oligonucleotide Inhibitors of *KHK* Expression

Ketohexokinase (KHK) Target Sequences

[0113] In some embodiments, the disclosure provides an oligonucleotide which is targeted to a target sequence comprising a ketohexokinase (*KHK*) mRNA. In some embodiments, the oligonucleotide, or a portion, fragment, or strand thereof (*e.g.*, an antisense strand or a guide strand of a dsRNA) binds or anneals to a target sequence comprising a *KHK* mRNA, thereby inhibiting *KHK* expression. In some embodiments, the oligonucleotide is targeted to a target sequence comprising a *KHK*-A isoform mRNA. In some embodiments, the oligonucleotide is targeted to a target sequence comprising a *KHK*-C isoform mRNA. In some embodiments, the oligonucleotide is targeted to a *KHK* target sequence for the purpose of inhibiting *KHK* expression *in vivo*. In some embodiments, the amount or extent of inhibition of *KHK* expression by an oligonucleotide targeted to a *KHK* target sequence correlates with the potency of the oligonucleotide. In some embodiments, the amount or extent of inhibition of *KHK* expression by an oligonucleotide targeted to a *KHK* target sequence correlates with the amount or extent of therapeutic benefit in a subject or patient having a disease, disorder or condition associated with the expression of *KHK* treated with the oligonucleotide.

[0114] Through examination of the nucleotide sequence of mRNAs encoding *KHK*, including mRNAs of multiple different species (*e.g.*, human, cynomolgus monkey, mouse, and rat; *see, e.g.*, Example 2) and as a result of *in vitro* and *in vivo* testing (*see, e.g.*, Examples 2-6), it has been discovered that certain nucleotide sequences of *KHK* mRNA are more amenable than others to oligonucleotide-based inhibition and are thus useful as target sequences for the oligonucleotides herein. In some embodiments, a sense strand of an oligonucleotide (*e.g.*, a dsRNA) described herein comprises a *KHK* target sequence. In some embodiments, a portion or region of the sense strand of a dsRNA described herein comprises a *KHK* target sequence. In some embodiments, a *KHK* target sequence comprises, or consists of, a sequence of any one of SEQ ID Nos: 4-387. In some embodiments, a *KHK* target sequence comprises, or consists of, nucleotides 1-19 of any one of SEQ ID Nos: 4-387. In some embodiments, a *KHK* target sequence comprises, or consists of, the sequence set forth in SEQ ID No: 39. In some embodiments, a *KHK* target sequence comprises, or consists of, nucleotides 1-19 of the sequence set forth in SEQ ID No: 39. In some embodiments, a *KHK* target sequence comprises, or consists of, the sequence set forth in SEQ ID No: 102. In some embodiments, a *KHK* target sequence comprises, or consists of, nucleotides 1-19 of the sequence set forth in SEQ ID No: 102. In some embodiments, a *KHK* target sequence comprises, or consists of, the sequence set forth in SEQ ID No: 104. In some embodiments, a *KHK* target sequence comprises, or consists of, nucleotides 1-19 of the sequence set forth in SEQ ID No: 104. In some embodiments, a *KHK* target sequence comprises, or consists of, the sequence set forth in SEQ ID No: 107. In some embodiments, a *KHK* target sequence comprises, or consists of, nucleotides 1-19 of the sequence set forth in SEQ ID No: 107. In some embodiments, a *KHK* target sequence comprises, or consists of, the sequence set forth in SEQ ID No: 191. In some embodiments, a *KHK* target sequence comprises, or consists of, nucleotides 1-19 of the sequence set forth in SEQ ID No: 191. In some embodiments, a *KHK* target sequence comprises, or consists of, the sequence set forth in SEQ ID No: 269. In some embodiments, a *KHK* target sequence comprises, or consists of, nucleotides 1-19 of the sequence set forth in SEQ ID No: 269.

KHK Targeting Sequences

[0115] In some embodiments, the oligonucleotides herein have regions of complementarity to *KHK* mRNA (e.g., within a target sequence of *KHK* mRNA) for purposes of targeting the mRNA in cells and inhibiting its expression. In some embodiments, the oligonucleotides herein comprise a *KHK* targeting sequence (e.g., an antisense strand or a guide strand of a dsRNA) having a region of complementarity that binds or anneals to a *KHK* target sequence by complementary (Watson-Crick) base pairing. The targeting sequence or region of complementarity is generally of a suitable length and base content to enable binding or annealing of the oligonucleotide (or a strand thereof) to a *KHK* mRNA for purposes of inhibiting its expression. In some embodiments, the targeting sequence or region of complementarity is at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 28, at least about 29 or at least about 30 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is about 12 to about 30 (e.g., 12 to 30, 12 to 22, 15 to 25, 17 to 21, 18 to 27, 19 to 27, or 15 to 30) nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 18 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 19 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 20 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 21 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 22 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 23 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 24 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 4-387, and the targeting sequence or region of complementarity is 18 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 4-387, and the targeting sequence or region of complementarity is 19 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 4-387, and the targeting sequence or region of complementarity is 20 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 4-387, and the targeting sequence or region of complementarity is 21 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 4-387, and the targeting sequence or region of complementarity is 22 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 4-387, and the targeting sequence or region of complementarity is 23 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 4-387, and the targeting sequence or region of complementarity is 24 nucleotides in length.

[0116] In some embodiments, an oligonucleotide herein comprises a targeting sequence or a region of complementarity (e.g., an antisense strand or a guide strand of a double-stranded oligonucleotide) that is fully complementary to a *KHK* target sequence. In some embodiments, the targeting sequence or region of complementarity is partially complementary to a *KHK* target sequence. In some embodiments, the targeting sequence or region of complementarity has up to 3 nucleotide mismatches to a *KHK* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of *KHK*. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of *KHK*. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of any one of SEQ ID NOs: 4-387.

In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of *KHK*. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to nucleotides 1-19 of a sequence of any one of SEQ ID NOs: 4-387. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to the sequence set forth in SEQ ID NO: 39. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 39. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to the sequence set forth in SEQ ID NO: 102. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 102. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to the sequence set forth in SEQ ID NO: 104. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 104. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to the sequence set forth in SEQ ID NO: 107. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 107. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to the sequence set forth in SEQ ID NO: 191. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 191. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to the sequence set forth in SEQ ID NO: 269. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 269. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of any one of SEQ ID NOs: 4-387. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to nucleotides 1-19 of a sequence of any one of SEQ ID NOs: 4-387. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to the sequence set forth in SEQ ID NO: 39. In some embodiments, the oligonucleotide comprises a targeting sequence or

region of complementarity that is partially complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 39. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to the sequence set forth in SEQ ID NO: 102. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 102. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to the sequence set forth in SEQ ID NO: 104. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 104. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to the sequence set forth in SEQ ID NO: 107. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 107. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to the sequence set forth in SEQ ID NO: 191. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 191. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to the sequence set forth in SEQ ID NO: 269. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to nucleotides 1-19 of the sequence set forth in SEQ ID NO: 269. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of any one of SEQ ID NOs: 872-878 and 886-911. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of any one of SEQ ID NOs: 872-878 and 886-911. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of any one of SEQ ID NOs: 887, 891, 892, 894, 897 and 909. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of any one of SEQ ID NOs: 887, 891, 892, 894, 897 and 909.

[0117] In some embodiments, the oligonucleotide herein comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a *KHK* mRNA, wherein the contiguous sequence of nucleotides is about 12 to about 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 28, 12 to 26, 12 to 24, 12 to 20, 12 to 18, 12 to 16, 14 to 22, 16 to 20, 18 to 20 or 18 to 19 nucleotides in length). In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a *KHK* mRNA, wherein the contiguous sequence of nucleotides is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a *KHK* mRNA, wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a *KHK* mRNA, wherein the contiguous sequence of nucleotides is 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence

or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387, optionally wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387, wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387, wherein the contiguous sequence of nucleotides is 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 872-878 and 886-911, optionally wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 872-878 and 886-911, wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 872-878 and 886-911, wherein the contiguous sequence of nucleotides is 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909, optionally wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909, wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909, wherein the contiguous sequence of nucleotides is 20 nucleotides in length.

[0118] In some embodiments, a targeting sequence or region of complementarity of an oligonucleotide is provided that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 4-387 and spans the entire length of an antisense strand. In some embodiments, a targeting sequence or region of complementarity of an oligonucleotide is provided that is complementary to contiguous nucleotides of nucleotides 1-19 a sequence as set forth in any one of SEQ ID NOs: 4-387 and spans the entire length of an antisense strand. In some embodiments, a region of complementarity of an oligonucleotide is provided that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 4-387 and spans a portion of the entire length of an antisense strand. In some embodiments, a region of complementarity of an oligonucleotide is provided that is complementary to contiguous nucleotides of nucleotides 1-19 a sequence as set forth in any one of SEQ ID NOs: 4-387 and spans a portion of the entire length of an antisense strand. In some embodiments, an oligonucleotide herein comprises a region of complementarity (e.g., on an antisense strand of a dsRNA) that is at least partially (e.g., fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-19 of a sequence as set forth in any one of SEQ ID NOs: 4-387. In some embodiments, an oligonucleotide herein comprises a region of complementarity (e.g., on an antisense strand of a dsRNA) that is at least partially (e.g., fully) complementary to a contiguous stretch of

nucleotides spanning nucleotides 1-20 of a sequence as set forth in any one of SEQ ID NOs: 4-387. In some embodiments, a targeting sequence or region of complementarity of an oligonucleotide is provided that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 872-878 and 886-911 and spans the entire length of an antisense strand. In some embodiments, a region of complementarity of an oligonucleotide that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 872-878 and 886-911 and spans a portion of the entire length of an antisense strand. In some embodiments, an oligonucleotide herein comprises a region of complementarity (e.g., on an antisense strand of a dsRNA) that is at least partially (e.g., fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-19 of a sequence as set forth in any one of SEQ ID NOs: 872-878 and 886-911. In some embodiments, an oligonucleotide herein comprises a region of complementarity (e.g., on an antisense strand of a dsRNA) that is at least partially (e.g., fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-20 of a sequence as set forth in any one of SEQ ID NOs: 872-878 and 886-911. In some embodiments, a targeting sequence or region of complementarity of an oligonucleotide is provided that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909 and spans the entire length of an antisense strand. In some embodiments, a region of complementarity of an oligonucleotide is provided that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909 and spans a portion of the entire length of an antisense strand. In some embodiments, an oligonucleotide herein comprises a region of complementarity (e.g., on an antisense strand of a dsRNA) that is at least partially (e.g., fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-19 of a sequence as set forth in any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909. In some embodiments, an oligonucleotide herein comprises a region of complementarity (e.g., on an antisense strand of a dsRNA) that is at least partially (e.g., fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-20 of a sequence as set forth in any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909.

[0119] In some embodiments, an oligonucleotide herein comprises a targeting sequence or region of complementarity having one or more base pair (bp) mismatches with the corresponding *KHK* target sequence. In some embodiments, the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *KHK* target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the *KHK* mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to inhibit *KHK* expression is maintained. Alternatively, the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *KHK* target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the *KHK* mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to inhibit *KHK* expression is maintained. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 1 mismatch with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 2 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 3 mismatches with the

corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 4 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 5 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having more than one mismatch (e.g., 2, 3, 4, 5 or more mismatches) with the corresponding target sequence, wherein at least 2 (e.g., all) of the mismatches are positioned consecutively (e.g., 2, 3, 4, 5 or more mismatches in a row), or wherein the mismatches are interspersed throughout the targeting sequence or region of complementarity. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having more than one mismatch (e.g., 2, 3, 4, 5 or more mismatches) with the corresponding target sequence, wherein at least 2 (e.g., all) of the mismatches are positioned consecutively (e.g., 2, 3, 4, 5 or more mismatches in a row), or wherein at least one or more non-mismatched base pair is located between the mismatches, or a combination thereof. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387, wherein the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *KHK* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of nucleotides 1-19 of any one of SEQ ID NOs: 4-387, wherein the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *KHK* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387, wherein the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *KHK* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of nucleotides 1-19 of any one of SEQ ID NOs: 4-387, wherein the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *KHK* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 872-878 and 886-911, wherein the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *KHK* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 872-878 and 886-911, wherein the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *KHK* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909, wherein the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *KHK* target

sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909, wherein the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *KHK* target sequence.

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Types of Oligonucleotides

[0120] A variety of oligonucleotide types and/or structures are useful for targeting *KHK* in the methods herein including, but not limited to, RNAi oligonucleotides, antisense oligonucleotides, miRNAs, *etc.* Any of the oligonucleotide types described herein or elsewhere are contemplated for use as a framework to incorporate a *KHK* targeting sequence herein for the purposes of inhibiting *KHK* expression.

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[0121] In some embodiments, the oligonucleotides herein inhibit *KHK* expression by engaging with RNA interference (RNAi) pathways upstream or downstream of Dicer involvement. For example, RNAi oligonucleotides have been developed with each strand having sizes of about 19-25 nucleotides with at least one 3' overhang of 1 to 5 nucleotides (see, *e.g.*, US Patent No. 8,372,968). Longer oligonucleotides also have been developed that are processed by Dicer to generate active RNAi products (see, *e.g.*, US Patent No. 8,883,996). Further work produced extended dsRNAs where at least one end of at least one strand is extended beyond a duplex targeting region, including structures where one of the strands includes a thermodynamically stabilizing tetraloop structure (see, *e.g.*, US Patent Nos. 8,513,207 and 8,927,705, as well as Intl. Patent Application Publication No. WO 2010/033225). Such structures may include single-stranded (ss) extensions (on one or both sides of the molecule) as well as double-stranded (ds) extensions.

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[0122] In some embodiments, the oligonucleotides herein engage with the RNAi pathway downstream of the involvement of Dicer (*e.g.*, Dicer cleavage). In some embodiments, the oligonucleotides described herein are Dicer substrates. In some embodiments, upon endogenous Dicer processing, double-stranded nucleic acids of 19-23 nucleotides in length capable of reducing *KHK* expression are produced. In some embodiments, the oligonucleotide has an overhang (*e.g.*, of 1, 2, or 3 nucleotides in length) in the 3' end of the sense strand. In some embodiments, the oligonucleotide has an overhang (*e.g.*, of 1, 2, or 3 nucleotides in length) in the 3' end of the antisense strand. In some embodiments, the oligonucleotide (*e.g.*, siRNA) comprises a 21-nucleotide guide strand that is antisense to a target RNA and a complementary passenger strand, in which both strands anneal to form a 19-bp duplex and 2 nucleotide overhangs at either or both 3' ends. Longer oligonucleotide designs also are available including oligonucleotides having a guide strand of 23 nucleotides and a passenger strand of 21 nucleotides, where there is a blunt end on the right side of the molecule (3' end of passenger strand/5' end of guide strand) and a two nucleotide 3'-guide strand overhang on the left side of the molecule (5' end of the passenger strand/3' end of the guide strand). In such molecules, there is a 21 bp duplex region. See, *e.g.*, US Patent Nos. 9,012,138; 9,012,621 and 9,193,753.

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[0123] In some embodiments, the oligonucleotides herein comprise sense and antisense strands that are both in the range of about 17 to 36 (*e.g.*, 17 to 36, 20 to 25 or 21-23) nucleotides in length. In some embodiments, the oligonucleotides described herein comprise an antisense strand of 19-30 nucleotides in length and a sense strand of 19-50 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric

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duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand. In some embodiments, an oligonucleotide herein comprises a sense and antisense strand that are both in the range of about 19-22 nucleotides in length. In some embodiments, the sense and antisense strands are of equal length. In some embodiments, an oligonucleotide comprises sense and antisense strands, such that there is a 3'-overhang on either the sense strand or the antisense strand, or both the sense and antisense strand. In some embodiments, for oligonucleotides that have sense and antisense strands that are both in the range of about 21-23 nucleotides in length, a 3' overhang on the sense, antisense, or both sense and antisense strands is 1 or 2 nucleotides in length. In some embodiments, the oligonucleotide has a guide strand of 22 nucleotides and a passenger strand of 20 nucleotides, where there is a blunt end on the right side of the molecule (3' end of passenger strand/5' end of guide strand) and a 2 nucleotide 3'-guide strand overhang on the left side of the molecule (5' end of the passenger strand/3' end of the guide strand). In such molecules, there is a 20 bp duplex region.

[0124] Other oligonucleotide designs for use with the compositions and methods herein include: 16-mer siRNAs (see, e.g., NUCLEIC ACIDS IN CHEMISTRY AND BIOLOGY. Blackburn (ed.), Royal Society of Chemistry, 2006), shRNAs (e.g., having 19 bp or shorter stems; see, e.g., Moore *et al.* (2010) METHODS MOL. BIOL. 629:139-156), blunt siRNAs (e.g., of 19 bps in length; see, e.g., Kraynack & Baker (2006) RNA 12:163-176), asymmetrical siRNAs (aiRNA; see, e.g., Sun *et al.* (2008) NAT. BIOTECHNOL. 26:1379-1382), asymmetric shorter-duplex siRNA (see, e.g., Chang *et al.* (2009) MOL. THER. 17:725-32), fork siRNAs (see, e.g., Hohjoh (2004) FEBS LETT. 557:193-198), ss siRNAs (Elsner (2012) NAT. BIOTECHNOL. 30:1063), dumbbell-shaped circular siRNAs (see, e.g., Abe *et al.* (2007) J. AM. CHEM. SOC. 129:15108-09), and small internally segmented interfering RNA (siRNA; see, e.g., Bramsen *et al.* (2007) NUCLEIC ACIDS RES. 35:5886-97). Further non-limiting examples of an oligonucleotide structures that may be used in some embodiments to reduce or inhibit the expression of *KHK* are microRNA (miRNA), short hairpin RNA (shRNA) and short siRNA (see, e.g., Hamilton *et al.* (2002) EMBO J. 21:4671-79; see also, US Patent Application Publication No. 2009/0099115).

[0125] Still, in some embodiments, an oligonucleotide for reducing or inhibiting *KHK* expression herein is single-stranded (ss). Such structures may include but are not limited to single-stranded RNAi molecules. Recent efforts have demonstrated the activity of ss RNAi molecules (see, e.g., Matsui *et al.* (2016) MOL. THER. 24:946-955). However, in some embodiments, oligonucleotides herein are antisense oligonucleotides (ASOs). An antisense oligonucleotide is a single-stranded oligonucleotide that has a nucleobase sequence which, when written in the 5' to 3' direction, comprises the reverse complement of a targeted segment of a particular nucleic acid and is suitably modified (e.g., as a gapmer) so as to induce RNaseH-mediated cleavage of its target RNA in cells or (e.g., as a mixer) so as to inhibit translation of the target mRNA in cells. ASOs for use herein may be modified in any suitable manner known in the art including, for example, as shown in US Patent No. 9,567,587 (including, e.g., length, sugar moieties of the nucleobase (pyrimidine, purine), and alterations of the heterocyclic portion of the nucleobase). Further, ASOs have been used for decades to reduce expression of specific target genes (see, e.g., Bennett *et al.* (2017) ANNU. REV. PHARMACOL. 57:81-105).

[0126] In some embodiments, the antisense oligonucleotide shares a region of complementarity with *KHK* mRNA. In some embodiments, the antisense oligonucleotide targets SEQ ID NO: 1. In some embodiments, the antisense

oligonucleotide targets SEQ ID NO: 2. In some embodiments, the antisense oligonucleotide targets SEQ ID NO: 3. In some embodiments, the antisense oligonucleotide is 15-50 nucleotides in length. In some embodiments, the antisense oligonucleotide is 15-25 nucleotides in length. In some embodiments, the antisense oligonucleotide is 22 nucleotides in length. In some embodiments, the antisense oligonucleotide is complementary to any one of SEQ ID NOs: 4-387.

5 In some embodiments, the antisense oligonucleotide is complementary to nucleotides 1-19 of any one of SEQ ID NOs: 4-387. In some embodiments, the antisense oligonucleotide is at least 15 contiguous nucleotides in length. In some embodiments, the antisense oligonucleotide is at least 19 contiguous nucleotides in length. In some embodiments, the antisense oligonucleotide is at least 20 contiguous nucleotides in length. In some embodiments, the antisense oligonucleotide differs by 1, 2, or 3 nucleotides from the target sequence.

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Double-Stranded Oligonucleotides

[0127] In some aspects, the disclosure provides double-stranded (ds) RNAi oligonucleotides for targeting *KHK* mRNA and inhibiting *KHK* expression (e.g., via the RNAi pathway) comprising a sense strand (also referred to herein as a passenger strand) and an antisense strand (also referred to herein as a guide strand). In some embodiments,

15 the sense strand and antisense strand are separate strands and are not covalently linked. In some embodiments, the sense strand and antisense strand are covalently linked. In some embodiments, the sense strand and antisense strand form a duplex region, wherein the sense strand and antisense strand, or a portion thereof, binds with one another in a complementary fashion (e.g., by Watson-Crick base pairing).

[0128] In some embodiments, the sense strand has a first region (R1) and a second region (R2), wherein R2 comprises a first subregion (S1), a tetraloop (L) or triloop (triL), and a second subregion (S2), wherein L or triL is located between S1 and S2, and wherein S1 and S2 form a second duplex (D2). D2 may have various length. In some

20 embodiments, D2 is about 1-6 bp in length. In some embodiments, D2 is 2-6, 3-6, 4-6, 5-6, 1-5, 2-5, 3-5 or 4-5 bp in length. In some embodiments, D2 is 1, 2, 3, 4, 5 or 6 bp in length. In some embodiments, D2 is 6 bp in length.

[0129] In some embodiments, R1 of the sense strand and the antisense strand form a first duplex (D1). In some

25 embodiments, D1 is at least about 15 (e.g., at least 15, at least 16, at least 17, at least 18, at least 19, at least 20 or at least 21) nucleotides in length. In some embodiments, D1 is in the range of about 12 to 30 nucleotides in length (e.g., 12 to 30, 12 to 27, 15 to 22, 18 to 22, 18 to 25, 18 to 27, 18 to 30 or 21 to 30 nucleotides in length). In some embodiments, D1 is at least 12 nucleotides in length (e.g., at least 12, at least 15, at least 20, at least 25, or at least 30 nucleotides in length). In some embodiments, D1 is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27,

30 28, 29 or 30 nucleotides in length. In some embodiments, D1 is 20 nucleotides in length. In some embodiments, D1 comprising sense strand and antisense strand does not span the entire length of the sense strand and/or antisense strand. In some embodiments, D1 comprising the sense strand and antisense strand spans the entire length of either the sense strand or antisense strand or both. In certain embodiments, D1 comprising the sense strand and antisense strand spans the entire length of both the sense strand and the antisense strand.

[0130] In some embodiments, a dsRNAi provided herein comprises a sense strand having a sequence of any one of SEQ ID NOs: 4-387; and an antisense strand comprising a complementary sequence selected from SEQ ID NOs: 388-771 as is arranged **Table 2**.

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[0131] In some embodiments, a dsRNAi oligonucleotide comprises a sense strand and an antisense strand comprising nucleotide sequences selected from:

- (a) SEQ ID NOs: 886 and 912, respectively;
- (b) SEQ ID NOs: 887 and 913, respectively;
- 5 (c) SEQ ID NOs: 910 and 937, respectively;
- (d) SEQ ID NOs: 888 and 914, respectively;
- (e) SEQ ID NOs: 889 and 915, respectively;
- (f) SEQ ID NOs: 890 and 916, respectively;
- (g) SEQ ID NOs: 891 and 917, respectively;
- 10 (h) SEQ ID NOs: 877 and 884, respectively;
- (i) SEQ ID NOs: 878 and 930, respectively;
- (j) SEQ ID NOs: 876 and 883, respectively;
- (k) SEQ ID NOs: 875 and 882, respectively;
- (l) SEQ ID NOs: 892 and 918, respectively;
- 15 (m) SEQ ID NOs: 893 and 919, respectively;
- (n) SEQ ID NOs: 894 and 920, respectively;
- (o) SEQ ID NOs: 904 and 931, respectively;
- (p) SEQ ID NOs: 895 and 921, respectively;
- (q) SEQ ID NOs: 905 and 932, respectively;
- 20 (r) SEQ ID NOs: 896 and 922, respectively;
- (s) SEQ ID NOs: 911 and 938, respectively;
- (t) SEQ ID NOs: 906 and 933, respectively;
- (u) SEQ ID NOs: 897 and 923, respectively;
- (v) SEQ ID NOs: 907 and 934, respectively;
- 25 (w) SEQ ID NOs: 908 and 935, respectively;
- (x) SEQ ID NOs: 903 and 929, respectively;
- (y) SEQ ID NOs: 901 and 927, respectively;
- (z) SEQ ID NOs: 874 and 881, respectively;
- (aa) SEQ ID NOs: 902 and 928, respectively;
- 30 (bb) SEQ ID NOs: 873 and 880, respectively;
- (cc) SEQ ID NOs: 872 and 879, respectively;
- (dd) SEQ ID NOs: 898 and 924, respectively;
- (ee) SEQ ID NOs: 899 and 925, respectively;
- (ff) SEQ ID NOs: 900 and 926, respectively; and
- 35 (gg) SEQ ID NOs: 909 and 936, respectively.

[0132] In some embodiments, a dsRNAi oligonucleotide comprises a sense strand and an antisense strand comprising nucleotide sequences selected from:

- (a) SEQ ID NOs: 887 and 913, respectively;
- (b) SEQ ID NOs: 891 and 917, respectively;
- (c) SEQ ID NOs: 892 and 918, respectively;
- (d) SEQ ID NOs: 894 and 920, respectively;
- 5 (e) SEQ ID NOs: 897 and 923, respectively; and
- (f) SEQ ID NOs: 909 and 936, respectively.

[0133] In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 887 and the antisense strand comprises the sequence of SEQ ID NO: 913. In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 891 and the antisense strand comprises the sequence of SEQ ID NO: 917. In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 892 and the antisense strand comprises the sequence of SEQ ID NO: 918. In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 894 and the antisense strand comprises the sequence of SEQ ID NO: 920. In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 897 and the antisense strand comprises the sequence of SEQ ID NO: 923. In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 909 and the antisense strand comprises the sequence of SEQ ID NO: 936.

[0134] It should be appreciated that, in some embodiments, sequences presented in the Sequence Listing may be referred to in describing the structure of an oligonucleotide (e.g., a dsRNAi oligonucleotide) or other nucleic acid. In such embodiments, the actual oligonucleotide or other nucleic acid may have one or more alternative nucleotides (e.g., an RNA counterpart of a DNA nucleotide or a DNA counterpart of an RNA nucleotide) and/or one or more modified nucleotides and/or one or more modified internucleotide linkages and/or one or more other modification when compared with the specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

[0135] In some embodiments, a dsRNAi oligonucleotide herein comprises a 25-nucleotide sense strand and a 27-nucleotide antisense strand that when acted upon by a Dicer enzyme results in an antisense strand that is incorporated into the mature RISC. In some embodiments, the sense strand of the dsRNA is longer than 27 nucleotides (e.g., 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 nucleotides). In some embodiments, the sense strand of the dsRNA is longer than 25 nucleotides (e.g., 26, 27, 28, 29 or 30 nucleotides). In some embodiments, the sense strand of the dsRNA comprises a nucleotide sequence selected from SEQ ID NOs: 4-387, wherein the nucleotide sequence is longer than 27 nucleotides (e.g., 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 nucleotides). In some embodiments, the sense strand of the dsRNA comprises a nucleotide sequence selected from SEQ ID NOs: 4-387, wherein the nucleotide sequence is longer than 25 nucleotides (e.g., 26, 27, 28, 29 or 30 nucleotides).

[0136] In some embodiments, oligonucleotides herein have one 5' end that is thermodynamically less stable when compared to the other 5' end. In some embodiments, an asymmetric oligonucleotide is provided that includes a blunt end at the 3' end of a sense strand and a 3'-overhang at the 3' end of an antisense strand. In some embodiments, the 3'-overhang on the antisense strand is about 1-8 nucleotides in length (e.g., 1, 2, 3, 4, 5, 6, 7 or 8 nucleotides in length). Typically, a dsRNAi oligonucleotide has a two-nucleotide overhang on the 3' end of the antisense (guide) strand.

However, other overhangs are possible. In some embodiments, an overhang is a 3'-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides. However, in some embodiments, the overhang is a 5'-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387, and a 5'-overhang comprising a length of between 1 and 6 nucleotides. In some embodiments, the oligonucleotide comprises a sense strand comprising a nucleotide sequence selected from SEQ ID NOs: 4-387, wherein the oligonucleotide comprises a 5'-overhang comprising a length of between 1 and 6 nucleotides. In some embodiments, the oligonucleotide comprises an antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 388-771, wherein the oligonucleotide comprises a 5'-overhang comprising a length of between 1 and 6 nucleotides. In some embodiments, the oligonucleotide comprises a sense strand comprising a nucleotide sequence selected from SEQ ID NOs: 4-387 and antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 388-771, wherein the oligonucleotide comprises a 5'-overhang comprising a length of between 1 and 6 nucleotides.

[0137] In some embodiments, two terminal nucleotides on the 3' end of an antisense strand are modified. In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand are complementary with the target mRNA (e.g., *KHK* mRNA). In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand are not complementary with the target mRNA. In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand of a dsRNAi oligonucleotide herein are unpaired. In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand of a dsRNAi oligonucleotide herein comprise an unpaired GG. In some embodiments, the two terminal nucleotides on the 3' end of an antisense strand of a dsRNAi oligonucleotide herein are not complementary to the target mRNA. In some embodiments, two terminal nucleotides on each 3' end of a dsRNAi oligonucleotide are GG. Typically, one or both of the two terminal GG nucleotides on each 3' end of a double-stranded oligonucleotide is not complementary with the target mRNA. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387, wherein the two terminal nucleotides on the 3' end of the antisense strand of a dsRNAi oligonucleotide herein comprise an unpaired GG. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of nucleotides 1-19 of any one of SEQ ID NOs: 4-387, wherein the two terminal nucleotides on the 3' end of the antisense strand of a dsRNAi oligonucleotide herein comprise an unpaired GG. In some embodiments, the oligonucleotide comprises an antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 388-771, wherein the two terminal nucleotides on the 3' end of the antisense strand of a dsRNAi oligonucleotide herein comprise an unpaired GG. In some embodiments, the oligonucleotide comprises a sense strand comprising a nucleotide sequence selected from SEQ ID NOs: 4-387 and antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 388-771, wherein the two terminal nucleotides on the 3' end of the antisense strand of a dsRNAi oligonucleotide herein comprise an unpaired GG.

[0138] In some embodiments, there is one or more (e.g., 1, 2, 3, 4 or 5) mismatch(es) between a sense and antisense strand. If there is more than one mismatch between a sense and antisense strand, they may be positioned consecutively (e.g., 2, 3 or more in a row), or interspersed throughout the region of complementarity. In some embodiments, the 3' end of the sense strand contains one or more mismatches. In some embodiments, two mismatches are incorporated at the 3' end of the sense strand. In some embodiments, base mismatches, or destabilization of segments at the 3' end of the sense strand of the dsRNAi oligonucleotide improves or increases the potency of the dsRNAi oligonucleotide. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein there is one or more (e.g., 1, 2, 3, 4 or 5) mismatch(es) between the sense and antisense strands.

Antisense Strands

[0139] In some embodiments, an antisense strand of a dsRNAi oligonucleotide is referred to as a "guide strand." For example, an antisense strand that engages with RNA-induced silencing complex (RISC) and binds to an *Argonaute* protein such as Ago2, or engages with or binds to one or more similar factors, and directs silencing of a target gene, as the antisense strand is referred to as a guide strand. In some embodiments, a sense strand complementary to a guide strand may be referred to as a "passenger strand."

[0140] In some embodiments, a dsRNAi oligonucleotide herein comprises an antisense strand of up to about 50 nucleotides in length (e.g., up to 50, up to 40, up to 35, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17 or up to 12 nucleotides in length). In some embodiments, a dsRNAi oligonucleotide comprises an antisense strand of at least about 12 nucleotides in length (e.g., at least 12, at least 15, at least 19, at least 21, at least 22, at least 25, at least 27, at least 30, at least 35 or at least 38 nucleotides in length). In some embodiments, a dsRNAi oligonucleotide comprises an antisense strand in a range of about 12 to about 40 (e.g., 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 22, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40 or 32 to 40) nucleotides in length. In some embodiments, a dsRNAi oligonucleotide comprises antisense strand of 15 to 30 nucleotides in length. In some embodiments, an antisense strand of any one of the dsRNAi oligonucleotides disclosed herein is of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 nucleotides in length. In some embodiments, a dsRNAi oligonucleotide comprises an antisense strand of 22 nucleotides in length.

[0141] In some embodiments, a dsRNAi oligonucleotide disclosed herein for targeting *KHK* comprises an antisense strand comprising or consisting of a sequence as set forth in any one of SEQ ID NOs: 388-771. In some embodiments, a dsRNAi oligonucleotide herein comprises an antisense strand comprising at least about 12 (e.g., at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at

least 22 or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 388-771. In some embodiments, a dsRNAi oligonucleotide disclosed herein for targeting *KHK* comprises an antisense strand comprising or consisting of a sequence as set forth in any one of SEQ ID NOs: 879-885 and 912-938. In some embodiments, a dsRNAi oligonucleotide herein comprises an antisense strand comprising at least about 12 (e.g., at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 879-885 and 912-938. In some embodiments, a dsRNAi oligonucleotide disclosed herein for targeting *KHK* comprises an antisense strand comprising or consisting of a sequence as set forth in any one of SEQ ID NOs: 913, 917, 918, 920, 923 and 936. In some embodiments, a dsRNAi oligonucleotide herein comprises an antisense strand comprising at least about 12 (e.g., at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 913, 917, 918, 920, 923 and 936.

[0142] In some embodiments, a dsRNAi oligonucleotide herein comprises an antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 948-953.

Sense Strands

[0143] In some embodiments, a dsRNAi oligonucleotide disclosed herein for targeting *KHK* mRNA and inhibiting *KHK* expression comprises a sense strand sequence as set forth in any one of SEQ ID NOs: 4-387. In some embodiments, a dsRNAi oligonucleotide has a sense strand that comprises at least about 12 (e.g., at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 4-387. In some embodiments, a dsRNAi oligonucleotide disclosed herein for targeting *KHK* mRNA and inhibiting *KHK* expression comprises a sense strand sequence as set forth in any one of SEQ ID NOs: 872-878 and 886-911. In some embodiments, a dsRNAi oligonucleotide has a sense strand that comprises at least about 12 (e.g., at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 872-878 and 886-911. In some embodiments, a dsRNAi oligonucleotide disclosed herein for targeting *KHK* mRNA and inhibiting *KHK* expression comprises a sense strand sequence as set forth in any one of SEQ ID NOs: 887, 891, 892, 894, 897 and 909. In some embodiments, a dsRNAi oligonucleotide has a sense strand that comprises at least about 12 (e.g., at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 887, 891, 892, 894, 897 and 909.

[0144] In some embodiments, a dsRNAi oligonucleotide herein comprises a sense strand (or passenger strand) of up to about 50 nucleotides in length (e.g., up to 50, up to 40, up to 36, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17 or up to 12 nucleotides in length). In some embodiments, a dsRNAi oligonucleotide may have a sense strand of at least about 12 nucleotides in length (e.g., at least 12, at least 15, at least 19, at least 21, at least 25, at least 27, at least 30, at least 36 or at least 38 nucleotides in length). In some embodiments, an oligonucleotide may have a sense strand in a range of about 12 to about 50 (e.g., 12 to 50, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to

36, 15 to 32, 15 to 28, 17 to 21, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40 or 32 to 40) nucleotides in length. In some embodiments, a dsRNAi oligonucleotide comprises a sense strand of 15 to 50 nucleotides in length. In some embodiments, a dsRNAi oligonucleotide comprises a sense strand of 18 to 36 nucleotides in length. In some embodiments, an oligonucleotide may have a sense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides in length. In some embodiments, a dsRNAi oligonucleotide comprises a sense strand of 36 nucleotides in length.

[0145] In some embodiments, a sense strand comprises a stem-loop structure at its 3' end. In some embodiments, the stem-loop is formed by intrastrand base pairing. In some embodiments, a sense strand comprises a stem-loop structure at its 5' end. In some embodiments, a stem is a duplex of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 nucleotides in length. In some embodiments, a stem-loop provides the dsRNAi oligonucleotide protection against degradation (e.g., enzymatic degradation), facilitates or improves targeting and/or delivery to a target cell, tissue, or organ (e.g., the liver), or both. For example, in some embodiments, the loop of a stem-loop provides nucleotides comprising one or more modifications that facilitate, improve, or increase targeting to a target mRNA (e.g., a *KHK* mRNA), inhibition of target gene expression (e.g., *KHK* expression), and/or delivery to a target cell, tissue, or organ (e.g., the liver), or a combination thereof. In some embodiments, the stem-loop itself or modification(s) to the stem-loop do not substantially affect the inherent gene expression inhibition activity of the dsRNAi oligonucleotide, but facilitates, improves, or increases stability (e.g., provides protection against degradation) and/or delivery of the oligonucleotide to a target cell, tissue, or organ (e.g., the liver). In certain embodiments, a dsRNAi oligonucleotide comprises a sense strand comprising (e.g., at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop between S1 and S2 of up to about 10 nucleotides in length (e.g., 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in length). In some embodiments, the loop (L) is 3 nucleotides in length. In some embodiments, the loop (L) is 4 nucleotides in length. In some embodiments, an oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387, and the oligonucleotide comprises a sense strand comprising (e.g., at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop between S1 and S2 of up to about 10 nucleotides in length (e.g., 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in length). In some embodiments, an oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides 1-19 of any one of SEQ ID NOs: 4-387, and the oligonucleotide comprises a sense strand comprising (e.g., at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop between S1 and S2 of up to about 10 nucleotides in length (e.g., 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in length). In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 872-878 and 886-911, and the oligonucleotide comprises a sense strand comprising (e.g., at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop between S1 and S2 of up to about 10 nucleotides in length (e.g., 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in length). In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909, and the oligonucleotide comprises a sense

strand comprising (e.g., at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop between S1 and S2 of up to about 10 nucleotides in length (e.g., 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in length).

[0146] In some embodiments, a loop (L) of a stem-loop having the structure S1-L-S2 as described above is a triloop. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387 and a triloop. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides 1-19 of any one of SEQ ID NOs: 4-387 and a triloop. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 872-878 and 886-911, and a triloop. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909, and a triloop. In some embodiments, the triloop comprises ribonucleotides, deoxyribonucleotides, modified nucleotides, delivery ligands, and combinations thereof.

[0147] In some embodiments, a loop (L) of a stem-loop having the structure S1-L-S2 as described above is a tetraloop (e.g., within a nicked tetraloop structure) comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387 and a tetraloop. In some embodiments, a loop (L) of a stem-loop having the structure S1-L-S2 as described above is a tetraloop (e.g., within a nicked tetraloop structure) comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides 1-19 of any one of SEQ ID NOs: 4-387 and a tetraloop. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 872-878 and 886-911, and a tetraloop. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 887, 891, 892, 894, 897, and 909, and a tetraloop. In some embodiments, the tetraloop comprises ribonucleotides, deoxyribonucleotides, modified nucleotides, delivery ligands, and combinations thereof.

[0148] In some embodiments, a dsRNAi oligonucleotide herein comprises a sense strand comprising a nucleotide sequence selected from SEQ ID NOs: 942-947.

Duplex Length

[0149] In some embodiments, a duplex formed between a sense and antisense strand is at least 12 (e.g., at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21) nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is in the range of 12-30 nucleotides in length (e.g., 12 to 30, 12 to 27, 12 to 22, 15 to 25, 18 to 30, 18 to 22, 18 to 25, 18 to 27, 18 to 30, 19 to 30 or 21 to 30 nucleotides in length). In some embodiments, a duplex formed between a sense and antisense strand is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand does not span the entire length of the sense strand and/or antisense

strand. In some embodiments, a duplex between a sense and antisense strand spans the entire length of either the sense or antisense strands. In some embodiments, a duplex between a sense and antisense strand spans the entire length of both the sense strand and the antisense strand. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein a duplex formed between a sense and antisense strand is in the range of 12-30 nucleotides in length (e.g., 12 to 30, 12 to 27, 12 to 22, 15 to 25, 18 to 30, 18 to 22, 18 to 25, 18 to 27, 18 to 30, 19 to 30 or 21 to 30 nucleotides in length).

Oligonucleotide Ends

[0150] In some embodiments, a dsRNAi oligonucleotide herein comprises sense and antisense strands, such that there is a 3'-overhang on either the sense strand or the antisense strand, or both the sense and antisense strand. In some embodiments, a dsRNAi oligonucleotide herein comprises sense and antisense strands that are separate strands which form an asymmetric duplex region having an overhang at the 3' terminus of the antisense strand. In some embodiments, a dsRNAi oligonucleotide provided herein has one 5' end that is thermodynamically less stable compared to the other 5' end. In some embodiments, an asymmetric dsRNAi oligonucleotide is provided that includes a blunt end at the 3' end of a sense strand and overhang at the 3' end of the antisense strand. In some embodiments, a 3' overhang on an antisense strand is 1-8 nucleotides in length (e.g., 1, 2, 3, 4, 5, 6, 7 or 8 nucleotides in length). In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the antisense strand comprises a 3' overhang of 1-8 nucleotides in length (e.g., 1, 2, 3, 4, 5, 6, 7 or 8 nucleotides in length).

[0151] Typically, an oligonucleotide for RNAi has a two (2) nucleotide overhang on the 3' end of the antisense (guide) strand. However, other overhangs are possible. In some embodiments, an overhang is a 3' overhang comprising a length of between one and six nucleotides, optionally one to five, one to four, one to three, one to two, two to six, two to five, two to four, two to three, three to six, three to five, three to four, four to six, four to five, five to six

nucleotides or one, two, three, four, five or six nucleotides. In some embodiments, the overhang is a 5' overhang comprising a length of between one and six nucleotides, optionally one to five, one to four, one to three, one to two, two to six, two to five, two to four, two to three, three to six, three to five, three to four, four to six, four to five, five to six nucleotides or one, two, three, four, five or six nucleotides. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the antisense strand comprises a 5' overhang of 1-6 nucleotides in length.

[0152] In some embodiments, one or more (e.g., 2, 3, 4) terminal nucleotides of the 3' end or 5' end of a sense and/or antisense strand are modified. For example, in some embodiments, one or two terminal nucleotides of the 3' end of the antisense strand are modified. In some embodiments, the last nucleotide at the 3' end of an antisense strand is modified, e.g., comprises 2' modification, e.g., a 2'-O-methoxyethyl. In some embodiments, the last one or two terminal nucleotides at the 3' end of an antisense strand are complementary with the target. In some embodiments, the last one or two nucleotides at the 3' end of the antisense strand are not complementary with the target.

[0153] In some embodiments, a dsRNAi oligonucleotide herein comprises a stem-loop structure at the 3' end of the sense strand and comprises two terminal overhang nucleotides at the 3' end of the antisense strand. In some embodiments, a dsRNAi oligonucleotide herein comprises a nicked tetraloop structure, wherein the 3' end of the sense strand comprises a stem-tetraloop structure and comprises two terminal overhang nucleotides at the 3' end of the antisense strand. In some embodiments, the two terminal overhang nucleotides are GG. Typically, one or both of the two terminal GG nucleotides of the antisense strand are not complementary with the target.

[0154] In some embodiments, the 5' end and/or the 3' end of a sense or antisense strand has an inverted cap nucleotide.

[0155] In some embodiments, one or more (e.g., 2, 3, 4, 5, 6) modified internucleotide linkages are provided between terminal nucleotides of the 3' end or 5' end of a sense and/or antisense strand. In some embodiments, modified internucleotide linkages are provided between overhang nucleotides at the 3' end or 5' end of a sense and/or antisense strand.

Oligonucleotide Modifications

[0156] In some embodiments, a dsRNAi oligonucleotide described herein comprises a modification. Oligonucleotides (e.g., dsRNAi oligonucleotides) may be modified in various ways to improve or control specificity, stability, delivery, bioavailability, resistance from nuclease degradation, immunogenicity, base-pairing properties, RNA distribution and cellular uptake and other features relevant to therapeutic or research use.

[0157] In some embodiments, the modification is a modified sugar. In some embodiments, the modification is a 5'-terminal phosphate group. In some embodiments, the modification is a modified internucleotide linkage. In some embodiments, the modification is a modified base. In some embodiments, an oligonucleotide described herein can comprise any one of the modifications described herein or any combination thereof. For example, in some
 5 embodiments, an oligonucleotide described herein comprises at least one modified sugar, a 5'-terminal phosphate group, at least one modified internucleotide linkage, and at least one modified base. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- 10 (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the oligonucleotide comprises at least one modified sugar, a 5'-terminal phosphate group, at least one modified
 15 internucleotide linkage, and at least one modified base.

[0158] The number of modifications on an oligonucleotide (e.g., a dsRNAi oligonucleotide) and the position of those nucleotide modifications may influence the properties of an oligonucleotide. For example, oligonucleotides may be delivered *in vivo* by conjugating them to or encompassing them in a lipid nanoparticle (LNP) or similar carrier. However, when an oligonucleotide is not protected by an LNP or similar carrier, it may be advantageous for at least
 20 some of the nucleotides to be modified. Accordingly, in some embodiments, all or substantially all the nucleotides of an oligonucleotide are modified. In some embodiments, more than half of the nucleotides are modified. In some embodiments, less than half of the nucleotides are modified. In some embodiments, the sugar moiety of all nucleotides comprising the oligonucleotide is modified at the 2' position. The modifications may be reversible or irreversible. In some embodiments, an oligonucleotide as disclosed herein has a number and type of modified nucleotides sufficient
 25 to cause the desired characteristics (e.g., protection from enzymatic degradation, capacity to target a desired cell after *in vivo* administration, and/or thermodynamic stability).

Sugar Modifications

[0159] In some embodiments, a dsRNAi oligonucleotide described herein comprises a modified sugar. In some
 30 embodiments, a modified sugar (also referred herein to a sugar analog) includes a modified deoxyribose or ribose moiety in which, for example, one or more modifications occur at the 2', 3', 4' and/or 5' carbon position of the sugar. In some embodiments, a modified sugar may also include non-natural alternative carbon structures such as those present in locked nucleic acids ("LNA"; see, e.g., Koshkin *et al.* (1998) TETRAHEDON 54:3607-30), unlocked nucleic acids ("UNA"; see, e.g., Snead *et al.* (2013) MOL. THER-NUCL. ACIDS 2:e103) and bridged nucleic acids ("BNA"; see, e.g.,
 35 Imanishi & Obika (2002) CHEM COMMUN. (CAMB) 21:1653-59).

[0160] In some embodiments, a nucleotide modification in a sugar comprises a 2'-modification. In some embodiments, a 2'-modification may be 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-fluoro (2'-F), 2'-

aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA) or 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA). In some embodiments, the modification is 2'-F, 2'-OMe or 2'-MOE. In some embodiments, a modification in a sugar comprises a modification of the sugar ring, which may comprise modification of one or more carbons of the sugar ring. For example, a modification of a sugar of a nucleotide may
 5 comprise a 2'-oxygen of a sugar is linked to a 1'-carbon or 4'-carbon of the sugar, or a 2'-oxygen is linked to the 1'-carbon or 4'-carbon *via* an ethylene or methylene bridge. In some embodiments, a modified nucleotide has an acyclic sugar that lacks a 2'-carbon to 3'-carbon bond. In some embodiments, a modified nucleotide has a thiol group, e.g., in the 4' position of the sugar.

[0161] In some embodiments, a dsRNAi oligonucleotide described herein comprises at least about 1 modified nucleotide (e.g., at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least
 10 40, at least 45, at least 50, at least 55, at least 60, or more). In some embodiments, the sense strand of the dsRNAi oligonucleotide comprises at least about 1 modified nucleotide (e.g., at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, or more). In some embodiments, the antisense strand of the dsRNAi oligonucleotide comprises at least about 1 modified nucleotide (e.g., at least 1, at least 5, at least 10, at least 15, at
 15 least 20, or more).

[0162] In some embodiments, all the nucleotides of the sense strand of the dsRNAi oligonucleotide are modified. In some embodiments, all the nucleotides of the antisense strand of the dsRNAi oligonucleotide are modified. In some embodiments, all the nucleotides of the dsRNAi oligonucleotide (*i.e.*, both the sense strand and the antisense strand) are modified. In some embodiments, the modified nucleotide comprises a 2'-modification (e.g., a 2'-F or 2'-OMe, 2'-
 20 MOE, and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid).

[0163] In some embodiments, the disclosure provides dsRNAi oligonucleotides having different modification patterns. Exemplary modification patterns are set forth in US Provisional Application No. 62/909,278 and in WO 2021/067744, both incorporated herein by this reference. In some embodiments, the modified dsRNAi oligonucleotides comprise a sense strand sequence having a modification pattern as set forth in the Examples and
 25 Sequence Listing and an antisense strand having a modification pattern as set forth in the Examples and Sequence Listing.

[0164] In some embodiments, a dsRNAi oligonucleotide disclosed herein comprises an antisense strand having nucleotides that are modified with 2'-F. In some embodiments, a dsRNAi oligonucleotide disclosed herein comprises an antisense strand comprising nucleotides that are modified with 2'-F and 2'-OMe. In some embodiments, a dsRNAi
 30 oligonucleotide disclosed herein comprises a sense strand having nucleotides that are modified with 2'-F. In some embodiments, a dsRNAi oligonucleotide disclosed herein comprises a sense strand comprising nucleotides that are modified with 2'-F and 2'-OMe.

[0165] In some embodiments, a dsRNAi oligonucleotide described herein comprises a sense strand with about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprising a 2'-fluoro modification. In
 35 some embodiments, about 11% of the nucleotides of the sense strand comprise a 2'-fluoro modification. In some embodiments, a dsRNAi oligonucleotide described herein comprises an antisense strand with about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprising a 2'-

fluoro modification. In some embodiments, about 32% of the nucleotides of the antisense strand comprise a 2'-fluoro modification. In some embodiments, the dsRNAi oligonucleotide has about 15-25%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, or 25% of its nucleotides comprising a 2'-fluoro modification. In some embodiments, about 19% of the nucleotides in the dsRNAi oligonucleotide comprise a 2'-fluoro modification.

[0166] In some embodiments, one or more of positions 8, 9, 10 or 11 of the sense strand is modified with a 2'-F group. In some embodiments, one or more of positions 3, 8, 9, 10, 12, 13 and 17 of the sense strand is modified with a 2'-F group. In some embodiments, one or more of positions 2, 3, 4, 5, 7, 10 and 14 of the antisense strand is modified with a 2'-F group. In some embodiments, one or more of positions 2, 3, 4, 5, 7, 8, 10, 14, 16 and 19 of the antisense strand is modified with a 2'-F group. In some embodiments, the sugar moiety at each of nucleotides at positions 1-7 and 12-20 in the sense strand is modified with a 2'-OMe. In some embodiments, the sugar moiety at each of nucleotides at positions 1-7, 12-27 and 31-36 in the sense strand is modified with a 2'-OMe. In some embodiments, the sugar moiety at each of nucleotides at positions 1-2, 4-7, 11, 14-16 and 18-20 in the sense strand is modified with a 2'-OMe. In some embodiments, the sugar moiety at each of nucleotides at positions 1-2, 4-7, 11, 14-16, 18-27 and 31-36 in the sense strand is modified with a 2'-OMe. In some embodiments, the sugar moiety at each of nucleotides at positions 1, 6, 8-9, 11-13, and 15-22 in the antisense strand is modified with a 2'-OMe. In some embodiments, the sugar moiety at each of nucleotides at positions 6, 9, 11-13, 15, 17, 18 and 20-22 in the antisense strand is modified with a 2'-OMe. In some embodiments, the sugar moiety at each of nucleotides at positions 1, 6, 9, 11-13, 15, 17, 18 and 20-22 in the antisense strand is modified with a 2'-OMe.

[0167] In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein one or more of positions 8, 9, 10 or 11 of the sense strand is modified with a 2'-F group.

[0168] In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein one or more of positions 3, 8, 9, 10, 12, 13 and 17 of the sense strand is modified with a 2'-F group.

[0169] In some embodiments, the antisense strand has 3 nucleotides that are modified at the 2'-position of the sugar moiety with a 2'-F. In some embodiments, the sugar moiety at positions 2, 5 and 14 and optionally up to 3 of the nucleotides at positions 1, 3, 7 and 10 of the antisense strand are modified with a 2'-F. In other embodiments, the sugar moiety at each of the positions 2, 5 and 14 of the antisense strand is modified with the 2'-F. In other
 5 embodiments, the sugar moiety at each of the positions 1, 2, 5 and 14 of the antisense strand is modified with the 2'-F. In still other embodiments, the sugar moiety at each of the positions 1, 2, 3, 5, 7 and 14 of the antisense strand is modified with the 2'-F. In yet another embodiment, the sugar moiety at each of the positions 1, 2, 3, 5, 10 and 14 of the antisense strand is modified with the 2'-F. In another embodiment, the sugar moiety at each of the positions 2, 3, 5, 7, 10 and 14 of the antisense strand is modified with the 2'-F.

[0170] In some embodiments, the antisense strand has 3 nucleotides that are modified at the 2'-position of the sugar moiety with a 2'-F. In some embodiments, the sugar moiety at positions 2, 5 and 14 and optionally up to 3 of the nucleotides at positions 3, 4, 7 and 10 of the antisense strand are modified with a 2'-F. In other embodiments, the sugar moiety at each of positions 2, 5 and 14 of the antisense strand is modified with the 2'-F. In other embodiments, the sugar moiety at each of positions 2, 4, 5 and 14 of the antisense strand is modified with the 2'-F. In still other
 15 embodiments, the sugar moiety at each of positions 2, 3, 4, 5, 7 and 14 of the antisense strand is modified with the 2'-F. In yet another embodiment, the sugar moiety at each of positions 2, 3, 4, 5, 10 and 14 of the antisense strand is modified with the 2'-F. In another embodiment, the sugar moiety at each of positions 2, 3, 4, 5, 7, 10 and 14 of the antisense strand is modified with the 2'-F. In some embodiments, the sugar moiety at each of positions 2, 3, 4, 5, 7, 8, 10, 14, 16 and 19 is modified with the 2'-F.

[0171] In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the sugar moiety at one or more positions 2, 3, 4, 5, 7, 10 and 14 of the antisense strand is modified with the 2'-F.

[0172] In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the sugar moiety at one or more positions 2, 3, 4, 5, 7, 8, 10, 14, 16 and 19 of the antisense strand is modified with the 2'-F.

[0173] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 2 and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 2, 5, and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 1, 2, 5, and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 1, 2, 3, 5, 7, and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 1, 2, 3, 5, 10, and 14 modified with 2'-F.

[0174] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 2 and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 2, 5, and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 2, 4, 5, and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 2, 3, 4, 5, 7, and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 2, 3, 4, 5, 10, and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 2, 3, 4, 5, 7, 10 and 14 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at positions 2, 3, 4, 5, 7, 8, 10, 14, 16 and 19 modified with 2'-F.

[0175] In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein one or more of positions 8, 9, 10 or 11 of the sense strand and one or more positions 2, 3, 4, 5, 7, 10 and 14 of the antisense strand is modified with the 2'-F.

[0176] In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and

(f) SEQ ID NOs: 887 and 913, respectively;

wherein one or more of positions 3, 8, 9, 10, 12, 13 and 17 of the sense strand and one or more positions 2, 3, 4, 5, 7, 8, 10, 14, 16 and 19 of the antisense strand is modified with the 2'-F.

[0177] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 5, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid (2'-FANA).

[0178] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 1, 2, 5, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid (2'-FANA).

[0179] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 4, 5, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid (2'-FANA).

[0180] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 1, 2, 3, 5, 7, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid (2'-FANA).

[0181] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 4, 5, 7, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid (2'-FANA).

[0182] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 1, 2, 3, 5, 10, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe),

2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

[0183] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 4, 5, 10, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

[0184] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 5, 7, 10, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

[0185] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 4, 5, 7, 10, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

[0186] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 4, 5, 7, 8, 10, 14, 16 and 19 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

[0187] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, or position 22 modified with 2'-F.

[0188] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, or position 22 modified with 2'-OMe.

[0189] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19,

position 20, position 21, or position 22 modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid (2'-FANA).

[0190] In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 8-11 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 3, 8, 9, 10, 12, 13 and 17 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 1-7 and 12-17 or 12-20 modified with 2'OMe. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety of each of the nucleotides at positions 1-7 and 12-17 or 12-20 of the sense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid (2'-FANA). In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 1-2, 4-7, 11, 14-16 and 18-20 modified with 2'OMe. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety of each of the nucleotides at positions 1-2, 4-7, 11, 14-16 and 18-20 of the sense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid (2'-FANA).

[0191] In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, position 22, position 23, position 24, position 25, position 26, position 27, position 28, position 29, position 30, position 31, position 32, position 33, position 34, position 35, or position 36 modified with 2'-F.

[0192] In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, position 22, position 23, position 24, position 25, position 26, position 27, position 28, position 29, position 30, position 31, position 32, position 33, position 34, position 35, or position 36 modified with 2'-OMe.

[0193] In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, position 22, position 23, position 24, position 25, position 26, position 27, position 28, position 29, position 30, position 31, position 32, position 33, position 34, position 35, or position 36 modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid (2'-FANA).

5'-Terminal Phosphate

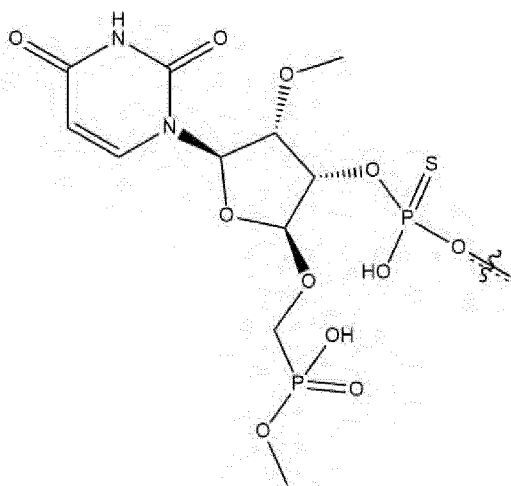
[0194] In some embodiments, an oligonucleotide described herein comprises a 5'-terminal phosphate. In some embodiments, 5'-terminal phosphate groups of an RNAi oligonucleotide enhance the interaction with Ago2. However, oligonucleotides comprising a 5'-phosphate group may be susceptible to degradation *via* phosphatases or other enzymes, which can limit their bioavailability *in vivo*. In some embodiments, an oligonucleotide (e.g., a double-stranded oligonucleotide) herein includes analogs of 5' phosphates that are resistant to such degradation. In some embodiments, the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate, or a combination thereof. In certain embodiments, the 5' end of an oligonucleotide strand is attached to chemical moiety that mimics the electrostatic and steric properties of a natural 5'-phosphate group ("phosphate mimic"). In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the oligonucleotide comprises a 5'-terminal phosphate.

[0195] In some embodiments, an oligonucleotide has a phosphate analog at a 4'-carbon position of the sugar (referred to as a "4'-phosphate analog"). See, e.g., Intl. Patent Application Publication No. WO 2018/045317. In some embodiments, an oligonucleotide herein comprises a 4'-phosphate analog at a 5'-terminal nucleotide. In some embodiments, a phosphate analog is an oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (e.g., at its 4'-carbon) or analog thereof. In other embodiments, a 4'-phosphate analog is a thiomethylphosphonate or an aminomethylphosphonate, in which the sulfur atom of the thiomethyl group or the nitrogen atom of the amino methyl group is bound to the 4'-carbon of the sugar moiety or analog thereof. In certain embodiments, a 4'-phosphate analog is an oxymethylphosphonate. In some embodiments, an oxymethylphosphonate is represented by the formula $-O-CH_2-PO(OH)_2$, $-O-CH_2-PO(OR)_2$, or $-O-CH_2-POOH(R)$, in which R is independently selected from H, CH₃, an alkyl group, CH₂CH₂CN, CH₂OCOC(CH₃)₃, CH₂OCH₂CH₂Si(CH₃)₃ or a protecting group. In certain embodiments, the alkyl group is CH₂CH₃. More typically, R is independently selected from H, CH₃ or CH₂CH₃. In some embodiment, R is CH₃. In some embodiments, the 4'-phosphate analog is 5'-methoxyphosphonate-4'-oxy.

[0196] In some embodiments, a dsRNAi oligonucleotide provided herein comprises an antisense strand comprising a 4'-phosphate analog at the 5'-terminal nucleotide, wherein 5'-terminal nucleotide comprises the following structure:



[0197] 5'-methoxyphosphonate-4'-oxy-2'-O-methyluridine phosphorothioate [MePhosphonate-4O-mUs]

Modified Internucleotide Linkage

[0198] In some embodiments, an oligonucleotide (e.g., a dsRNAi oligonucleotide) herein comprises a modified internucleotide linkage. In some embodiments, phosphate modifications or substitutions result in an oligonucleotide that comprises at least about 1 (e.g., at least 1, at least 2, at least 3 or at least 5) modified internucleotide linkage. In some embodiments, any one of the oligonucleotides disclosed herein comprises about 1 to about 10 (e.g., 1 to 10, 2 to 8, 4 to 6, 3 to 10, 5 to 10, 1 to 5, 1 to 3 or 1 to 2) modified internucleotide linkages. In some embodiments, any one of the oligonucleotides disclosed herein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 modified internucleotide linkages.

[0199] A modified internucleotide linkage may be a phosphorodithioate linkage, a phosphorothioate linkage, a phosphotriester linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a phosphoramidite linkage, a phosphonate linkage or a boranophosphate linkage. In some embodiments, at least one modified internucleotide linkage of any one of the oligonucleotides as disclosed herein is a phosphorothioate linkage.

[0200] In some embodiments, an oligonucleotide provided herein (e.g., a dsRNAi oligonucleotide) has a phosphorothioate linkage between one or more of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In some embodiments, the oligonucleotide described herein has a phosphorothioate linkage between each of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the oligonucleotide comprises a modified internucleotide linkage. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- 5 (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and,
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the oligonucleotide comprises a phosphorothioate linkage between one or more of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- 15 (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the oligonucleotide comprises a phosphorothioate linkage between each of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

Base Modifications

In some embodiments, oligonucleotides herein (e.g., dsRNAi oligonucleotides) have one or more modified nucleobases. In some embodiments, modified nucleobases (also referred to herein as base analogs) are linked at the 1' position of a nucleotide sugar moiety. In certain embodiments, a modified nucleobase is a nitrogenous base. In certain embodiments, a modified nucleobase does not contain nitrogen atom. See, e.g., US Patent Application Publication No. 2008/0274462. In some embodiments, a modified nucleotide comprises a universal base. In some
30 embodiments, a modified nucleotide does not contain a nucleobase (abasic). In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- 35 (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the oligonucleotide comprises one or more modified nucleobases.

[0201] In some embodiments, a universal base is a heterocyclic moiety located at the 1' position of a nucleotide sugar moiety in a modified nucleotide, or the equivalent position in a nucleotide sugar moiety substitution, that, when present in a duplex, can be positioned opposite more than one type of base without substantially altering structure of the duplex. In some embodiments, compared to a reference single-stranded nucleic acid (*e.g.*, oligonucleotide) that is fully complementary to a target nucleic acid, a single-stranded nucleic acid containing a universal base forms a duplex with the target nucleic acid that has a lower T_m than a duplex formed with the complementary nucleic acid. In some embodiments, when compared to a reference single-stranded nucleic acid in which the universal base has been replaced with a base to generate a single mismatch, the single-stranded nucleic acid containing the universal base forms a duplex with the target nucleic acid that has a higher T_m than a duplex formed with the nucleic acid comprising the mismatched base.

[0202] Non-limiting examples of universal-binding nucleotides include, but are not limited to, inosine, 1- β -D-ribofuranosyl-5-nitroindole and/or 1- β -D-ribofuranosyl-3-nitropyrrole (see, US Patent Application Publication No. 2007/0254362; Van Aerschot *et al.* (1995) NUCLEIC ACIDS RES. 23:4363-4370; Loakes *et al.* (1995) NUCLEIC ACIDS RES. 23:2361-66; and Loakes & Brown (1994) NUCLEIC ACIDS RES. 22:4039-43).

Targeting Ligands

[0203] In some embodiments, it is desirable to target the oligonucleotides of the disclosure (*e.g.*, dsRNAi oligonucleotides) to one or more cells or one or more organs. Such a strategy can help to avoid undesirable effects in other organs or avoid undue loss of the oligonucleotide to cells, tissue or organs that would not benefit from the oligonucleotide. Accordingly, in some embodiments, oligonucleotides disclosed herein (*e.g.*, dsRNAi oligonucleotides) are modified to facilitate targeting and/or delivery to a particular tissue, cell, or organ (*e.g.*, to facilitate delivery of the oligonucleotide to the liver). In some embodiments, an oligonucleotide comprises at least one nucleotide (*e.g.*, 1, 2, 3, 4, 5, 6 or more nucleotides) conjugated to one or more targeting ligand(s). In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the oligonucleotide comprises a targeting ligand conjugated to at least once nucleotide,

[0204] In some embodiments, the targeting ligand comprises a carbohydrate, amino sugar, cholesterol, peptide, polypeptide, protein, or part of a protein (*e.g.*, an antibody or antibody fragment), or lipid. In some embodiments, the targeting ligand is an aptamer. For example, a targeting ligand may be an RGD peptide that is used to target tumor vasculature or glioma cells, CREKA peptide to target tumor vasculature or stoma, transferring, lactoferrin, or an

aptamer to target transferrin receptors expressed on CNS vasculature, or an anti-EGFR antibody to target EGFR on glioma cells. In certain embodiments, the targeting ligand is one or more GalNAc moieties.

[0205] In some embodiments, 1 or more (e.g., 1, 2, 3, 4, 5 or 6) nucleotides of an oligonucleotide are each conjugated to a separate targeting ligand. In some embodiments, 2 to 4 nucleotides of an oligonucleotide are each conjugated to a separate targeting ligand. In some embodiments, targeting ligands are conjugated to 2 to 4 nucleotides at either ends of the sense or antisense strand (e.g., targeting ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense or antisense strand) such that the targeting ligands resemble bristles of a toothbrush and the oligonucleotide resembles a toothbrush. For example, an oligonucleotide may comprise a stem-loop at either the 5' or 3' end of the sense strand and 1, 2, 3 or 4 nucleotides of the loop of the stem may be individually conjugated to a targeting ligand. In some embodiments, an oligonucleotide (e.g., a dsRNAi oligonucleotide) provided by the disclosure comprises a stem-loop at the 3' end of the sense strand, wherein the loop of the stem-loop comprises a triloop or a tetraloop, and wherein the 3 or 4 nucleotides comprising the triloop or tetraloop, respectively, are individually conjugated to a targeting ligand.

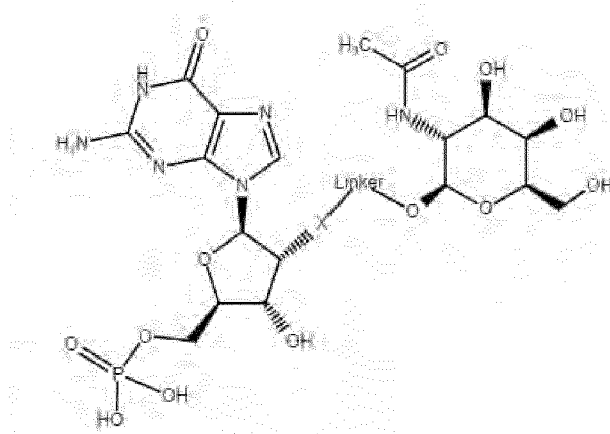
[0206] GalNAc is a high affinity ligand for the ASGPR, which is primarily expressed on the sinusoidal surface of hepatocyte cells and has a major role in binding, internalizing and subsequent clearing circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins). Conjugation (either indirect or direct) of GalNAc moieties to oligonucleotides of the instant disclosure can be used to target these oligonucleotides to the ASGPR expressed on cells. In some embodiments, an oligonucleotide of the instant disclosure is conjugated to at least one or more GalNAc moieties, wherein the GalNAc moieties target the oligonucleotide to an ASGPR expressed on human liver cells (e.g., human hepatocytes). In some embodiments, the GalNAc moiety targets the oligonucleotide to the liver.

[0207] In some embodiments, an oligonucleotide of the instant disclosure is conjugated directly or indirectly to a monovalent GalNAc. In some embodiments, the oligonucleotide is conjugated directly or indirectly to more than one monovalent GalNAc (i.e., is conjugated to 2, 3 or 4 monovalent GalNAc moieties, and is typically conjugated to 3 or 4 monovalent GalNAc moieties). In some embodiments, an oligonucleotide is conjugated to one or more bivalent GalNAc, trivalent GalNAc or tetravalent GalNAc moieties.

[0208] In some embodiments, 1 or more (e.g., 1, 2, 3, 4, 5 or 6) nucleotides of an oligonucleotide are each conjugated to a GalNAc moiety. In some embodiments, 2 to 4 nucleotides of a tetraloop are each conjugated to a separate GalNAc. In some embodiments, 1 to 3 nucleotides of a triloop are each conjugated to a separate GalNAc. In some embodiments, targeting ligands are conjugated to 2 to 4 nucleotides at either ends of the sense or antisense strand (e.g., ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense or antisense strand) such that the GalNAc moieties resemble bristles of a toothbrush and the oligonucleotide resembles a toothbrush. In some embodiments, GalNAc moieties are conjugated to a nucleotide of the sense strand. For example, three (3) or four (4) GalNAc moieties can be conjugated to nucleotides in the tetraloop of the sense strand where each GalNAc moiety is conjugated to 1 nucleotide.

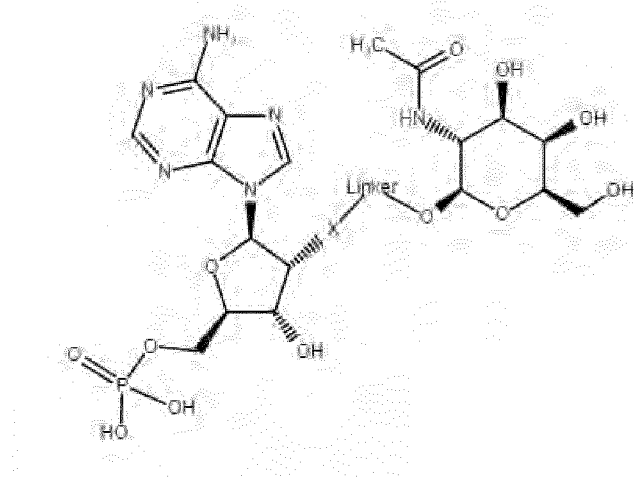
[0209] In some embodiments, the tetraloop is any combination of adenine and guanine nucleotides.

[0210] In some embodiments, the tetraloop (L) has a monovalent GalNAc moiety attached to any one or more guanine nucleotides of the tetraloop *via* any linker described herein, as depicted below (X=heteroatom):



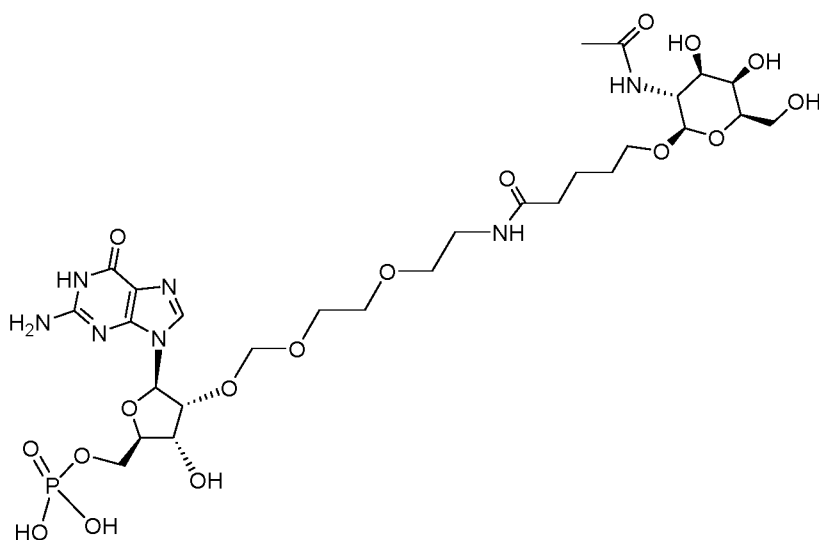
[0211] In some embodiments, the tetraloop (L) has a monovalent GalNAc attached to any one or more adenine

5 nucleotides of the tetraloop *via* any linker described herein, as depicted below (X=heteroatom):

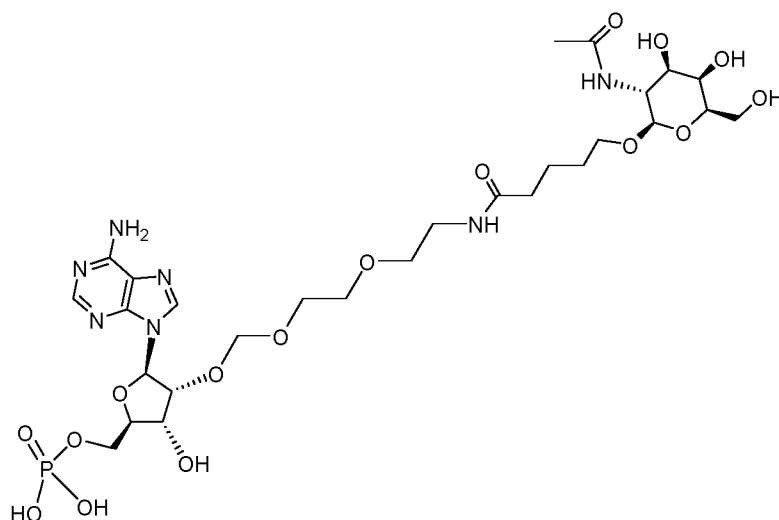


[0212] In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc attached to a guanine

10 nucleotide referred to as [ademG-GalNAc] or 2'-aminodiethoxymethanol-Guanine-GalNAc, as depicted below:



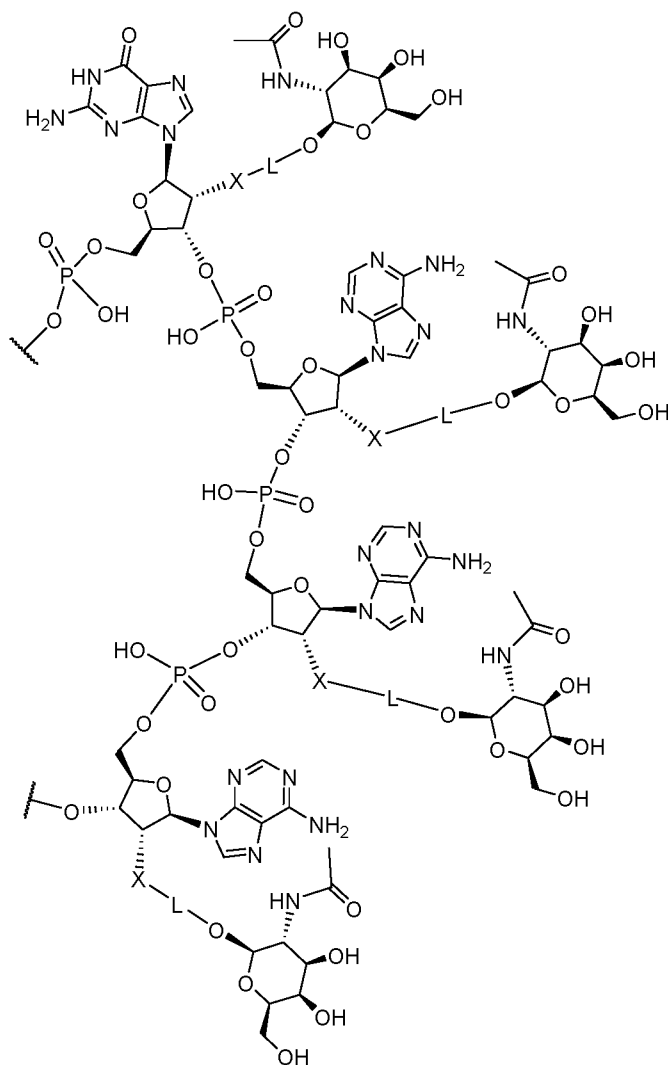
[0213] In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc attached to an adenine nucleotide, referred to as [ademA-GalNAc] or 2'-aminodiethoxymethanol-Adenine-GalNAc, as depicted below:



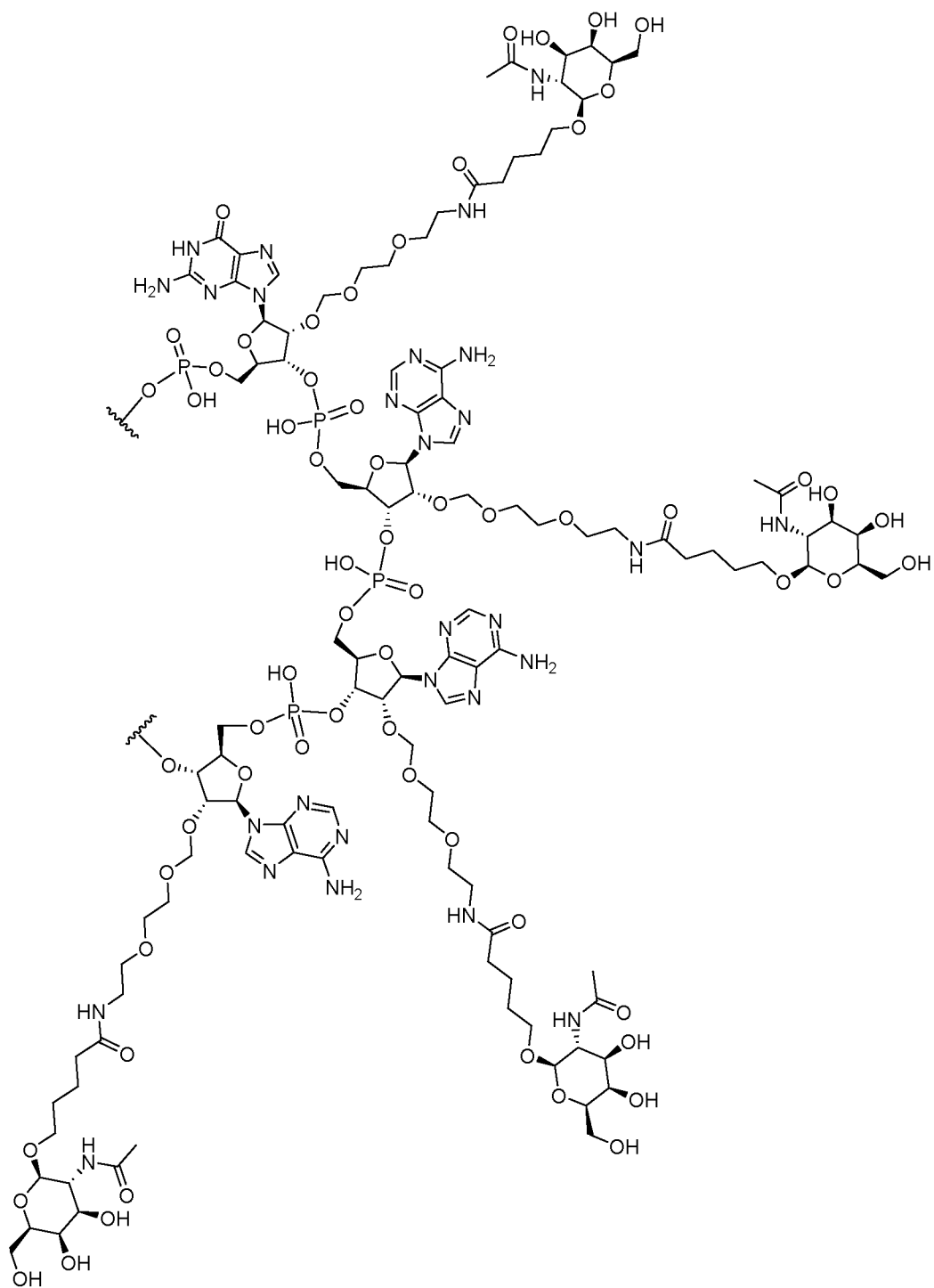
5

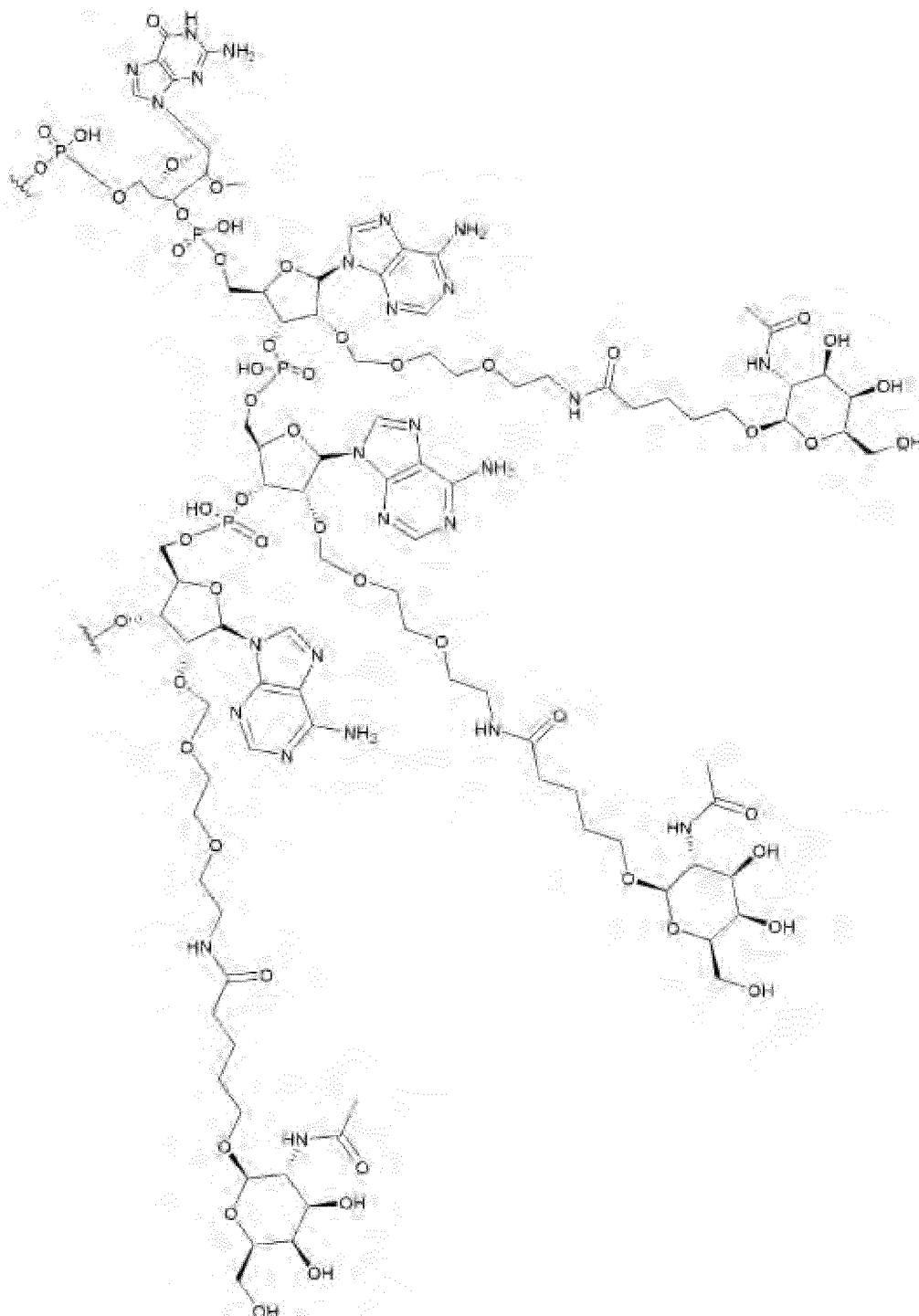
[0214] An example of such conjugation is shown below for a loop comprising from 5' to 3' the nucleotide sequence GAAA (L = linker, X = heteroatom). Such a loop may be present, for example, at positions 27-30 of a sense strand provided herein, as shown in **FIGs. 2 and 4A**. In the chemical formula, $\frac{3}{2}$ is used to describe an attachment point to the oligonucleotide strand.

10



[0215] Appropriate methods or chemistry (e.g., click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide using a click linker. In some
 5 embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in Intl. Patent Application Publication No. WO 2016/100401. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is stable. Examples are shown below for a loop comprising from 5' to 3' the nucleotides GAAA, in which GalNAc moieties are attached to nucleotides of the loop using an acetal linker. Such a loop may be present, for
 10 example, at positions 27-30 of the sense strand as shown in **FIGs. 2 and 4A**. In the chemical formula,  is an attachment point to the oligonucleotide strand.





[0216] As mentioned, various appropriate methods or chemistry synthetic techniques (e.g., click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide using a click linker. In some embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in Intl. Patent Application Publication No. WO 2016/100401. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is a stable linker.

[0217] In some embodiments, a duplex extension (e.g., of up to 3, 4, 5 or 6 bp in length) is provided between a targeting ligand (e.g., a GalNAc moiety) and a dsRNA. In some embodiments, the oligonucleotides herein (e.g.,

dsRNAi oligonucleotides) do not have a GalNAc conjugated thereto.

[0218] In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the oligonucleotide comprises at least one GalNAc moiety conjugated to a nucleotide.

Exemplary KHK-Targeting dsRNAi Oligonucleotides

[0219] In some embodiments, the disclosure provides dsRNAi oligonucleotides that target *KHK* mRNA and reduce *KHK* expression (referred to herein as *KHK*-targeting dsRNAi oligonucleotides), wherein the oligonucleotides comprise a sense strand and an antisense strand that form a duplex region, and wherein the antisense strand comprises a region of complementarity to *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length. In some embodiments, the disclosure provides dsRNAi oligonucleotides that target *KHK* mRNA and reduce *KHK* expression (referred to herein as *KHK*-targeting dsRNAi oligonucleotides), wherein the oligonucleotides comprise a sense strand and an antisense strand that form a duplex region, and wherein the antisense strand comprises a region of complementarity to *KHK* mRNA target sequence of nucleotides 1-19 of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length. In some embodiments, the region of complementarity is 15-20 nucleotides in length. In some embodiments, the region of complementarity is 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, or 20 nucleotides in length. In some embodiments, the region of complementarity is at least 19 contiguous nucleotides in length. In some embodiments, the region of complementarity is at least 20 nucleotides in length. In some embodiments, the region of complementarity is 19 nucleotides in length. In some embodiments, the region of complementarity is 20 nucleotides in length.

[0220] In some embodiments, the sense strand is 15 to 50 nucleotides in length. In some embodiments, the sense strand is 18 to 36 nucleotides in length. In some embodiments, the sense strand comprises a nucleotide sequence selected from SEQ ID NOs: 909, 894, 897, 892, 891 and 887, and is 15 to 50 nucleotides in length. In some embodiments, the sense strand is 36 nucleotides in length. In some embodiments, the antisense strand is 15 to 30 nucleotides in length. In some embodiments, the antisense strand comprises a nucleotide sequence selected from SEQ ID NOs: 936, 920, 923, 917, 918 and 913, and is 15 to 50 nucleotides in length. In some embodiments, the antisense strand is 22 nucleotides in length. In some embodiments, the sense strand is 36 nucleotides in length and the antisense strand is 22 nucleotides in length and the sense and antisense strand form a duplex region that is at least 19 nucleotides in length. In some embodiments, the duplex region is 20 nucleotides in length.

[0221] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides for reducing *KHK* expression provided by the disclosure comprise a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length. In some embodiments, S1 and S2 are 1-10 nucleotides in length and are the same length. In some embodiments, S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length. In some embodiments, S1 and S2 are 6 nucleotides in length. In some embodiments the loop is 3 nucleotides in length. In some embodiments, the loop is 4 nucleotides in length. In some embodiments, the loop is 5 nucleotides in length. In some embodiments, L is a triloop or a tetraloop. In some embodiments, L is a triloop. In some embodiments, L is a tetraloop. In some embodiments, the tetraloop comprises the sequence 5'-GAAA-3'. In some embodiments, the stem loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 871). In some embodiments, up to 4 nucleotides comprising L are each conjugated to a targeting ligand. In some embodiments, 1 nucleotide, 2 nucleotides, 3 nucleotides, or 4 nucleotides comprising L are each conjugated to a targeting ligand. In some embodiments, 3 nucleotides comprising L are each conjugated to a targeting ligand. In some embodiments, L is a tetraloop comprising the sequence 5'-GAAA-3', wherein each adenosine (A) nucleoside comprising the tetraloop is conjugated to a targeting ligand comprising a monovalent N-acetylgalactosamine (GalNAc) moiety.

[0222] In some embodiments, the antisense strand comprises a 3' overhang of one or more nucleotides in length. In some embodiments, the 3' overhang is two (2) nucleotides in length. In some embodiments, the sequence of the 3' overhang is 5'-GG-3'.

[0223] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides for reducing *KHK* expression provided by the disclosure comprise a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region of at least 19 nucleotides in length, optionally 20 nucleotides in length, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length. In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides for reducing *KHK* expression provided by the disclosure comprise a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region of at least 19 nucleotides in length, optionally 20 nucleotides in length, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of nucleotides 1-19 of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

[0224] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides for reducing *KHK* expression provided by the disclosure comprises at least one modified nucleotide. In some embodiments, the modified nucleotide comprises a five (5) carbon sugar (e.g., ribose) with a 2'-modification. In some embodiments, the 2'-modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid.

In some embodiments, the 2'-modification is 2'-fluoro or 2'-O-methyl. In some embodiments, all nucleotides comprising the *KHK*-targeting dsRNAi oligonucleotides are modified. In some embodiments, all nucleotides comprising the *KHK*-targeting dsRNAi oligonucleotides are modified with a 2'-modification selected from 2'-fluoro and 2'-O-methyl. In some
 5 of 2'-fluoro and 2'-O-methyl. In some embodiments, the sense and antisense strand of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 909 and 936, respectively;
- (b) SEQ ID NOs: 894 and 920, respectively;
- (c) SEQ ID NOs: 897 and 923, respectively;
- 10 (d) SEQ ID NOs: 892 and 918, respectively;
- (e) SEQ ID NOs: 891 and 917, respectively; and
- (f) SEQ ID NOs: 887 and 913, respectively;

wherein the oligonucleotide is modified with a combination of 2'-fluoro and 2'-O-methyl.

[0225] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides comprises at least one modified
 15 internucleotide linkage. In some embodiments, the at least one modified internucleotide linkage is a phosphorothioate linkage.

[0226] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides comprise an antisense strand wherein the 4'-carbon of the sugar of the 5'-terminal nucleotide of the antisense strand comprises a phosphate analog. In some
 20 embodiments, the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate. In some embodiments, the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.

[0227] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides for reducing *KHK* expression provided by the disclosure comprise a sense strand and an antisense strand, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15
 25 contiguous nucleotides in length. In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides for reducing *KHK* expression provided by the disclosure comprise a sense strand and an antisense strand, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of nucleotides 1-19 of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length. In some embodiments, the 5'-terminal
 30 nucleotide of the antisense strand comprises 5'-methoxyphosphonate-4'-oxy-2'-O-methyluridine [MePhosphonate-4O-mU], as described herein. In some embodiments, the 5'-terminal nucleotide of the antisense strand comprises a phosphorothioate linkage. In some embodiments, the antisense strand and the sense strand comprise one or more 2'-fluoro (2'-F) and 2'-O-methyl (2'-OMe) modified nucleotides and at least one phosphorothioate linkage. In some embodiments, the antisense strand comprises four (4) phosphorothioate linkages and the sense strand comprises one
 35 (1) phosphorothioate linkage. In some embodiments, the antisense strand comprises five (5) phosphorothioate linkages and the sense strand comprises one (1) phosphorothioate linkage.

[0228] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides for reducing *KHK* expression comprise:

a sense strand comprising a 2'-F modified nucleotide at positions 8-11, a 2'-OMe modified nucleotide at positions 1-7, 12-27, and 31-36, a GalNAc-conjugated nucleotide at position 28, 29 and 30; and a phosphorothioate linkage between positions 1 and 2;

an antisense strand comprising a 2'-F modified nucleotide at positions 2, 3, 4, 5, 7, 10 and 14, a 2'-OMe at positions 1, 6, 8, 9, 11-13, and 15-22, a phosphorothioate linkage between positions 1 and 2, positions 2 and 3, positions 3 and 4, positions 20 and 21, and positions 21 and 22, and a 5'-terminal nucleotide at position 1 comprising a 4'-phosphate analog, optionally wherein the 5'-terminal nucleotide comprises 5'-methoxyphosphonate-4'-oxy-2'-O-methyluridine [MePhosphonate-4O-mU]; wherein positions 1-20 of the antisense strand form a duplex region with positions 1-20 of the sense strand, wherein positions 21-36 of the sense strand form a stem-loop, wherein positions 27-30 form the loop of the stem-loop, optionally wherein positions 27-30 comprise a tetraloop, wherein positions 21 and 22 of the antisense strand comprise an overhang, and wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 886 and 912, respectively;
- (b) SEQ ID NOs: 887 and 913, respectively;
- (c) SEQ ID NOs: 910 and 937, respectively;
- (d) SEQ ID NOs: 888 and 914, respectively;
- (e) SEQ ID NOs: 889 and 915, respectively;
- (f) SEQ ID NOs: 890 and 916, respectively;
- (g) SEQ ID NOs: 891 and 917, respectively;
- (h) SEQ ID NOs: 877 and 884, respectively;
- (i) SEQ ID NOs: 878 and 930, respectively;
- (j) SEQ ID NOs: 876 and 883, respectively;
- (k) SEQ ID NOs: 875 and 882, respectively;
- (l) SEQ ID NOs: 892 and 918, respectively;
- (m) SEQ ID NOs: 893 and 919, respectively;
- (n) SEQ ID NOs: 894 and 920, respectively;
- (o) SEQ ID NOs: 904 and 931, respectively;
- (p) SEQ ID NOs: 895 and 921, respectively;
- (q) SEQ ID NOs: 905 and 932, respectively;
- (r) SEQ ID NOs: 896 and 922, respectively;
- (s) SEQ ID NOs: 911 and 938, respectively;
- (t) SEQ ID NOs: 906 and 933, respectively;
- (u) SEQ ID NOs: 897 and 923, respectively;
- (v) SEQ ID NOs: 907 and 934, respectively;
- (w) SEQ ID NOs: 908 and 935, respectively;
- (x) SEQ ID NOs: 903 and 929, respectively;
- (y) SEQ ID NOs: 901 and 927, respectively;

- (z) SEQ ID NOs: 874 and 881, respectively;
- (aa) SEQ ID NOs: 902 and 928, respectively;
- (bb) SEQ ID NOs: 873 and 880, respectively;
- (cc) SEQ ID NOs: 872 and 879, respectively;
- 5 (dd) SEQ ID NOs: 898 and 924, respectively;
- (ee) SEQ ID NOs: 899 and 925, respectively;
- (ff) SEQ ID NOs: 900 and 926, respectively; and
- (gg) SEQ ID NOs: 909 and 936, respectively.

In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides for reducing *KHK* expression comprise:

10 a sense strand comprising a 2'-F modified nucleotide at positions 8-11, a 2'-OMe modified nucleotide at positions 1-7, 12-27, and 31-36, a GalNAc-conjugated nucleotide at position 28, 29 and 30; and a phosphorothioate linkage between positions 1 and 2;

an antisense strand comprising a 2'-F modified nucleotide at positions 2, 3, 4, 5, 7, 10 and 14, a 2'-OMe at positions 1, 6, 8, 9, 11-13, and 15-22, a phosphorothioate linkage between positions 1 and 2, positions 2 and 3, 15 positions 20 and 21, and positions 21 and 22, and a 5'-terminal nucleotide at position 1 comprising a 4'-phosphate analog, optionally wherein the 5'-terminal nucleotide comprises 5'-methoxyphosphonate-4'-oxy-2'-O-methyluridine [MePhosphonate-4O-mU]; wherein positions 1-20 of the antisense strand form a duplex region with positions 1-20 of the sense strand, wherein positions 21-36 of the sense strand form a stem-loop, wherein positions 27-30 form the loop of the stem-loop, optionally wherein positions 27-30 comprise a tetraloop, wherein positions 21 and 22 of the antisense strand comprise an overhang, and wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 886 and 912, respectively;
- (b) SEQ ID NOs: 887 and 913, respectively;
- (c) SEQ ID NOs: 910 and 937, respectively;
- 25 (d) SEQ ID NOs: 888 and 914, respectively;
- (e) SEQ ID NOs: 889 and 915, respectively;
- (f) SEQ ID NOs: 890 and 916, respectively;
- (g) SEQ ID NOs: 891 and 917, respectively;
- (h) SEQ ID NOs: 877 and 884, respectively;
- 30 (i) SEQ ID NOs: 878 and 930, respectively;
- (j) SEQ ID NOs: 876 and 883, respectively;
- (k) SEQ ID NOs: 875 and 882, respectively;
- (l) SEQ ID NOs: 892 and 918, respectively;
- (m) SEQ ID NOs: 893 and 919, respectively;
- 35 (n) SEQ ID NOs: 894 and 920, respectively;
- (o) SEQ ID NOs: 904 and 931, respectively;
- (p) SEQ ID NOs: 895 and 921, respectively;

- (q) SEQ ID NOs: 905 and 932, respectively;
- (r) SEQ ID NOs: 896 and 922, respectively;
- (s) SEQ ID NOs: 911 and 938, respectively;
- (t) SEQ ID NOs: 906 and 933, respectively;
- 5 (u) SEQ ID NOs: 897 and 923, respectively;
- (v) SEQ ID NOs: 907 and 934, respectively;
- (w) SEQ ID NOs: 908 and 935, respectively;
- (x) SEQ ID NOs: 903 and 929, respectively;
- (y) SEQ ID NOs: 901 and 927, respectively;
- 10 (z) SEQ ID NOs: 874 and 881, respectively;
- (aa) SEQ ID NOs: 902 and 928, respectively;
- (bb) SEQ ID NOs: 873 and 880, respectively;
- (cc) SEQ ID NOs: 872 and 879, respectively;
- (dd) SEQ ID NOs: 898 and 924, respectively;
- 15 (ee) SEQ ID NOs: 899 and 925, respectively;
- (ff) SEQ ID NOs: 900 and 926, respectively; and
- (gg) SEQ ID NOs: 909 and 936, respectively.

[0229] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression provided by
 20 the disclosure comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 887 and an
 antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 913. In some embodiments, a
KHK-targeting dsRNAi oligonucleotide for reducing *KHK* expression provided by the disclosure comprises a sense
 strand comprising the nucleotide sequence as set forth in SEQ ID NO: 891 and an antisense strand comprising the
 nucleotide sequence as set forth in SEQ ID NO: 917. In some embodiments, a *KHK*-targeting dsRNAi
 25 oligonucleotide for reducing *KHK* expression provided by the disclosure comprises a sense strand comprising the
 nucleotide sequence as set forth in SEQ ID NO: 892 and an antisense strand comprising the nucleotide sequence as
 set forth in SEQ ID NO: 918. In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK*
 expression provided by the disclosure comprises a sense strand comprising the nucleotide sequence as set forth in
 SEQ ID NO: 894 and an antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 920. In
 30 some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression provided by the
 disclosure comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 897 and an
 antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 923. In some embodiments, a
KHK-targeting dsRNAi oligonucleotide for reducing *KHK* expression provided by the disclosure comprises a sense
 strand comprising the nucleotide sequence as set forth in SEQ ID NO: 909 and an antisense strand comprising the
 35 nucleotide sequence as set forth in SEQ ID NO: 936.

[0230] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i)
 an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence

comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 948; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0231] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 949; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0232] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 950; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0233] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 951; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0234] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 952; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0235] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 953; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0236] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is

set forth in SEQ ID NO: 948; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3'terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0237] In some embodiments, a KHK-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 949; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3'terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0238] In some embodiments, a KHK-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 950; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3'terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0239] In some embodiments, a KHK-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 951; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3'terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0240] In some embodiments, a KHK-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 952; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3'terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0241] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 953; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0242] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 948; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 942, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0243] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 949; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 943, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0244] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 950; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 944, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0245] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 951; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 945, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0246] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 952; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 946, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0247] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 953; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 947, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0248] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 948; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 942, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0249] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 949; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 943, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0250] In some embodiments, a *KHK*-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 950; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the region of complementarity to

5 **[0251]** In some embodiments, a KHK-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 951; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3'terminus, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 945, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0252] In some embodiments, a KHK-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 952; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 946, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0253] In some embodiments, a KHK-targeting dsRNAi oligonucleotide for reducing *KHK* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 953; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 947, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

Sense Strand: 5'-mX-S-mX-mX-mX-mX-mX-fX-fX-fX-fX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mX-mX-mX-mX-mX-mX-3'.

Antisense Strand: 5'-[MePhosphonate-4O-mX]-S-fX-S-fX- S-fX-fX-mX-fX-mX-mX-fX-mX-mX-mX-fX-mX-

wherein mX= 2'-O-methyl modified nucleotide, fX =2'- fluoro modified nucleotide, -S- = phosphorothioate linkage, phosphodiester linkage, [MePhosphonate-4O-mX] = 5'-methoxyphosphonate-4-oxy modified nucleotide, and mA-GalNAc = GalNAc attached to an adenine nucleotide

Sense Strand: 5'-mX-S-mX-fX-mX-mX-mX-mX-fX-fX-fX-mX-fX-fX-mX-mX-mX-fX-mX-mX-mX-mX-mX-X-mX-mX-[ademA-GalNAc]- [ademA-GalNAc]- [ademA-GalNAc]-mX-mX-mX-mX-mX-mX- 3'.

wherein mX= 2'-O-methyl modified nucleotide, fX =2'- fluoro modified nucleotide, -S- = phosphorothioate linkage, phosphodiester linkage, [MePhosphonate-4O-mX] = 5'-methoxyphosphonate-4-oxy modified nucleotide, and mA-GalNAc = GalNAc attached to an adenine nucleotide

[0257] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- 89 -

- (d) SEQ ID NOs: 777 and 822, respectively;
- (e) SEQ ID NOs: 778 and 823, respectively;
- (f) SEQ ID NOs: 779 and 824, respectively;
- (g) SEQ ID NOs: 780 and 825, respectively;
- 5 (h) SEQ ID NOs: 781 and 826, respectively;
- (i) SEQ ID NOs: 782 and 827, respectively;
- (j) SEQ ID NOs: 783 and 828, respectively;
- (k) SEQ ID NOs: 784 and 829, respectively;
- (l) SEQ ID NOs: 785 and 830, respectively;
- 10 (m) SEQ ID NOs: 786 and 831, respectively;
- (n) SEQ ID NOs: 787 and 832, respectively;
- (o) SEQ ID NOs: 788 and 833, respectively;
- (p) SEQ ID NOs: 789 and 834, respectively;
- (q) SEQ ID NOs: 790 and 835, respectively;
- 15 (r) SEQ ID NOs: 791 and 836, respectively;
- (s) SEQ ID NOs: 792 and 837, respectively;
- (t) SEQ ID NOs: 793 and 838, respectively;
- (u) SEQ ID NOs: 794 and 839, respectively;
- (v) SEQ ID NOs: 795 and 840, respectively;
- 20 (w) SEQ ID NOs: 796 and 841, respectively;
- (x) SEQ ID NOs: 797 and 842, respectively;
- (y) SEQ ID NOs: 798 and 843, respectively;
- (z) SEQ ID NOs: 799 and 844, respectively;
- (aa) SEQ ID NOs: 800 and 845, respectively;
- 25 (bb) SEQ ID NOs: 801 and 846, respectively;
- (cc) SEQ ID NOs: 802 and 847, respectively;
- (dd) SEQ ID NOs: 803 and 848, respectively; and
- (ee) SEQ ID NOs: 804 and 849, respectively.

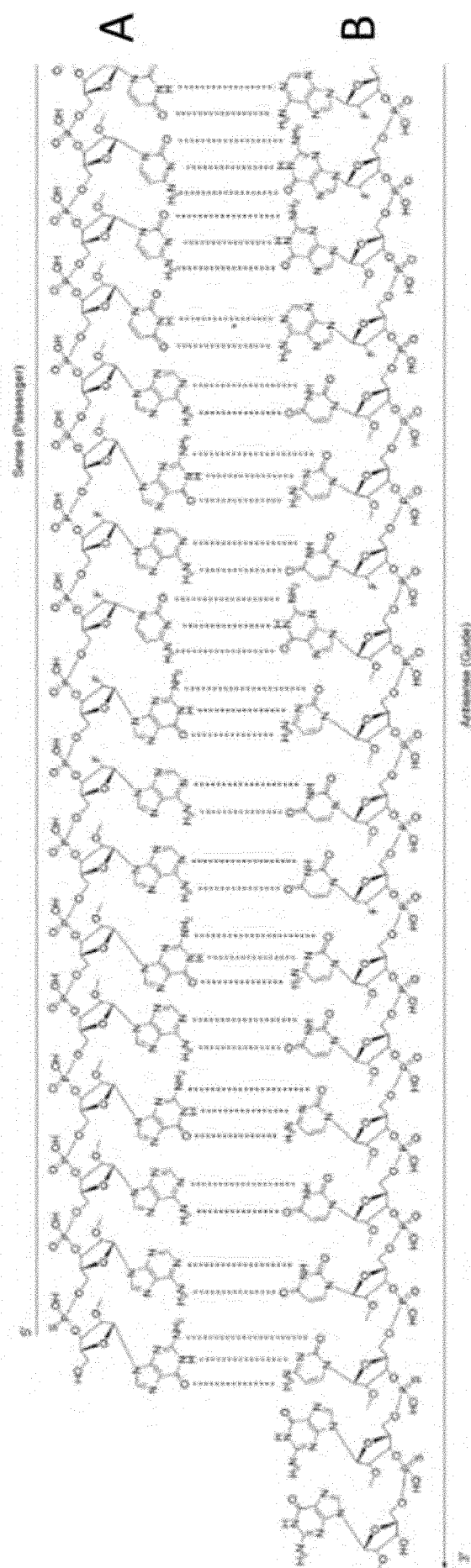
[0258] In some embodiments, a *KHK* -targeting dsRNAi oligonucleotide for reducing *KHK* expression provided by
 30 the disclosure comprising a sense strand selected from SEQ ID NOs:805-818 and an antisense strand selected from
 SEQ ID NOs: 850-863.

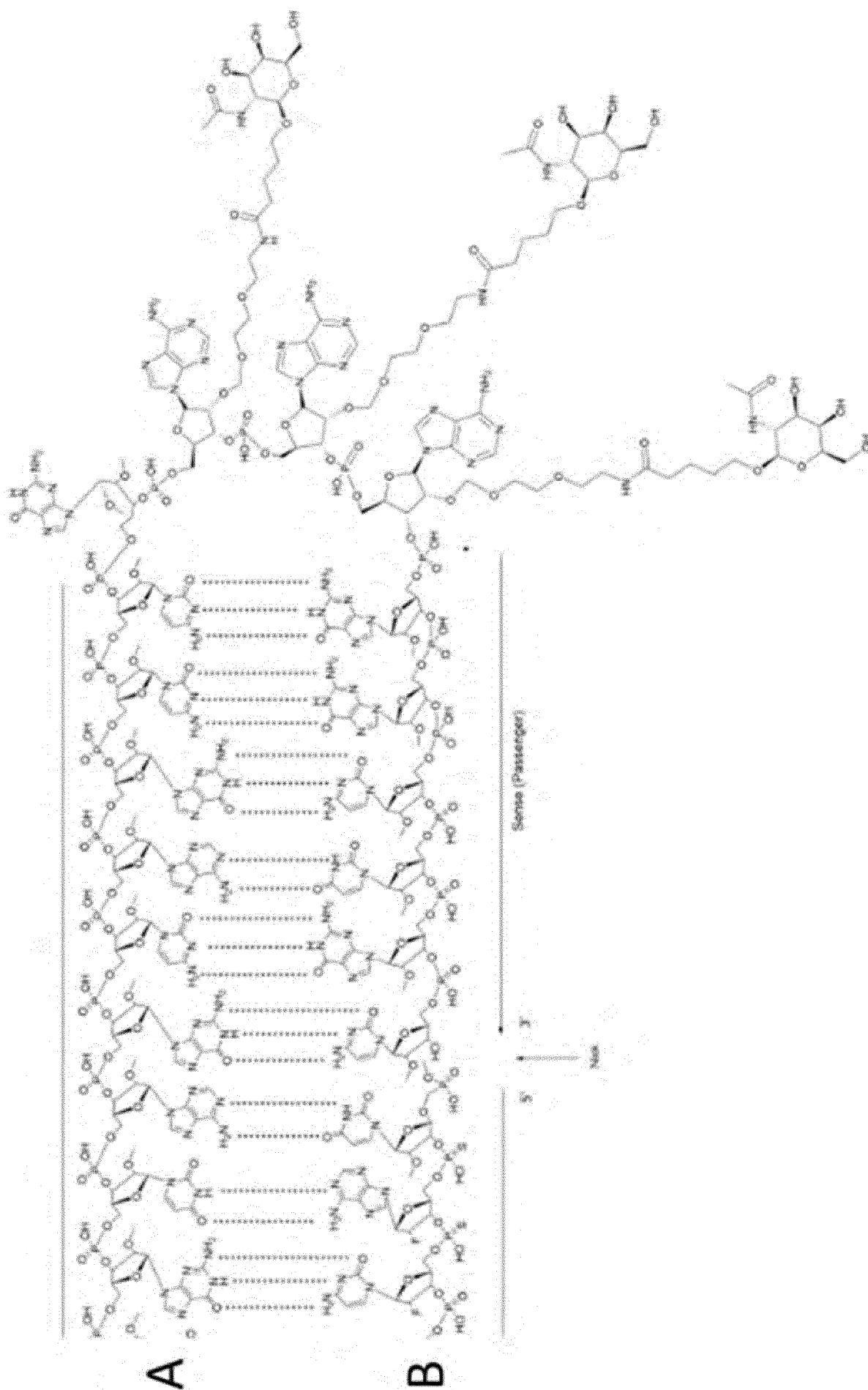
[0259] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides sense and antisense strands comprise
 nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 805 and 850, respectively;
- 35 (b) SEQ ID NOs: 806 and 851, respectively;
- (c) SEQ ID NOs: 807 and 852, respectively;
- (d) SEQ ID NOs: 808 and 853, respectively;

- 5 (e) SEQ ID NOs: 809 and 854, respectively;
(f) SEQ ID NOs: 810 and 855, respectively;
(g) SEQ ID NOs: 811 and 856, respectively;
(h) SEQ ID NOs: 812 and 857, respectively;
(i) SEQ ID NOs: 813 and 858, respectively;
(j) SEQ ID NOs: 814 and 859, respectively;
(k) SEQ ID NOs: 815 and 860, respectively;
(l) SEQ ID NOs: 816 and 861, respectively;
(m) SEQ ID NOs: 817 and 862, respectively and;
10 (n) SEQ ID NOs: 818 and 863, respectively.

[0260] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides comprise a sense strand comprising SEQ ID NO: 775 and an antisense strand comprising SEQ ID NO: 820, wherein said dsRNA is in the form of a conjugate having the structure of:

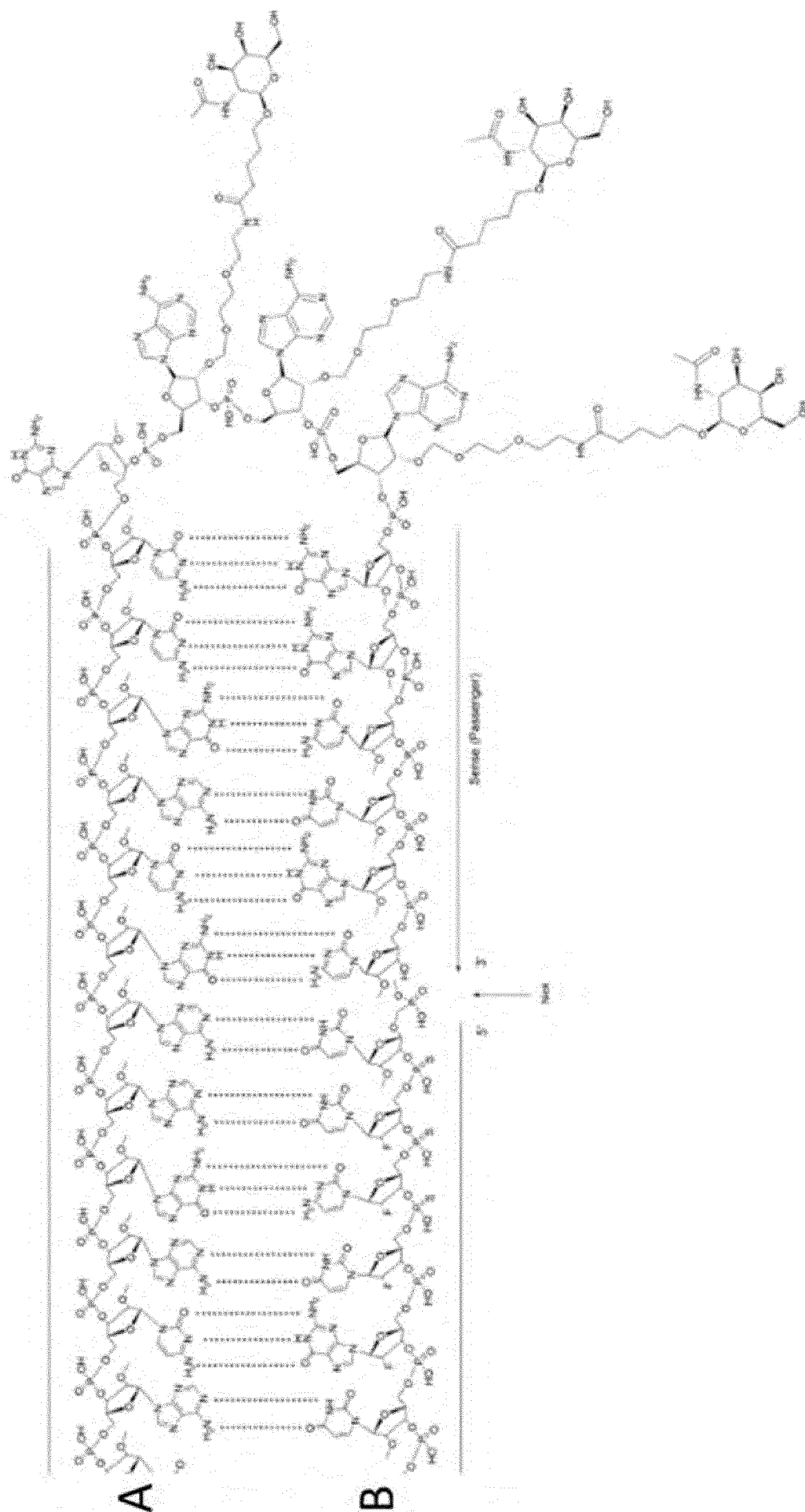




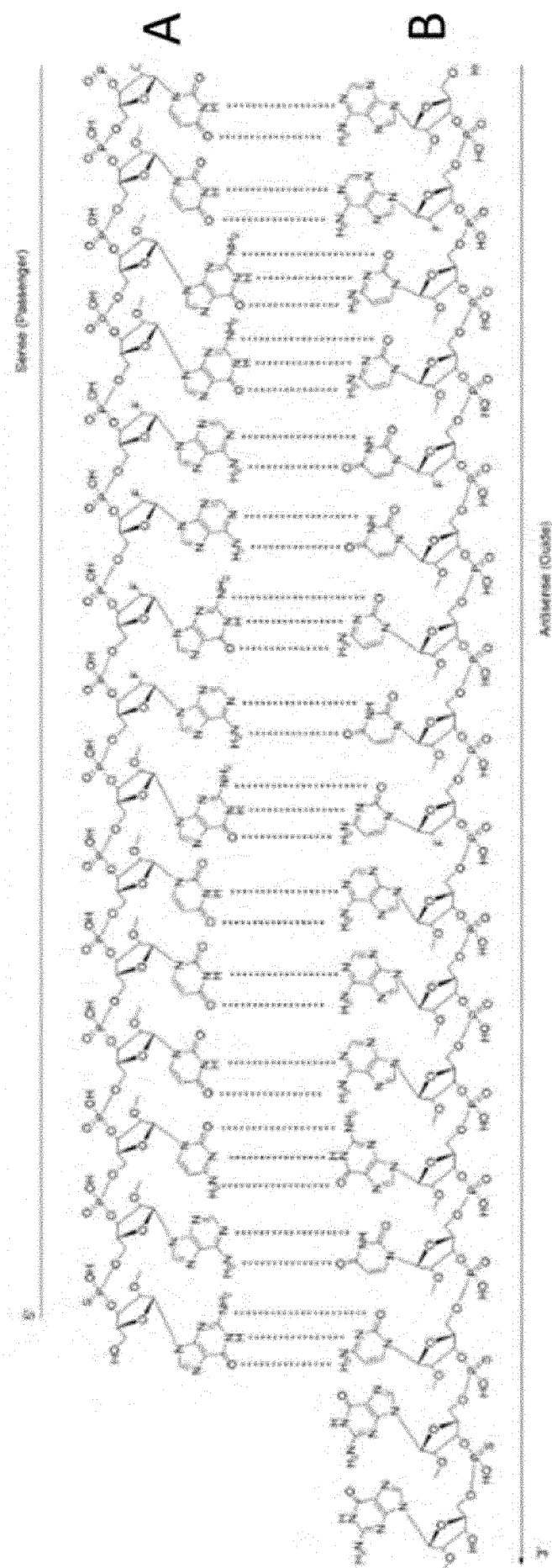
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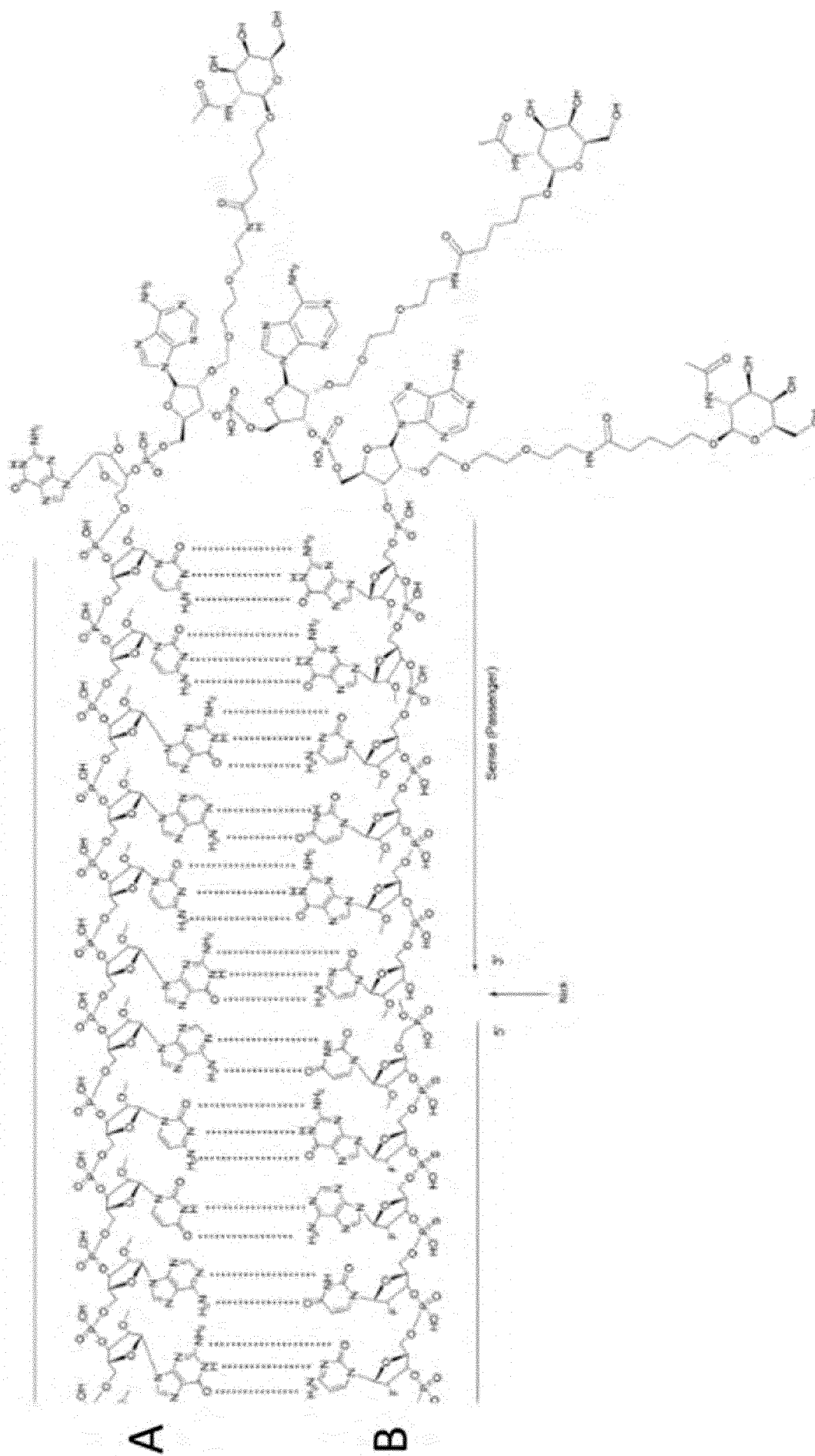
[0261] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides comprise a sense strand comprising SEQ ID NO: 779 and an antisense strand comprising SEQ ID NO: 824, wherein said dsRNA is in the form of a conjugate having the structure of:





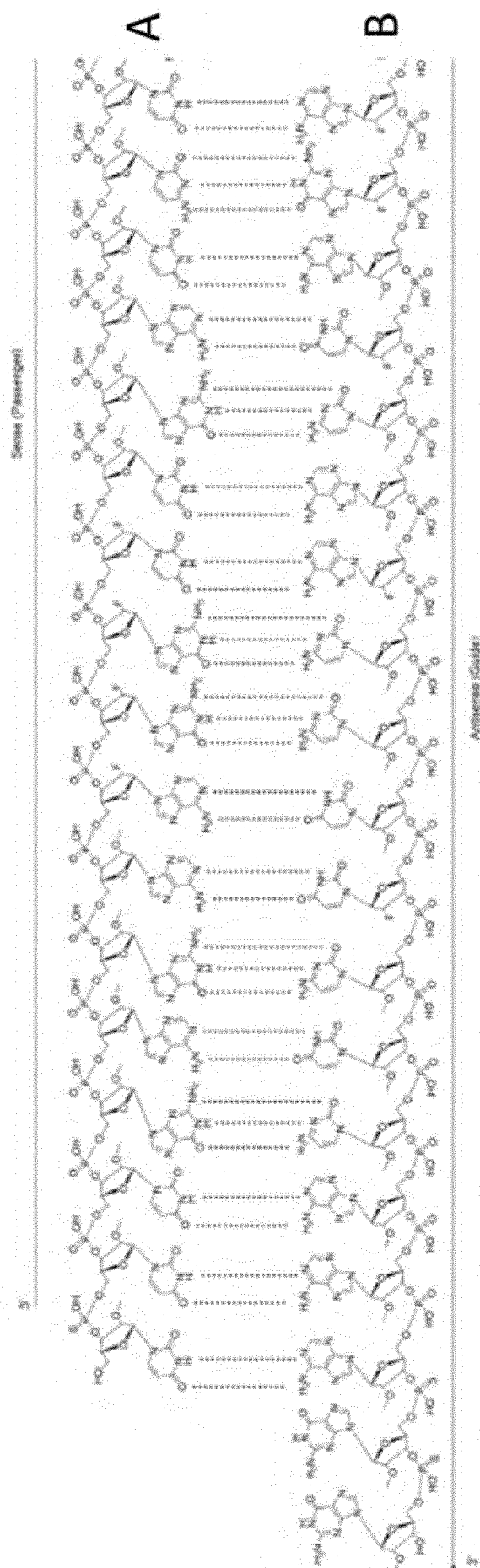
[0262] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides comprise a sense strand comprising SEQ ID NO: 780 and an antisense strand comprising SEQ ID NO: 825, wherein said dsRNA is in the form of a conjugate having the structure of:

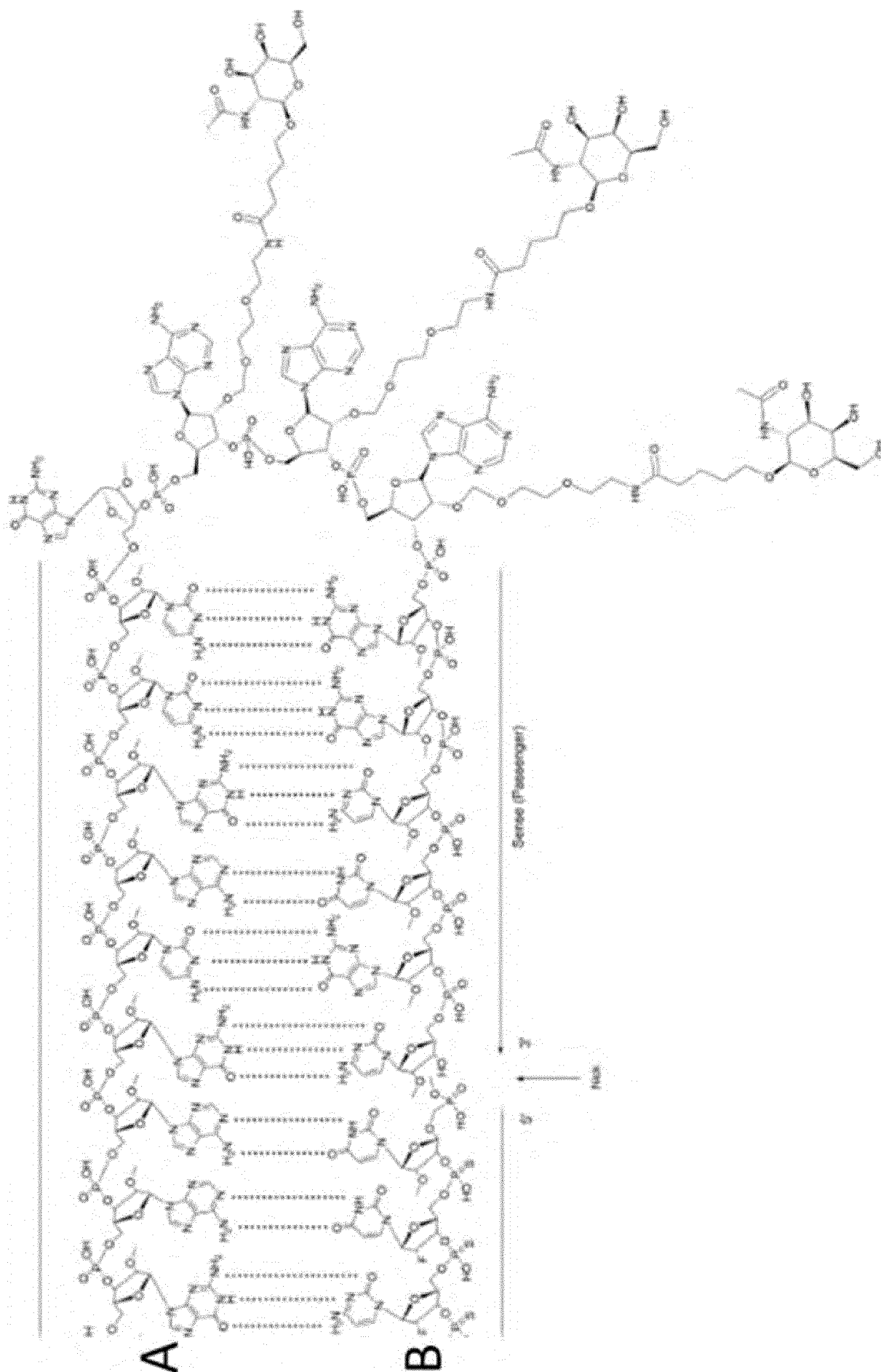




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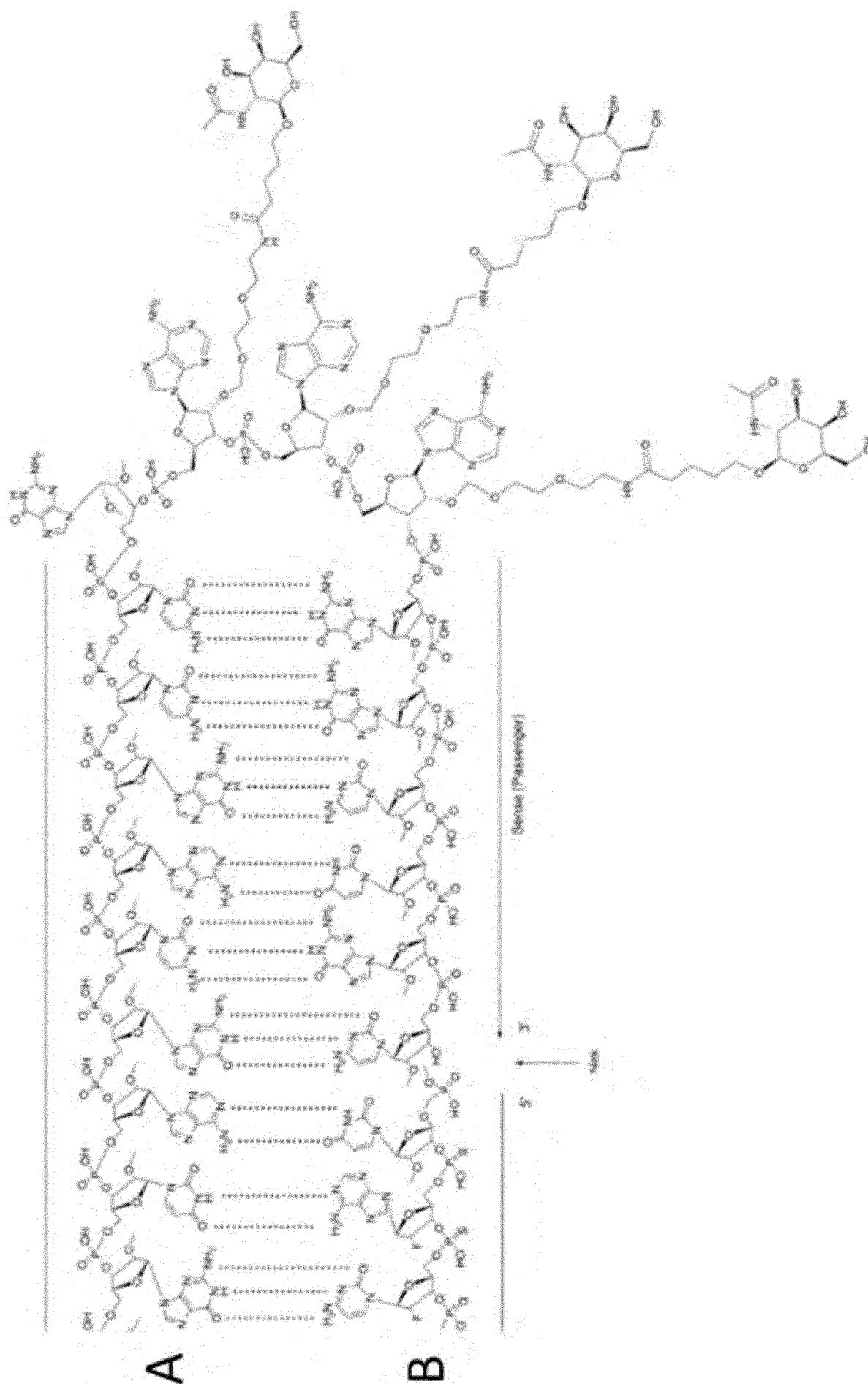
[0263] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides comprise a sense strand comprising SEQ ID NO: 782 and an antisense strand comprising SEQ ID NO: 827, wherein said dsRNA is in the form of a conjugate having the structure of:



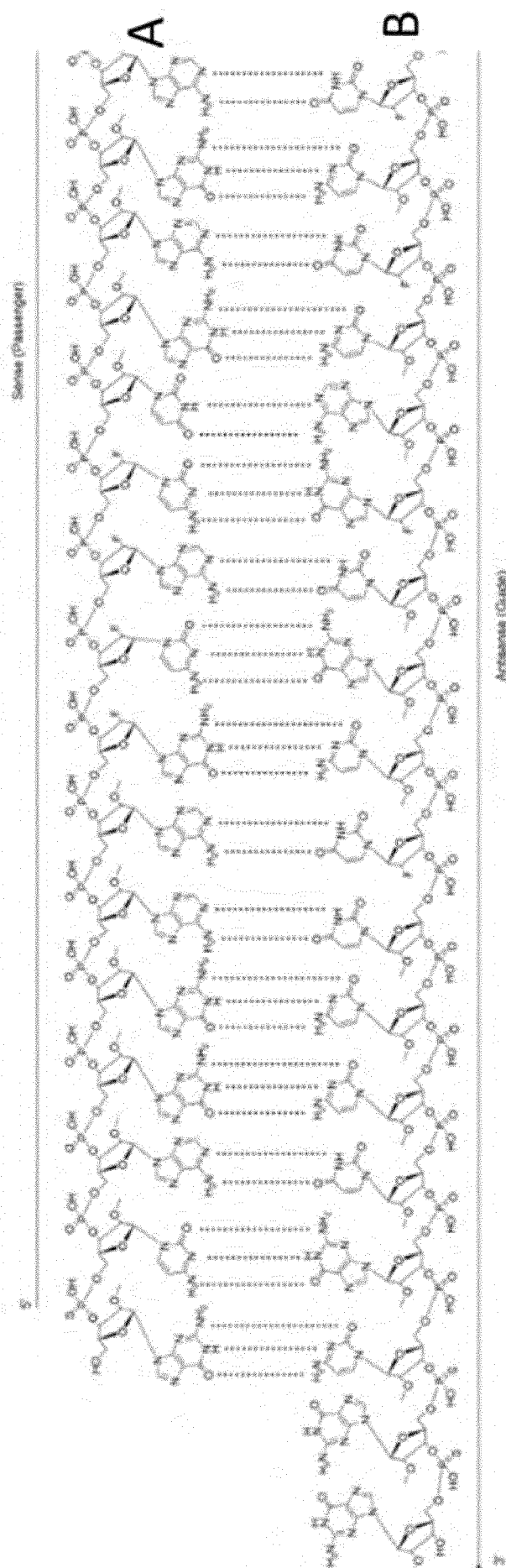


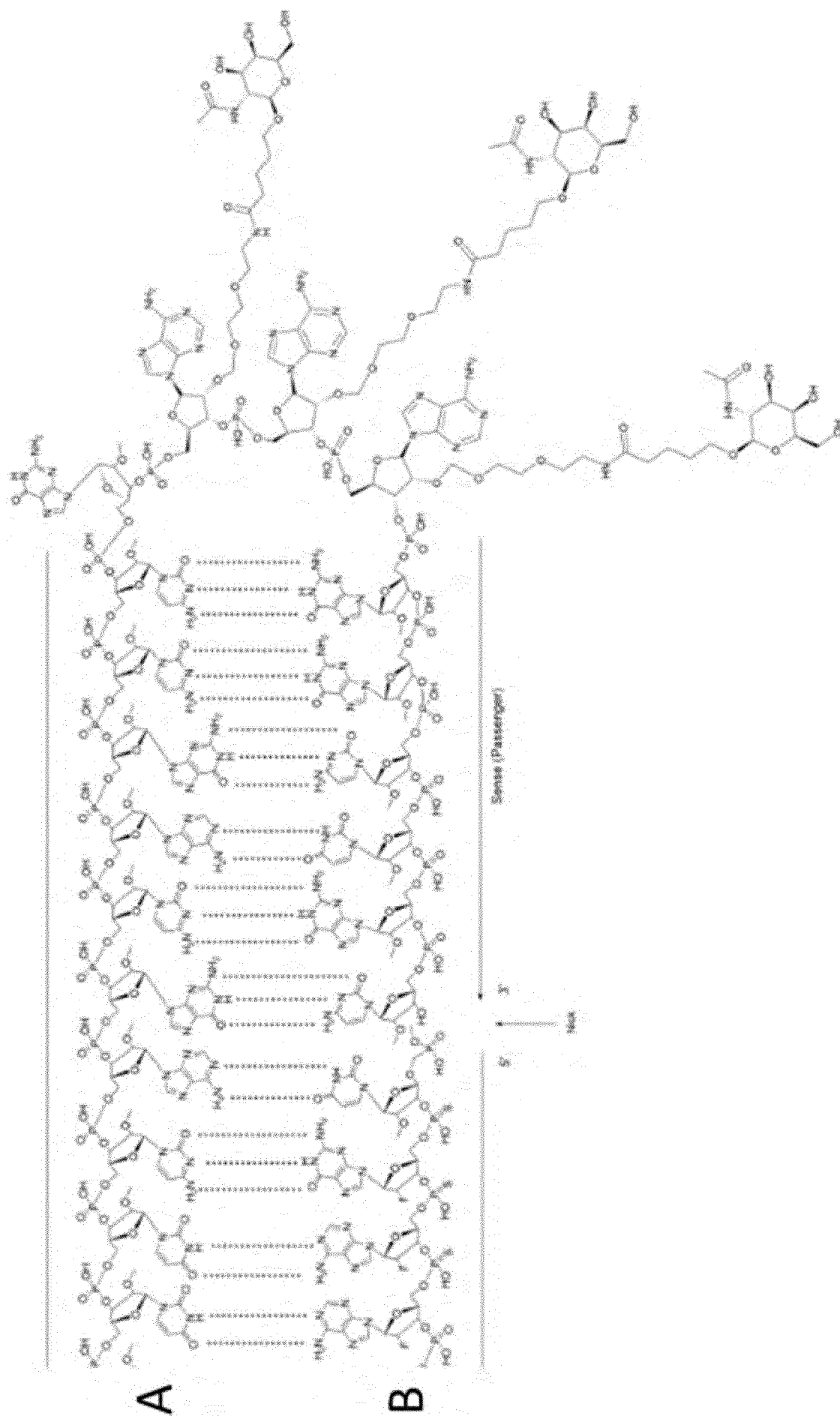
[0264] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides comprise a sense strand comprising SEQ ID NO: 785 and an antisense strand comprising SEQ ID NO: 830, wherein said dsRNA is in the form of a conjugate having the structure of:





[0265] In some embodiments, the *KHK*-targeting dsRNAi oligonucleotides comprise a sense strand comprising SEQ ID NO: 804 and an antisense strand comprising SEQ ID NO: 849, wherein said dsRNA is in the form of a conjugate having the structure of:





Formulations

[0266] Various formulations have been developed to facilitate oligonucleotide use. For example, oligonucleotides (e.g., dsRNAi oligonucleotides) can be delivered to a subject or a cellular environment using a formulation that minimizes degradation, facilitates delivery and/or uptake, or provides another beneficial property to the oligonucleotides in the formulation. In some embodiments, provided herein are compositions comprising oligonucleotides (e.g., dsRNAi oligonucleotides) reduce the expression of *KHK*. Such compositions can be suitably formulated such that when administered to a subject, either into the immediate environment of a target cell or systemically, a sufficient portion of the oligonucleotides enter the cell to reduce *KHK* expression. Any variety of suitable oligonucleotide formulations can be used to deliver oligonucleotides for the reduction of *KHK* as disclosed herein. In some embodiments, an oligonucleotide is formulated in buffer solutions such as phosphate buffered saline solutions, liposomes, micellar structures, and capsids. Any of the oligonucleotides described herein may be provided not only as nucleic acids, but also in the form of a pharmaceutically acceptable salt.

[0267] Formulations of oligonucleotides with cationic lipids can be used to facilitate transfection of the oligonucleotides into cells. For example, cationic lipids, such as lipofectin, cationic glycerol derivatives, and polycationic molecules (e.g., polylysine), can be used. Suitable lipids include Oligofectamine, Lipofectamine (Life Technologies), NC388 (Ribozyme Pharmaceuticals, Inc., Boulder, Colo.), or FuGene 6 (Roche) all of which can be used according to the manufacturer's instructions.

[0268] Accordingly, in some embodiments, a formulation comprises a lipid nanoparticle. In some embodiments, an excipient comprises a liposome, a lipid, a lipid complex, a microsphere, a microparticle, a nanosphere or a nanoparticle, or may be otherwise formulated for administration to the cells, tissues, organs, or body of a subject in need thereof (see, e.g., Remington: THE SCIENCE AND PRACTICE OF PHARMACY, 22nd edition, Pharmaceutical Press, 2013).

[0269] In some embodiments, the formulations herein comprise an excipient. In some embodiments, an excipient confers to a composition improved stability, improved absorption, improved solubility and/or therapeutic enhancement of the active ingredient. In some embodiments, an excipient is a buffering agent (e.g., sodium citrate, sodium phosphate, a tris base, or sodium hydroxide) or a vehicle (e.g., a buffered solution, petrolatum, dimethyl sulfoxide, or mineral oil). In some embodiments, an oligonucleotide is lyophilized for extending its shelf-life and then made into a solution before use (e.g., administration to a subject). Accordingly, an excipient in a composition comprising any one of the oligonucleotides described herein may be a lyoprotectant (e.g., mannitol, lactose, polyethylene glycol or polyvinylpyrrolidone) or a collapse temperature modifier (e.g., dextran, Ficoll™ or gelatin).

[0270] In some embodiments, a pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral (e.g., intravenous, intramuscular, intraperitoneal, intradermal, subcutaneous), oral (e.g., inhalation), transdermal (e.g., topical), transmucosal and rectal administration.

[0271] 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 dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). The carrier can be a solvent or

dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Sterile injectable solutions can be prepared by incorporating the oligonucleotides in a required amount in a selected solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

[0272] In some embodiments, a composition may contain at least about 0.1% of the therapeutic agent (e.g., a dsRNAi oligonucleotide for reducing *KHK* expression) or more, although the percentage of the active ingredient(s) may be between about 1% to about 80% or more of the weight or volume of the total composition. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

Methods of Use

Reducing *KHK* Expression

[0273] In some embodiments, the disclosure provides methods for contacting or delivering to a cell or population of cells an effective amount of oligonucleotides (e.g., dsRNAi oligonucleotides) herein to reduce *KHK* expression. In some embodiments, a reduction of *KHK* expression is determined by measuring a reduction in the amount or level of *KHK* mRNA, *KHK* protein, or *KHK* activity in a cell. The methods include those described herein and known to one of ordinary skill in the art.

[0274] Methods provided herein are useful in any appropriate cell type. In some embodiments, a cell is any cell that expresses *KHK* mRNA (e.g., hepatocytes). In some embodiments, the cell is a primary cell obtained from a subject. In some embodiments, the primary cell has undergone a limited number of passages such that the cell substantially maintains its natural phenotypic properties. In some embodiments, a cell to which the oligonucleotide is delivered is *ex vivo* or *in vitro* (i.e., can be delivered to a cell in culture or to an organism in which the cell resides).

[0275] In some embodiments, the oligonucleotides herein are delivered to a cell or population of cells using a nucleic acid delivery method known in the art including, but not limited to, injection of a solution containing the oligonucleotides, bombardment by particles covered by the oligonucleotides, exposing the cell or population of cells to a solution containing the oligonucleotides, or electroporation of cell membranes in the presence of the oligonucleotides. Other methods known in the art for delivering oligonucleotides to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, and cationic liposome transfection such as calcium phosphate, and others.

[0276] In some embodiments, reduction of *KHK* expression is determined by an assay or technique that evaluates one or more molecules, properties, or characteristics of a cell or population of cells associated with *KHK* expression, or by an assay or technique that evaluates molecules that are directly indicative of *KHK* expression in a cell or population of cells (e.g., *KHK* mRNA or *KHK* protein). In some embodiments, the extent to which an oligonucleotide provided herein reduces *KHK* expression is evaluated by comparing *KHK* expression in a cell or population of cells contacted with the oligonucleotide to an appropriate control (e.g., an appropriate cell or population of cells not contacted with the oligonucleotide or contacted with a control oligonucleotide). In some embodiments, a control amount or level

of *KHK* expression in a control cell or population of cells is predetermined, such that the control amount or level need not be measured in every instance the assay or technique is performed. The predetermined level or value can take a variety of forms. In some embodiments, a predetermined level or value can be single cut-off value, such as a median or mean.

[0277] In some embodiments, contacting or delivering an oligonucleotide (e.g., dsRNAi oligonucleotides) described herein to a cell or a population of cells results in a reduction in *KHK* expression in a cell or population of cells not contacted with the oligonucleotide or contacted with a control oligonucleotide. In some embodiments, the reduction in *KHK* expression is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of *KHK* expression. In some embodiments, the control amount or level of *KHK* expression is an amount or level of *KHK* mRNA and/or *KHK* protein in a cell or population of cells that has not been contacted with an oligonucleotide herein. In some embodiments, the effect of delivery of an oligonucleotide to a cell or population of cells according to a method herein is assessed after any finite period or amount of time (e.g., minutes, hours, days, weeks, months). For example, in some embodiments, *KHK* expression is determined in a cell or population of cells at least about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 24 hours; or at least about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, about 56 days, about 63 days, about 70 days, about 77 days, or about 84 days or more after contacting or delivering the oligonucleotide to the cell or population of cells. In some embodiments, *KHK* expression is determined in a cell or population of cells at least about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months or more after contacting or delivering the oligonucleotide to the cell or population of cells.

[0278] In some embodiments, an oligonucleotide is delivered in the form of a transgene that is engineered to express in a cell the oligonucleotide or strands comprising the oligonucleotide (e.g., its sense and antisense strands). In some embodiments, an oligonucleotide is delivered using a transgene engineered to express any oligonucleotide disclosed herein. Transgenes may be delivered using viral vectors (e.g., adenovirus, retrovirus, vaccinia virus, poxvirus, adeno-associated virus, or herpes simplex virus) or non-viral vectors (e.g., plasmids or synthetic mRNAs). In some embodiments, transgenes can be injected directly to a subject.

Treatment Methods

[0279] The disclosure provides oligonucleotides for use as a medicament, in particular for use in a method for the treatment of diseases, disorders, and conditions associated with expression of *KHK*. The disclosure also provides oligonucleotides for use, or adaptable for use, to treat a subject (e.g., a human having a disease, disorder or condition associated with *KHK* expression) that would benefit from reducing *KHK* expression. In some respects, the disclosure provides oligonucleotides for use, or adapted for use, to treat a subject having a disease, disorder or condition associated with expression of *KHK*. The disclosure also provides oligonucleotides for use, or adaptable for use, in the manufacture of a medicament or pharmaceutical composition for treating a disease, disorder or condition associated

with *KHK* expression. In some embodiments, the oligonucleotides for use, or adaptable for use, target *KHK* mRNA and reduce *KHK* expression (e.g., via the RNAi pathway). In some embodiments, the oligonucleotides for use, or adaptable for use, target *KHK* mRNA and reduce the amount or level of *KHK* mRNA, *KHK* protein and/or *KHK* activity.

[0280] In addition, in some embodiments of the methods herein, a subject having a disease, disorder, or condition associated with *KHK* expression or is predisposed to the same is selected for treatment with an oligonucleotide (e.g., a double-stranded oligonucleotide) herein. In some embodiments, the method comprises selecting an individual having a marker (e.g., a biomarker) for a disease, disorder, or condition associated with *KHK* expression or predisposed to the same, such as, but not limited to, *KHK* mRNA, *KHK* protein, or a combination thereof. Likewise, and as detailed below, some embodiments of the methods provided by the disclosure include steps such as measuring or obtaining a baseline value for a marker of *KHK* expression (e.g., *KHK*), and then comparing such obtained value to one or more other baseline values or values obtained after the subject is administered the oligonucleotide to assess the effectiveness of treatment.

[0281] The disclosure also provides methods of treating a subject having, suspected of having, or at risk of developing a disease, disorder or condition associated with a *KHK* expression with an oligonucleotide provided herein.

In some aspects, the disclosure provides methods of treating or attenuating the onset or progression of a disease, disorder or condition associated with *KHK* expression using the oligonucleotides herein. In other aspects, the disclosure provides methods to achieve one or more therapeutic benefits in a subject having a disease, disorder, or condition associated with *KHK* expression using the oligonucleotides provided herein. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of any one or more of the oligonucleotides provided herein. In some embodiments, treatment comprises reducing *KHK* expression. In some embodiments, the subject is treated therapeutically. In some embodiments, the subject is treated prophylactically.

[0282] In some embodiments of the methods herein, one or more oligonucleotides (e.g., dsRNAi oligonucleotides) herein, or a pharmaceutical composition comprising one or more oligonucleotides, is administered to a subject having a disease, disorder or condition associated with *KHK* expression such that *KHK* expression is reduced in the subject, thereby treating the subject. In some embodiments, an amount or level of *KHK* mRNA is reduced in the subject. In some embodiments, an amount or level of *KHK* protein is reduced in the subject. In some embodiments, an amount or level of *KHK* activity is reduced in the subject. In some embodiments, an amount or level of triglyceride (TG) (e.g., one or more TG(s) or total TGs) is reduced in the subject. In some embodiments, an amount or level of plasma glucose is reduced in the subject. In some embodiments, an amount or level of blood pressure (e.g., systolic pressure, diastolic pressure, or both) is reduced in the subject. In some embodiments, an amount or level of abdominal fat is reduced in the subject. In some embodiments, an amount or level of cholesterol (e.g., total cholesterol, LDL cholesterol, and/or HDL cholesterol) is reduced in the subject. In some embodiments, an amount or level of liver steatosis is reduced in the subject. In some embodiments, an amount or level of liver fibrosis is reduced in the subject. In some embodiments, the ratio of total cholesterol to HDL cholesterol is altered in the subject. In some embodiments, any combination of the following is reduced or altered in the subject: *KHK* expression, an amount or level of *KHK* mRNA, an amount or level of *KHK* protein, an amount or level of *KHK* activity, an amount or level of blood glucose, an amount or level of abdominal fat, an amount or level of blood pressure, an amount or level of TG, an amount or level of cholesterol and/or the ratio

of total cholesterol to HDL cholesterol, an amount or level of liver steatosis, and amount or level of liver fibrosis.

[0283] In some embodiments of the methods herein, an oligonucleotide (e.g., dsRNAi oligonucleotides) herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with KHK such that KHK expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to KHK expression prior to administration of one or more oligonucleotides or pharmaceutical composition. In some embodiments, KHK expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to KHK expression in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide or oligonucleotides, pharmaceutical composition or treatment.

[0284] In some embodiments of the methods herein, an oligonucleotide or oligonucleotides herein, or a pharmaceutical composition comprising the oligonucleotide or oligonucleotides, is administered to a subject having a disease, disorder or condition associated with KHK expression such that an amount or level of KHK mRNA is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of KHK mRNA prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of KHK mRNA is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of KHK mRNA in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide or oligonucleotides, pharmaceutical composition or treatment.

[0285] In some embodiments of the methods herein, an oligonucleotide or oligonucleotides herein, or a pharmaceutical composition comprising the oligonucleotide or oligonucleotides, is administered to a subject having a disease, disorder or condition associated with KHK expression such that an amount or level of KHK protein is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of KHK protein prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of KHK protein is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of KHK protein in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide, oligonucleotides or pharmaceutical composition or treatment.

[0286] In some embodiments of the methods herein, an oligonucleotide or oligonucleotides (e.g., dsRNAi

oligonucleotides) herein, or a pharmaceutical composition comprising the oligonucleotide or oligonucleotides, is administered to a subject having a disease, disorder or condition associated with KHK such that an amount or level of KHK activity/expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of KHK activity prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of KHK activity is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of KHK activity in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0287] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with KHK expression such that an amount or level of TG (e.g., one or more TGs or total TGs) is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of TG prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of TG is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of TG in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0288] Generally, a normal or desirable TG range for a human patient is <150mg/dL of blood, with <100 being considered ideal. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG of ≥ 150 mg/dL. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG in the range of 150 to 199 mg/dL, which is considered borderline high TG levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG in the range of 200 to 499mg/dL, which is considered high TG levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG in the range of 500mg/dL or higher (i.e., ≥ 500 mg/dL), which is considered very high TG levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG which is ≥ 150 mg/dL, ≥ 200 mg/dL or ≥ 500 mg/dL. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG of 200 to 499mg/dL, or 500mg/dL or higher. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG which is ≥ 200 mg/dL. In some embodiments of the methods herein, an oligonucleotide (e.g., dsRNAi oligonucleotide) herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with KHK expression such that an amount or level of cholesterol (e.g., total cholesterol,

LDL cholesterol, and/or HDL cholesterol) is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of cholesterol prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of cholesterol is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of cholesterol in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0289] Generally, a normal or desirable cholesterol range (total cholesterol) for an adult human patient is <200mg/dL of blood. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of cholesterol of ≥ 200 mg/dL. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of cholesterol in the range of 200 to 239 mg/dL, which is considered borderline high cholesterol levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of cholesterol in the range of 240mg/dL and higher (i.e., ≥ 240 mg/dL), which is considered high cholesterol levels. In some embodiments, the patient selected from treatment or treated is identified or determined to have an amount or level of cholesterol of 200 to 239 mg/dL, or 240mg/dL or higher. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of cholesterol which is ≥ 200 mg/dL or ≥ 240 mg/dL or higher.

[0290] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder, or condition associated with KHK expression such that an amount or level of liver fibrosis is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of liver fibrosis prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of liver fibrosis is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of liver fibrosis in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0291] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with KHK expression such that an amount or level of liver steatosis is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of liver steatosis prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of liver steatosis is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%,

about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of liver steatosis in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

5 **[0292]** Suitable methods for determining KHK expression, the amount or level of KHK mRNA, KHK protein, KHK activity, TG, plasma glucose or cholesterol amount or activity in the subject, or in a sample from the subject, are known in the art. Further, the Examples set forth herein illustrate methods for determining KHK expression.

[0293] In some embodiments, KHK expression, the amount or level of KHK mRNA, KHK protein, KHK activity, TG, plasma glucose, or cholesterol, is reduced in a cell (e.g., a hepatocyte), a population or a group of cells (e.g., an organoid), an organ (e.g., liver), blood or a fraction thereof (e.g., plasma), a tissue (e.g., liver tissue), a sample (e.g., a liver biopsy sample), or any other appropriate biological material obtained or isolated from the subject. In some
10 embodiments, KHK expression, the amount or level of KHK mRNA, KHK protein, KHK activity, TG, plasma glucose or cholesterol or any combination thereof, is reduced in more than one type of cell (e.g., a hepatocyte and one or more other type(s) of cell), more than one groups of cells, more than one organ (e.g., liver and one or more other organ(s)),
15 more than one fraction of blood (e.g., plasma and one or more other blood fraction(s)), more than one type of tissue (e.g., liver tissue and one or more other type(s) of tissue), or more than one type of sample (e.g., a liver biopsy sample and one or more other type(s) of biopsy sample).

[0294] Generally, a normal or desirable blood sugar level for a human patient is < 140mg/dL. Blood sugar levels between 140 and 199mg/dL two hours after eating indicates pre-diabetes, and >200mg/dL indicates diabetes. In some
20 embodiments, the patient selected for treatment or treated is identified or determined to have a level of blood sugar between about 140mg/dL and about 199mg/dL, which is considered pre-diabetes. In some embodiments, the patient selected for treatment or treated is identified or determined to have a level of blood sugar $\geq$ 200mg/dL, which is considered diabetes. In some embodiments of the methods herein, an oligonucleotide (e.g., dsRNAi oligonucleotide) herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease,
25 disorder or condition associated with *KHK* expression such that an amount or level of blood sugar is reduced to a normal or pre-diabetes range.

[0295] Examples of a disease, disorder or condition associated with KHK expression include, but are not limited to, glucose intolerance, pre-diabetes, type-1 diabetes, type-2 diabetes, metabolic liver diseases, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), drug-induced liver diseases, alcohol-induced liver
30 diseases, infectious agent induced liver diseases, inflammatory liver diseases, immune system dysfunction-mediated liver diseases, dyslipidemia, cardiovascular diseases, restenosis, syndrome X, metabolic syndrome, diabetes, obesity, hypertension, chronic cholangiopathies such as Primary Sclerosing Cholangitis (PSC), Primary Biliary Cholangitis (PBC), biliary atresia, progressive familial intrahepatic cholestasis type 3 (PFIC3), inflammatory bowel diseases, Crohn's disease, ulcerative colitis, liver cancer, hepatocellular carcinoma, gastrointestinal cancer, gastric cancer,
35 colorectal cancer, metabolic disease-induced liver fibrosis or cirrhosis, NAFLD induced fibrosis or cirrhosis, NASH-induced fibrosis or cirrhosis, alcohol-induced liver fibrosis or cirrhosis, drug-induced liver fibrosis or cirrhosis, radiation- or chemotherapy-induced fibrosis or cirrhosis, biliary tract fibrosis, liver fibrosis or cirrhosis due to any chronic

cholestatic disease, gut fibrosis of any etiology, Crohn's disease induced fibrosis, ulcerative colitis-induced fibrosis, intestine (e.g. small intestine) fibrosis, colon fibrosis, stomach fibrosis, disease of elevated uric acid (e.g. hyperuricemia, gout), sugar craving, alcohol craving, aldolase B deficiency, hereditary fructose intolerance, chronic kidney disease, diabetic nephropathy, kidney fibrosis, liver failure, liver function loss, coagulopathy, steatohepatitis, disorders of glycemic control, and other KHK-associated metabolic-related disorders and diseases. Of particular interest herein are metabolic syndrome, hypertriglyceridemia, NAFLD, NASH, obesity, or a combination thereof.

[0296] Because of their high specificity, the oligonucleotides herein (e.g., dsRNAi oligonucleotides) specifically target mRNAs of target genes of cells and tissue(s), or organs(s) (e.g., liver). In preventing disease, the target gene may be one which is required for initiation or maintenance of the disease or which has been identified as being associated with a higher risk of contracting the disease. In treating disease, the oligonucleotide can be brought into contact with the cells, tissue(s), or organ(s) (e.g., liver) exhibiting or responsible for mediating the disease. For example, an oligonucleotide substantially identical to all or part of a wild-type (*i.e.*, native) or mutated gene associated with a disorder or condition associated with KHK expression may be brought into contact with or introduced into a cell or tissue type of interest such as a hepatocyte or other liver cell.

[0297] In some embodiments, the target gene may be a target gene from any mammal, such as a human target. Any gene may be silenced according to the method described herein.

[0298] Methods described herein typically involve administering to a subject an effective amount of an oligonucleotide herein (e.g., a dsRNAi oligonucleotide), that is, an amount capable of producing a desirable therapeutic result. A therapeutically acceptable amount may be an amount that can therapeutically treat a disease or disorder. The appropriate dosage for any one subject will depend on certain factors, including the subject's size, body surface area, age, the particular composition to be administered, the active ingredient(s) in the composition, time and route of administration, general health, and other drugs being administered concurrently.

[0299] In some embodiments, a subject is administered any one of the compositions herein either enterally (e.g., orally, by gastric feeding tube, by duodenal feeding tube, *via* gastrostomy or rectally), parenterally (e.g., subcutaneous injection, intravenous injection or infusion, intra-arterial injection or infusion, intraosseous infusion, intramuscular injection, intracerebral injection, intracerebroventricular injection, intrathecal), topically (e.g., epicutaneous, inhalational, *via* eye drops, or through a mucous membrane), or by direct injection into a target organ (e.g., the liver of a subject). Typically, oligonucleotides herein are administered intravenously or subcutaneously.

[0300] As a non-limiting set of examples, the oligonucleotides herein (e.g., dsRNAi oligonucleotides) would typically be administered quarterly (once every three months), bi-monthly (once every two months), monthly or weekly. For example, the oligonucleotides may be administered every week or at intervals of two, or three weeks. Alternatively, the oligonucleotides may be administered daily. In some embodiments, a subject is administered one or more loading doses of the oligonucleotide followed by one or more maintenance doses of the oligonucleotide.

[0301] In some embodiments the oligonucleotides herein are administered alone or in combination. In some embodiments the oligonucleotides herein are administered in combination concurrently, sequentially (in any order), or intermittently. For example, two oligonucleotides may be co-administered concurrently. Alternatively, one oligonucleotide may be administered and followed any amount of time later (e.g., one hour, one day, one week or one

month) by the administration of a second oligonucleotide.

[0302] In some embodiments, the subject to be treated is a human or non-human primate or other mammalian subject. Other exemplary subjects include domesticated animals such as dogs and cats; livestock such as horses, cattle, pigs, sheep, goats, and chickens; and animals such as mice, rats, guinea pigs, and hamsters.

[0303] In some embodiments, a single dose of one or more oligonucleotides (e.g., dsRNAi oligonucleotides) herein, or a pharmaceutical composition comprising the oligonucleotide(s), is administered to a subject having a disease, disorder, or condition associated with KHK expression such that an amount or level of KHK mRNA and/or KHK protein, preferably of KHK protein, is reduced in the subject. Said reduction of an amount or level of KHK mRNA and/or KHK protein may be determined by comparison with the amount or level of KHK mRNA and/or KHK protein in a subject (e.g., a reference or control subject) not receiving the oligonucleotide(s) or pharmaceutical composition or receiving one or more control oligonucleotides or pharmaceutical compositions or treatments, or – preferably - by comparison with the amount or level of KHK mRNA and/or KHK protein prior to administration of the oligonucleotide(s) or pharmaceutical composition. Said amount or level of KHK mRNA and/or KHK protein may be determined from liver biopsy samples from the subject. Said single dose may be administered subcutaneously. Said dose of the oligonucleotide(s) may be below 10 mg/kg bodyweight of the subject, e.g. 6 mg/kg or below, in particular from 0.01 mg/kg to 5 mg/kg. Said reduction of an amount or level of KHK mRNA and/or KHK protein may be detectable more than 10 days after the single dose administration of the oligonucleotide(s), e.g. it may remain detectable at day 28, 56, and/or 84 after administration. Said reduction of an amount or level of KHK mRNA and/or KHK protein may be, e.g., at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99%. In a preferred embodiment, the reduction of an amount or level of KHK mRNA and/or KHK protein remains detectable at day 28, optionally at day 56 and/or 84, after subcutaneous administration of a single dose of one or more oligonucleotides (e.g., dsRNAi oligonucleotides) herein, or a pharmaceutical composition comprising the oligonucleotide(s).

Kits

[0304] In some embodiments, the disclosure provides a kit comprising an oligonucleotide herein, and instructions for use. In some embodiments, the kit comprises an oligonucleotide herein, and a package insert containing instructions for use of the kit and/or any component thereof. In some embodiments, the kit comprises, in a suitable container, an oligonucleotide herein, one or more controls, and various buffers, reagents, enzymes and other standard ingredients well known in the art. In some embodiments, the container comprises at least one vial, well, test tube, flask, bottle, syringe, or other container means, into which the oligonucleotide is placed, and in some instances, suitably aliquoted. In some embodiments where an additional component is provided, the kit contains additional containers into which this component is placed. The kits can also include a means for containing the oligonucleotide and any other reagent in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained. Containers and/or kits can include labeling with instructions for use and/or warnings.

[0305] In some embodiments, a kit comprises an oligonucleotide herein, and a pharmaceutically acceptable carrier, or a pharmaceutical composition comprising the oligonucleotide and instructions for treating or delaying

progression of a disease, disorder or condition associated with KHK expression in a subject in need thereof.

Definitions

[0306] As used herein, the term “antisense oligonucleotide” encompasses a nucleic acid-based molecule which has a sequence complementary to all or part of the target mRNA, in particular seed sequence thereby capable of forming a duplex with a mRNA. Thus, the term “antisense oligonucleotide”, as used herein, may be referred to as “complementary nucleic acid-based inhibitor”.

[0307] As used herein, “approximately” or “about”, as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0308] As used herein, “administer”, “administering”, “administration” and the like refers to providing a substance (e.g., an oligonucleotide) to a subject in a manner that is pharmacologically useful (e.g., to treat a condition in the subject).

[0309] As used herein, “attenuate”, “attenuating”, “attenuation” and the like refers to reducing or effectively halting. As a non-limiting example, one or more of the treatments herein may reduce or effectively halt the onset or progression of dyslipidemia/hypertriglyceridemia/hyperlipidemia, NAFLD, NASH, or glucose intolerance in a subject. This attenuation may be exemplified by, for example, a decrease in one or more aspects (e.g., symptoms, tissue characteristics, and cellular, inflammatory or immunological activity, etc.) of dyslipidemia/hypertriglyceridemia/hyperlipidemia, NAFLD, NASH, or glucose intolerance, no detectable progression (worsening) of one or more aspects of dyslipidemia/hypertriglyceridemia/hyperlipidemia, NAFLD, NASH, or glucose intolerance, or no detectable aspects of dyslipidemia/hypertriglyceridemia/hyperlipidemia, NAFLD, NASH, or glucose intolerance in a subject when they might otherwise be expected.

[0310] As used herein, “complementary” refers to a structural relationship between two nucleotides (e.g., on two opposing nucleic acids or on opposing regions of a single nucleic acid strand) that permits the two nucleotides to form base pairs with one another. For example, a purine nucleotide of one nucleic acid that is complementary to a pyrimidine nucleotide of an opposing nucleic acid may base pair together by forming hydrogen bonds with one another. In some embodiments, complementary nucleotides can base pair in the Watson-Crick manner or in any other manner that allows for the formation of stable duplexes. In some embodiments, two nucleic acids may have regions of multiple nucleotides that are complementary with each other to form regions of complementarity, as described herein.

[0311] As used herein, “deoxyribonucleotide” refers to a nucleotide having a hydrogen in place of a hydroxyl at the 2' position of its pentose sugar when compared with a ribonucleotide. A modified deoxyribonucleotide is a deoxyribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the sugar, phosphate group or base.

[0312] As used herein, “double-stranded oligonucleotide” or “ds oligonucleotide” refers to an oligonucleotide that is substantially in a duplex form. In some embodiments, the complementary base-pairing of duplex region(s) of a double-

stranded oligonucleotide is formed between antiparallel sequences of nucleotides of covalently separate nucleic acid strands. In some embodiments, complementary base-pairing of duplex region(s) of a double-stranded oligonucleotide is formed between antiparallel sequences of nucleotides of nucleic acid strands that are covalently linked. In some embodiments, complementary base-pairing of duplex region(s) of a double-stranded oligonucleotide is formed from single nucleic acid strand that is folded (*e.g.*, *via* a hairpin) to provide complementary antiparallel sequences of nucleotides that base pair together. In some embodiments, a double-stranded oligonucleotide comprises two covalently separate nucleic acid strands that are fully duplexed with one another. However, in some embodiments, a double-stranded oligonucleotide comprises two covalently separate nucleic acid strands that are partially duplexed (*e.g.*, having overhangs at one or both ends). In some embodiments, a double-stranded oligonucleotide comprises antiparallel sequence of nucleotides that are partially complementary, and thus, may have one or more mismatches, which may include internal mismatches or end mismatches.

[0313] As used herein, “duplex,” in reference to nucleic acids (*e.g.*, oligonucleotides), refers to a structure formed through complementary base pairing of two antiparallel sequences of nucleotides.

[0314] As used herein, “excipient” refers to a non-therapeutic agent that may be included in a composition, for example, to provide or contribute to a desired consistency or stabilizing effect.

[0315] As used herein, the phrase “glucose intolerance” refers to a metabolic condition resulting in higher-than-normal levels of blood glucose. Glucose intolerance can include type 1, type 1.5, and type 2 diabetes.

[0316] As used herein, “hepatocyte” or “hepatocytes” refers to cells of the parenchymal tissues of the liver. These cells make up about 70%-85% of the liver's mass and manufacture serum albumin, FBN and the prothrombin group of clotting factors (except for Factors 3 and 4). Markers for hepatocyte lineage cells include, but are not limited to, transthyretin (Ttr), glutamine synthetase (Glut), hepatocyte nuclear factor 1a (Hnf1a) and hepatocyte nuclear factor 4a (Hnf4a). Markers for mature hepatocytes may include, but are not limited to, cytochrome P450 (Cyp3a11), fumarylacetoacetate hydrolase (Fah), glucose 6-phosphate (G6p), albumin (Alb) and OC2-2F8. See, *e.g.*, Huch *et al.* (2013) *Nature* 494:247-50.

[0317] As used herein, a “hepatotoxic agent” refers to a chemical compound, virus or other substance that is itself toxic to the liver or can be processed to form a metabolite that is toxic to the liver. Hepatotoxic agents may include, but are not limited to, carbon tetrachloride (CCl₄), acetaminophen (paracetamol), vinyl chloride, arsenic, chloroform, nonsteroidal anti-inflammatory drugs (such as aspirin and phenylbutazone).

[0318] As used herein, the term “ketohexokinase” or “KHK” refers to an enzyme, specifically a hepatic fructokinase, that catalyzes the phosphorylation of fructose. The KHK gene encodes two protein isoforms (KHK-A and KHK-C). The two products are generated from the same primary transcript by alternative splicing. The term “KHK” is intended to refer to both isoforms unless stated otherwise. ‘KHK’ may also refer to the gene which encodes the protein.

[0319] As used herein, “labile linker” refers to a linker that can be cleaved (*e.g.*, by acidic pH). A “fairly stable linker” refers to a linker that cannot be cleaved.

[0320] As used herein, “liver inflammation” or “hepatitis” refers to a physical condition in which the liver becomes swollen, dysfunctional and/or painful, especially as a result of injury or infection, as may be caused by exposure to a hepatotoxic agent. Symptoms may include jaundice (yellowing of the skin or eyes), fatigue, weakness, nausea,

vomiting, appetite reduction and weight loss. Liver inflammation, if left untreated, may progress to fibrosis, cirrhosis, liver failure or liver cancer.

[0321] As used herein, "liver fibrosis", "Liver Fibrosis" or "fibrosis of the liver" refers to an excessive accumulation in the liver of extracellular matrix proteins, which could include collagens (I, III, and IV), FBN, undulin, elastin, laminin, hyaluronan and proteoglycans resulting from inflammation and liver cell death. Liver fibrosis, if left untreated, may progress to cirrhosis, liver failure or liver cancer.

[0322] As used herein, "loop" refers to an unpaired region of a nucleic acid (e.g., oligonucleotide) that is flanked by two antiparallel regions of the nucleic acid that are sufficiently complementary to one another, such that under appropriate hybridization conditions (e.g., in a phosphate buffer, in a cell), the two antiparallel regions, which flank the unpaired region, hybridize to form a duplex (referred to as a "stem").

[0323] As used herein, "Metabolic syndrome" or "metabolic liver disease" refers to a disorder characterized by a cluster of associated medical conditions and associated pathologies including, but not limited to the following medical conditions: abdominal obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, liver fibrosis, and low levels of high-density lipoprotein (HDL) levels. As used herein, the term metabolic syndrome or metabolic liver disease may encompass a wide array of direct and indirect manifestations, diseases and pathologies associated with metabolic syndrome and metabolic liver disease, with an expanded list of conditions used throughout the document.

[0324] As used herein, "modified internucleotide linkage" refers to an internucleotide linkage having one or more chemical modifications when compared with a reference internucleotide linkage comprising a phosphodiester bond. In some embodiments, a modified nucleotide is a non-naturally occurring linkage. Typically, a modified internucleotide linkage confers one or more desirable properties to a nucleic acid in which the modified internucleotide linkage is present. For example, a modified internucleotide linkage may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, etc.

[0325] As used herein, "modified nucleotide" refers to a nucleotide having one or more chemical modifications when compared with a corresponding reference nucleotide selected from: adenine ribonucleotide, guanine ribonucleotide, cytosine ribonucleotide, uracil ribonucleotide, adenine deoxyribonucleotide, guanine deoxyribonucleotide, cytosine deoxyribonucleotide and thymidine deoxyribonucleotide. In some embodiments, a modified nucleotide is a non-naturally occurring nucleotide. In some embodiments, a modified nucleotide has one or more chemical modification in its sugar, nucleobase and/or phosphate group. In some embodiments, a modified nucleotide has one or more chemical moieties conjugated to a corresponding reference nucleotide. Typically, a modified nucleotide confers one or more desirable properties to a nucleic acid in which the modified nucleotide is present. For example, a modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, etc.

[0326] As used herein, "nicked tetraloop structure" refers to a structure of a RNAi oligonucleotide that is characterized by separate sense (passenger) and antisense (guide) strands, in which the sense strand has a region of complementarity with the antisense strand, and in which at least one of the strands, generally the sense strand, has a tetraloop configured to stabilize an adjacent stem region formed within the at least one strand.

[0327] As used herein, “oligonucleotide” refers to a short nucleic acid (e.g., less than about 100 nucleotides in length). An oligonucleotide may be single-stranded (ss) or ds. An oligonucleotide may or may not have duplex regions. As a set of non-limiting examples, an oligonucleotide may be, but is not limited to, a small interfering RNA (siRNA), microRNA (miRNA), short hairpin RNA (shRNA), dicer substrate interfering RNA (DsiRNA), antisense oligonucleotide, short siRNA or ss siRNA. In some embodiments, a double-stranded (dsRNA) is an RNAi oligonucleotide.

[0328] As used herein, “overhang” (or “overhang sequence”) refers to terminal non-base pairing nucleotide(s) resulting from one strand or region extending beyond the terminus of a complementary strand with which the one strand or region forms a duplex. In some embodiments, an overhang comprises one or more unpaired nucleotides extending from a duplex region at the 5' terminus or 3' terminus of a dsRNA. In certain embodiments, the overhang is a 3' or 5' overhang on the antisense strand or sense strand of a dsRNA.

[0329] As used herein, “phosphate analog” refers to a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. In some embodiments, a phosphate analog is positioned at the 5' terminal nucleotide of an oligonucleotide in place of a 5'-phosphate, which is often susceptible to enzymatic removal. In some embodiments, a 5' phosphate analog contains a phosphatase-resistant linkage. Examples of phosphate analogs include, but are not limited to, 5' phosphonates, such as 5' methylene phosphonate (5'-MP) and 5'-(E)-vinylphosphonate (5'-VP). In some embodiments, an oligonucleotide has a phosphate analog at a 4'-carbon position of the sugar (referred to as a “4'-phosphate analog”) at a 5'-terminal nucleotide. An example of a 4'-phosphate analog is oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (e.g., at its 4'-carbon) or analog thereof. See, e.g., US Patent Publication No. 2019-0177729. Other modifications have been developed for the 5' end of oligonucleotides (see, e.g., Intl. Patent Application No. WO 2011/133871; US Patent No. 8,927,513; and Prakash *et al.* (2015) NUCLEIC ACIDS RES. 43:2993-3011).

[0330] As used herein, “reduced expression” of a gene (e.g., KHK) refers to a decrease in the amount or level of RNA transcript (e.g., KHK mRNA) or protein encoded by the gene and/or a decrease in the amount or level of activity of the gene in a cell, a population of cells, a sample, or a subject, when compared to an appropriate reference (e.g., a reference cell, population of cells, sample or subject). For example, the act of contacting a cell with an oligonucleotide herein (e.g., an oligonucleotide comprising an antisense strand having a nucleotide sequence that is complementary to a nucleotide sequence comprising KHK mRNA) may result in a decrease in the amount or level of KHK mRNA, protein and/or activity (e.g., via degradation of KHK mRNA by the RNAi pathway) when compared to a cell that is not treated with the dsRNA. Similarly, and as used herein, “reducing expression” refers to an act that results in reduced expression of a gene (e.g., KHK).

[0331] As used herein, “reduction of KHK expression” refers to a decrease in the amount or level of KHK mRNA, KHK protein and/or KHK activity in a cell, a population of cells, a sample or a subject when compared to an appropriate reference (e.g., a reference cell, population of cells, sample, or subject).

[0332] As used herein, “region of complementarity” refers to a sequence of nucleotides of a nucleic acid (e.g., a dsRNA) that is sufficiently complementary to an antiparallel sequence of nucleotides to permit hybridization between the two sequences of nucleotides under appropriate hybridization conditions (e.g., in a phosphate buffer, in a cell, *etc.*). In some embodiments, an oligonucleotide herein comprises a targeting sequence having a region of complementarity

to a mRNA target sequence. In some embodiments, the region of complementarity is full complementary. In some embodiments, the region of complementarity is partially complementary (e.g., up to 3 nucleotide mismatches).

[0333] As used herein, "ribonucleotide" refers to a nucleotide having a ribose as its pentose sugar, which contains a hydroxyl group at its 2' position. A modified ribonucleotide is a ribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the ribose, phosphate group or base.

[0334] As used herein, "RNAi oligonucleotide" refers to either (a) a double-stranded oligonucleotide having a sense strand (passenger) and antisense strand (guide), in which the antisense strand or part of the antisense strand is used by the *Argonaute 2* (Ago2) endonuclease in the cleavage of a target mRNA (e.g., KHK mRNA) or (b) a single-stranded oligonucleotide having a single antisense strand, where that antisense strand (or part of that antisense strand) is used by the Ago2 endonuclease in the cleavage of a target mRNA (e.g., KHK mRNA).

[0335] As used herein, "strand" refers to a single, contiguous sequence of nucleotides linked together through internucleotide linkages (e.g., phosphodiester linkages or phosphorothioate linkages). In some embodiments, a strand has two free ends (e.g., a 5' end and a 3' end).

[0336] As used herein, "subject" means any mammal, including mice, rabbits, and humans. In one embodiment, the subject is a human or NHP. Moreover, "individual" or "patient" may be used interchangeably with "subject."

[0337] As used herein, "synthetic" refers to a nucleic acid or other molecule that is artificially synthesized (e.g., using a machine (e.g., a solid-state nucleic acid synthesizer)) or that is otherwise not derived from a natural source (e.g., a cell or organism) that normally produces the molecule.

[0338] As used herein, "targeting ligand" refers to a molecule (e.g., a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid) that selectively binds to a cognate molecule (e.g., a receptor) of a tissue or cell of interest and that is conjugatable to another substance for purposes of targeting the other substance to the tissue or cell of interest. For example, in some embodiments, a targeting ligand may be conjugated to an oligonucleotide for purposes of targeting the oligonucleotide to a specific tissue or cell of interest. In some embodiments, a targeting ligand selectively binds to a cell surface receptor. Accordingly, in some embodiments, a targeting ligand when conjugated to an oligonucleotide facilitates delivery of the oligonucleotide into a particular cell through selective binding to a receptor expressed on the surface of the cell and endosomal internalization by the cell of the complex comprising the oligonucleotide, targeting ligand and receptor. In some embodiments, a targeting ligand is conjugated to an oligonucleotide *via* a linker that is cleaved following or during cellular internalization such that the oligonucleotide is released from the targeting ligand in the cell.

[0339] As used herein, "tetraloop" refers to a loop that increases stability of an adjacent duplex formed by hybridization of flanking sequences of nucleotides. The increase in stability is detectable as an increase in melting temperature (T_m) of an adjacent stem duplex that is higher than the T_m of the adjacent stem duplex expected, on average, from a set of loops of comparable length consisting of randomly selected sequences of nucleotides. For example, a tetraloop can confer a T_m of at least about 50°C, at least about 55°C, at least about 56°C, at least about 58°C, at least about 60°C, at least about 65°C or at least about 75°C in 10 mM Na_2HPO_4 to a hairpin comprising a duplex of at least 2 base pairs (bp) in length. In some embodiments, a tetraloop can confer a T_m of at least about

50°C, at least about 55°C, at least about 56°C, at least about 58°C, at least about 60°C, at least about 65°C or at least about 75°C in 10 mM NaH₂PO₄ to a hairpin comprising a duplex of at least 2 base pairs (bp) in length. In some embodiments, a tetraloop may stabilize a bp in an adjacent stem duplex by stacking interactions. In addition, interactions among the nucleotides in a tetraloop include, but are not limited to, non-Watson-Crick base pairing, stacking interactions, hydrogen bonding and contact interactions (Cheong *et al.* (1990) NATURE 346:680-82; Heus & Pardi (1991) SCIENCE 253:191-94). In some embodiments, a tetraloop comprises or consists of 3 to 6 nucleotides and is typically 4 to 5 nucleotides. In certain embodiments, a tetraloop comprises or consists of 3, 4, 5 or 6 nucleotides, which may or may not be modified (e.g., which may or may not be conjugated to a targeting moiety). In one embodiment, a tetraloop consists of 4 nucleotides. Any nucleotide may be used in the tetraloop and standard IUPAC-IUB symbols for such nucleotides may be used as described in Cornish-Bowden (1985) *Nucleic Acids Res.* 13:3021-3030. For example, the letter "N" may be used to mean that any base may be in that position, the letter "R" may be used to show that A (adenine) or G (guanine) may be in that position, and "B" may be used to show that C (cytosine), G (guanine), or T (thymine) may be in that position. Examples of tetraloops include the UCG family of tetraloops (e.g., UUCG), the GNRA family of tetraloops (e.g., GAAA), and the CUUG tetraloop (Woese *et al.* (1990) PROC. NATL. ACAD. SCI. USA 87:8467-8471; Antao *et al.* (1991) NUCLEIC ACIDS RES. 19:5901-5905). Examples of DNA tetraloops include the d(GNNA) family of tetraloops (e.g., d(GTTA), the d(GNRA)) family of tetraloops, the d(GNAB) family of tetraloops, the d(CNNG) family of tetraloops, and the d(TNCG) family of tetraloops (e.g., d(TTCG)). See, e.g., Nakano *et al.* (2002) BIOCHEM. 41:14281-92; Okabe *et al.* (2000) NIPPON KAGAKKAI KOEN YOKOSHU 78:731. In some embodiments, the tetraloop is contained within a nicked tetraloop structure.

[0340] As used herein, "treat" or "treating" refers to the act of providing care to a subject in need thereof, for example, by administering a therapeutic agent (e.g., an oligonucleotide herein) to the subject, for purposes of improving the health and/or well-being of the subject with respect to an existing condition (e.g., a disease, disorder) or to prevent or decrease the likelihood of the occurrence of a condition. In some embodiments, treatment involves reducing the frequency or severity of at least one sign, symptom or contributing factor of a condition (e.g., disease, disorder) experienced by a subject.

EXAMPLES

[0341] While the disclosure has been described with reference to the specific embodiments set forth in the following Examples, it should be understood by those skilled in the art that various changes may be made, and equivalents may be substituted without departing from the true spirit and scope of the disclosure. Further, the following Examples are offered by way of illustration and are not intended to limit the scope of the disclosure in any manner. In addition, modifications may be made to adapt to a situation, material, composition of matter, process, process step or steps, to the objective, spirit, and scope of the disclosure. All such modifications are intended to be within the scope of the disclosure. Standard techniques well known in the art or the techniques specifically described below were utilized.

RNAi agents targeting KHK have been described and tested *in vitro* (e.g., WO 2015123264 and WO 2020060986). The following studies describe the identification of novel dsRNAi agents useful for reducing or inhibiting KHK expression based on *in vitro* and *in vivo* screening, including studies in non-human primates. The novel dsRNAi agents

comprise 36mer sense strands and 22mer antisense strands with a stem loop having a nicked tetraloop conjugated to GalNAc moieties at the 3' end of the sense strand for reducing KHK mRNA. The presence of a nick within the stem loop provides a pre-cut antisense strand to form a pre-processed binding substrate for the Dicer enzyme, allowing Dicer to efficiently bind and hand off the double stranded molecule to Ago2. The tetraloop provides a thermodynamically stabilizing element to prevent the loop from opening and exposing the 5'-end of the antisense strand and the 3'-end of the sense strand, thereby providing increased nuclease resistance. Accordingly, the present dsRNAi agents are particularly useful for inhibiting KHK expression *in vitro* and *in vivo* as described in the following examples.

In comparison to dsRNAi agents described in the prior art, the dsRNAi agents presented herein may, in particular, show improved *in vitro* and/or *in vivo* reduction or inhibition of KHK expression as determined on the KHK mRNA and/or KHK protein level. Such improvement may relate to the size and/or duration of the inhibitory action. Thus, for instance, for medical uses of the dsRNAi agents according to this invention, lower doses and/or lower dose frequencies may be applicable. Also, dsRNAi agents presented herein may benefit from advantageous safety and tolerability features like high specificity, low off-target effects or reduced immunogenicity.

Example 1: Preparation of Double-Stranded RNAi Oligonucleotides

Oligonucleotide Synthesis and Purification

[0342] The double-stranded RNAi (dsRNA) oligonucleotides described in the foregoing Examples are chemically synthesized using methods described herein. Generally, dsRNAi oligonucleotides are synthesized using solid phase oligonucleotide synthesis methods as described for 19-23mer siRNAs (see, e.g., Scaringe *et al.* (1990) NUCLEIC ACIDS RES. 18:5433-5441 and Usman *et al.* (1987) J. AM. CHEM. SOC. 109:7845-7845; see also, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,008,400; 6,111,086; 6,117,657; 6,353,098; 6,362,323; 6,437,117 and 6,469,158) in addition to using known phosphoramidite synthesis (see, e.g. Hughes and Ellington (2017) COLD SPRING HARB PERSPECT BIOL. 9(1):a023812; Beaucage S.L., Caruthers M.H., *Studies on Nucleotide Chemistry V: Deoxynucleoside Phosphoramidites—A New Class of Key Intermediates for Deoxypolynucleotide Synthesis*, TETRAEDRON LETT. 1981; 22:1859–62. doi: 10.1016/S0040-4039(01)90461-7). dsRNAi oligonucleotides having a 19mer core sequence were formatted into constructs having a 25mer sense strand and a 27mer antisense strand to allow for processing by the RNAi machinery. The 19mer core sequence is complementary to a region in the KHK mRNA.

[0343] Individual RNA strands were synthesized and HPLC purified according to standard methods (Integrated DNA Technologies; Coralville, IA). For example, RNA oligonucleotides were synthesized using solid phase phosphoramidite chemistry, deprotected and desalted on NAP-5 columns (Amersham Pharmacia Biotech; Piscataway, NJ) using standard techniques (Damha & Olgivie (1993) METHODS MOL. BIOL. 20:81-114; Wincott *et al.* (1995) NUCLEIC ACIDS RES. 23:2677-84). The oligomers were purified using ion-exchange high performance liquid chromatography (IE-HPLC) on an Amersham Source 15Q column (1.0 cm×25 cm; Amersham Pharmacia Biotech) using a 15 min step-linear gradient. The gradient varied from 90:10 Buffers A:B to 52:48 Buffers A:B, where Buffer A is 100 mM Tris pH 8.5 and Buffer B is 100 mM Tris pH 8.5, 1 M NaCl. Samples were monitored at 260 nm and peaks corresponding to the full-length oligonucleotide species were collected, pooled, desalted on NAP-5 columns, and lyophilized.

[0344] The purity of each oligomer was determined by capillary electrophoresis (CE) on a Beckman PACE 5000

(Beckman Coulter, Inc.; Fullerton, CA). The CE capillaries have a 100 µm inner diameter and contain ssDNA 100R Gel (Beckman-Coulter). Typically, about 0.6 nmole of oligonucleotide was injected into a capillary, run in an electric field of 444 V/cm, and was detected by UV absorbance at 260 nm. Denaturing Tris-Borate-7 M-urea running buffer was purchased from Beckman-Coulter. Oligoribonucleotides were obtained that were at least 90% pure as assessed by CE for use in experiments described below. Compound identity was verified by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy on a Voyager DE™ Biospectrometry Work Station (Applied Biosystems; Foster City, CA) following the manufacturer's recommended protocol. Relative molecular masses of all oligomers were obtained, often within 0.2% of expected molecular mass.

Preparation of Duplexes

[0345] Single strand RNA oligomers were resuspended (e.g., at 100 µM concentration) in duplex buffer consisting of 100 mM potassium acetate, 30 mM HEPES, pH 7.5. Complementary sense and antisense strands were mixed in equal molar amounts to yield a final solution of, for example, 50 µM duplex. Samples were heated to 100°C for 5' in RNA buffer (IDT) and were allowed to cool to room temperature before use. The dsRNA oligonucleotides were stored at -20° C. Single strand RNA oligomers were stored lyophilized or in nuclease-free water at -80° C.

Example 2: Generation of *KHK*-Targeting Double-Stranded (DS) RNAi Oligonucleotides

Identification of *KHK* mRNA Target Sequences

[0346] Ketohexokinase (*KHK*) is an enzyme involved in fructose metabolism. *KHK* has two isoforms, differing by one alternative exon, with distinct substrates and mechanisms of action. The isoform *KHK-A* is encoded by Exon 3A whereas the *KHK-C* isoform is encoded by Exon 3C. To generate RNAi oligonucleotide inhibitors of *KHK-A* and *KHK-C* expression, a computer-based algorithm was used to computationally identify *KHK* mRNA target sequences suitable for assaying inhibition of *KHK* expression by the RNAi pathway. The algorithm provided RNAi oligonucleotide guide (antisense) strand sequences each having a region of complementarity to a suitable *KHK* target sequence of human *KHK* mRNA (e.g., SEQ ID NO: 1; **Table 1**). Some of the guide strand sequences identified by the algorithm were also complementary to the corresponding *KHK* target sequence of monkey and/or mouse *KHK* mRNA (SEQ ID NO: 2 and 3, respectively; **Table 1**). *KHK* RNAi oligonucleotides comprising a region of complementarity to homologous *KHK* mRNA target sequences with nucleotide sequence similarity are predicted to have the ability to target homologous *KHK* mRNAs.

Table 1: Sequences of Human, Monkey and Mouse *KHK* mRNA

Species	Ref Seq #	SEQ ID NO
Human (Hs)	NM_006488.3	1
Cynomolgus monkey (Mf)	XM_005576322.2	2
Mouse (Mm)	NM_008439.4	3

[0347] RNAi oligonucleotides (formatted as DsiRNA oligonucleotides) were generated as described in **Example 1** for evaluation *in vitro*. Each DsiRNA was generated with the same modification pattern, and each with a unique guide

strand having a region of complementarity to a *KHK* target sequence identified by the algorithm (**Table 2**). Modifications for the sense and anti- sense DsiRNA included the following (X- any nucleotide ; *m*- 2'-O-methyl modified nucleotide; *r*- ribosyl modified nucleotide):

5 **Sense Strand:**

rXmXrXmXrXrXrXrXrXrXrXmXrXmXrXrXrXrXrXXX

Anti-sense Strand:

mXmXmXmXrXrXrXrXrXmXmXrXrXrXrXrXrXmXrXmXmXmX

10 *In Vitro Cell-Based Assays*

[0348] The ability of each of the modified DsiRNA in **Table 2** to reduce *KHK* mRNA was measured using *in vitro* cell-based assays. Briefly, human hepatoma (Hep3B) cells expressing endogenous human *KHK* gene were transfected with each of the DsiRNAs listed in **Table 2** (Sense Strand SEQ ID NOs: 4-387) at 1 nM in separate wells of a multi-well cell-culture plate. Cells were maintained for 24 hours following transfection with the modified DsiRNA, and then the amount of remaining *KHK* mRNA from the transfected cells was determined using TAQMAN®-based qPCR assays. Two qPCR assays, a 3' assay (Forward-1026; TGGAGGTGGAGAAGCCA, Reverse-1157; GACCATACAAGCCCCTCAAG, Probe-1080; TGGTGTTCAGCAAAGATGTGGC) and a 5' assay (Forward-496; AGGAAGCTCTGGGAGTA, Reverse-596; CTCCTTAGGGTACTTGTC, Probe-518; ATGGAAGAGAAGCAGATCCTGTGCG) were used to determine *KHK* mRNA levels as measured using PCR probes conjugated to 6-carboxy-fluorescein (FAM). Each primer pair (*KHK*-825 for *KHK*-C isoform, NM_006488.3) and *KHK*-All (both isoforms) (*KHK*-F495, *KHK*-F1026 for *KHK*-All (both isoforms) was assayed for % remaining RNA as shown in **Table 2 and FIG. 1**. DsiRNAs resulting in less than or equal to 10% *KHK* mRNA remaining in DsiRNA-transfected cells when compared to mock-transfected cells were considered DsiRNA "hits". The Hep3B cell-based assay evaluating the ability of the DsiRNAs listed in **Table 2** to inhibit *KHK* expression identified several candidate DsiRNAs.

[0349] Taken together, these results show that DsiRNAs designed to target human *KHK* mRNA inhibit *KHK* expression in cells, as determined by a reduced amount of *KHK* mRNA in DsiRNA-transfected cells relative to control cells. These results demonstrate that the nucleotide sequences comprising the DsiRNA are useful for generating RNAi oligonucleotides to inhibit *KHK* expression. Further, these results demonstrate that multiple *KHK* mRNA target sequences are suitable for the RNAi-mediated inhibition of *KHK* expression.

Table 2. Analysis of *KHK* mRNA in HepB3 cells

			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
4	388	KHK-115-154	28.3	2.4	33.1	2.7	30.22	6.148	30.5
5	389	KHK-116-155	27.8	5.9	33.3	6.5	25.691	8.728	28.9
6	390	KHK-117-156	26.7	9.9	47.5	14.6	32.656	13.903	35.6
7	391	KHK-118-157	43.7	6.3	63.9	6.4	47.299	13.144	51.6
8	392	KHK-119-158	34.6	8.6	57.5	14.7	22.791	11.895	38.3
9	393	KHK-120-159	31.4	3.8	49.7	3.5	40.388	5.289	40.5
10	394	KHK-121-160	35.8	4.4	53.2	5.7	43.359	8.043	44.1
11	395	KHK-122-161	41.8	3.7	67.6	6.5	39.75	5.587	49.7
12	396	KHK-123-162	49.5	3.7	66.7	4.6	41.386	7.102	52.5
13	397	KHK-124-163	30.9	2.5	49.6	4.4	40.966	7.589	40.5
14	398	KHK-125-164	39.5	3.7	52.5	5.1	43.748	9.465	45.3
15	399	KHK-126-165	37.1	2.8	57.9	5.2	53.25	7.484	49.4
16	400	KHK-127-166	38.6	3.1	63.0	4.3	45.393	5.073	49.0
17	401	KHK-128-167	31.1	2.6	44.6	3.3	47.943	5.962	41.2
18	402	KHK-179	28.9	23.1	81.2	21.2	62.845	5.928	57.6
19	403	KHK-181-220	43.4	5.3	57.6	5.6	56.679	10.519	52.5
20	404	KHK-182-221	33.8	1.8	40.4	3.4	50.153	10.698	41.5
21	405	KHK-183-222	48.9	3.5	57.7	5.4	58.074	7.904	54.9
22	406	KHK-184-223	37.0	2.6	38.5	3.0	49.417	4.396	41.6
23	407	KHK-185-224	34.3	4.0	44.8	4.3	53.186	7.765	44.1
24	408	KHK-186-225	36.1	4.9	42.4	5.0	51.087	6.631	43.2
25	409	KHK-187-226	48.5	3.9	48.2	4.5	81.75	6.116	59.5
26	410	KHK-188-227	50.9	2.8	50.5	5.6	75.858	6.936	59.1
27	411	KHK-431-470	38.7	2.5	42.1	3.8	52.142	5.549	44.3
28	412	KHK-432-471	74.1	38.8	65.5	11.0	50.476	11.385	63.3
29	413	KHK-433-472	53.1	8.6	72.4	9.0	47.428	12.036	57.7

			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
30	414	KHK-507-545-376-218	23.8	3.1	31.1	2.5	84.241	10.972	46.4
31	415	KHK-508-546-377-219	15.7	1.8	43.7	2.6	52.076	6.767	37.2
32	416	KHK-509-547-378-220	10.9	2.4	24.5	4.2	25.526	5.12	20.3
33	417	KHK-510-548-379-221	9.1	3.2	15.0	5.0	15.853	4.385	13.3
34	418	KHK-511-549-380-222	10.4	3.0	23.8	3.5	17.016	6.998	17.1
35	419	KHK-512-550-381-223	6.5	2.2	28.8	8.3	33.059	5.266	22.8
36	420	KHK-513-551-382-224	25.4	8.6	25.2	3.2	22.514	5.225	24.4
37	421	KHK-514-552-383-225	16.4	4.8	33.5	11.4	45.353	14.944	31.7
38	422	KHK-515-553-384-226	66.1	4.5	47.0	3.6	150.28	13.471	87.8
39	423	KHK-516-554-385-227	10.6	2.6	19.4	5.6	27.145	7.112	19.0
40	424	KHK-517-555-386-228	12.0	3.4	24.7	6.3	24.382	9.127	20.4
41	425	KHK-518-556-387-229	15.9	5.6	23.1	6.5	16.128	6.295	18.4
42	426	KHK-520-558-389-231	8.9	1.9	15.6	3.4	20.589	4.844	15.0
43	427	KHK-521-559-390-232	5.0	2.9	23.6	6.4	23.218	8.661	17.3
44	428	KHK-522-560-391-233	9.7	1.7	12.3	2.7	12.226	3.342	11.4
45	429	KHK-541-579	17.8	1.5	26.0	2.6	27.272	5.808	23.7
46	430	KHK-544-582	22.9	2.7	18.4	1.9	59.795	8.985	33.7
47	431	KHK-546-584	30.6	5.8	42.2	7.1	35.433	9.834	36.1

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
48	432	KHK-547-585	12.2	1.9	17.8	2.6	20.431	7.549	16.8
49	433	KHK-548-586	11.8	2.3	25.1	7.8	7.622	2.199	14.8
50	434	KHK-549-587	12.2	2.0	15.0	3.6	14.783	3.155	14.0
51	435	KHK-550-588	15.9	6.2	23.7	8.1	18.365	7.143	19.3
52	436	KHK-551-589	24.7	4.2	34.8	6.1	14.11	5.994	24.5
53	437	KHK-552-590	24.6	4.3	30.5	5.3	22.483	8.443	25.9
54	438	KHK-553-591	16.1	1.6	27.3	4.3	21.753	4.168	21.7
55	439	KHK-554-592	18.9	6.7	26.3	9.0	20.976	8.622	22.1
56	440	KHK-555-593	22.2	7.1	27.2	10.4	24.612	15.246	24.7
57	441	KHK-556-594	25.9	7.5	32.3	9.9	24.205	11.232	27.5
58	442	KHK-557-595	15.1	1.9	18.9	2.2	29.27	5.8	21.1
59	443	KHK-558-596	25.6	8.0	24.2	11.2	29.227	13.255	26.4
60	444	KHK-559-597	21.3	1.9	29.7	1.8	23.268	4.973	24.8
61	445	KHK-560-598	58.6	2.8	77.3	4.2	61.287	4.768	65.7
62	446	KHK-561-599	14.7	2.2	28.9	3.3	23.131	4.888	22.3
63	447	KHK-562-600	15.1	5.1	21.2	6.5	22.347	6.503	19.6
64	448	KHK-563-601	34.7	1.7	47.5	2.5	63.417	8.195	48.5
65	449	KHK-564-602	19.2	1.8	30.1	2.4	44.737	9.177	31.3
66	450	KHK-565-603	55.7	3.1	73.0	5.6	106.349	11.887	78.3
67	451	KHK-566-604	19.7	1.0	30.1	2.8	31.606	2.125	27.1
68	452	KHK-567-605	9.9	0.5	15.4	1.3	14.15	2.218	13.2
69	453	KHK-568-606	15.6	1.0	19.6	1.1	21.246	2.662	18.8
70	454	KHK-569-607	45.3	5.4	53.3	5.9	42.462	12.958	47.0
71	455	KHK-570-608	14.6	1.4	21.6	2.3	24.089	3.615	20.1
72	456	KHK-571-609	15.4	1.8	17.4	1.9	28.812	4.966	20.6
73	457	KHK-572-610	27.2	1.2	33.3	2.2	38.47	4.931	33.0
74	458	KHK-573-611	20.6	1.7	23.1	2.1	50.396	5.757	31.4

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
75	459	KHK-574-612	19.8	1.6	27.3	2.2	29.683	5.49	25.6
76	460	KHK-575-613	31.1	1.9	31.2	2.4	37.359	5.282	33.2
77	461	KHK-576-614	30.0	4.0	32.2	1.9	19.014	3.763	27.1
78	462	KHK-577-615	20.8	1.9	31.6	2.8	22.807	5.999	25.1
79	463	KHK-638-676	25.1	2.0	27.0	2.0	38.226	3.255	30.1
80	464	KHK-641-679	29.0	1.7	33.5	2.0	30.662	5.567	31.0
81	465	KHK-642-680	22.6	2.6	31.3	2.7	12.983	3.632	22.3
82	466	KHK-643-681	39.1	2.1	41.5	2.4	38.644	6.762	39.7
83	467	KHK-644-682	25.3	3.2	34.7	7.5	11.343	4.407	23.8
84	468	KHK-645-683	15.9	5.0	21.0	3.1	21.433	1.586	19.5
85	469	KHK-646-684	22.8	1.8	30.8	2.2	13.876	3.967	22.5
86	470	KHK-647-685	38.8	1.5	41.9	2.4	32.316	6.062	37.7
87	471	KHK-650-688	40.6	2.1	42.3	3.2	41.675	12.029	41.5
88	472	KHK-676-714	56.0	2.4	52.8	2.8	71.792	10.911	60.2
89	473	KHK-713-722	71.9	3.5	78.9	3.4	49.345	10.259	66.7
90	474	KHK-826-835	87.0	6.4	101.5	5.1	76.866	14.977	88.5
91	475	KHK-827-836	62.3	2.7	98.9	8.8	29.087	3.652	63.4
92	476	KHK-829-838	100.3	4.5	86.8	5.3	17.67	3.397	68.3
93	477	KHK-830-839	67.4	3.2	81.8	3.6	17.686	2.276	55.6
94	478	KHK-831-840	61.7	3.4	69.8	5.2	13.313	3.649	48.3
95	479	KHK-832-841	82.3	4.4	80.0	4.4	34.692	4.011	65.7
96	480	KHK-857-895	73.2	10.7	53.0	13.9	88.908	21.326	71.7
97	481	KHK-858-896	25.9	1.6	23.5	2.4	34.15	5.07	27.8
98	482	KHK-859-897	42.4	2.4	51.3	4.2	47.048	2.926	46.9
99	483	KHK-860-898- 729-571	9.9	1.8	19.1	2.7	13.298	2.656	14.1
100	484	KHK-861-899- 730-572	5.0	0.6	3.3	0.4	2.869	0.815	3.7

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
101	485	KHK-862-900	10.8	1.5	12.2	0.9	12.047	3.121	11.7
102	486	KHK-865	6.3	0.7	7.6	0.5	5.2	0.828	6.4
103	487	KHK-880	11.8	0.8	11.5	1.6	15.705	2.293	13.0
104	488	KHK-882-920	6.5	0.8	6.5	0.9	4.934	1.748	6.0
105	489	KHK-883-921	6.0	1.0	5.3	1.1	5.884	1.209	5.7
106	490	KHK-884-922	11.6	1.4	13.2	1.4	8.24	2.55	11.0
107	491	KHK-885-923	7.9	0.7	9.9	1.0	7.119	2.941	8.3
108	492	KHK-886-924	10.7	7.4	10.9	7.0	4.814	1.257	8.8
109	493	KHK-887-925	14.2	0.7	16.2	1.1	22.141	2.292	17.5
110	494	KHK-888-926	13.3	1.1	17.9	1.4	17.895	1.465	16.4
111	495	KHK-889-927	11.5	0.8	12.3	0.8	13.253	2.142	12.3
112	496	KHK-890-928	8.5	0.7	7.1	0.9	9.332	1.26	8.3
113	497	KHK-891-929	9.0	1.6	8.1	1.3	10.279	2.136	9.1
114	498	KHK-892-930	6.0	1.0	9.4	1.2	7.1	2.124	7.5
115	499	KHK-893-931	11.1	1.0	12.6	1.2	8.773	1.823	10.8
116	500	KHK-894-932	16.1	2.3	19.0	1.7	8.757	1.518	14.6
117	501	KHK-895-933	9.2	0.5	7.4	0.4	14.47	1.915	10.3
118	502	KHK-896-934	10.4	1.1	10.5	1.5	19.901	4.905	13.6
119	503	KHK-897-935	13.1	0.8	14.2	0.9	24.106	2.363	17.1
120	504	KHK-898-936	28.7	1.4	32.0	2.9	25.261	2.143	28.7
121	505	KHK-899-937	10.3	0.8	10.6	1.1	13.265	2.804	11.4
122	506	KHK-900-938	9.2	0.9	10.4	0.8	8.036	1.468	9.2
123	507	KHK-901-939	10.7	2.1	15.3	3.3	9.39	2.386	11.8
124	508	KHK-902-940	17.6	1.2	17.4	2.2	13.271	2.387	16.1
125	509	KHK-903-941	11.5	0.8	15.2	1.2	6.246	1.494	11.0
126	510	KHK-904-942	16.1	3.0	20.6	2.5	12.783	3.392	16.5
127	511	KHK-905-943	10.7	1.7	20.3	0.9	12.273	1.446	14.4

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
128	512	KHK-906-944	13.2	2.9	24.9	2.4	6.582	2.052	14.9
129	513	KHK-907-945	18.6	11.2	54.3	31.6	14.417	4.546	29.1
130	514	KHK-908-946- 777-619	26.7	14.6	46.4	21.7	125.267	92.567	66.1
131	515	KHK-909-947- 778-620	7.0	2.5	12.9	4.2	10.062	3.153	10.0
132	516	KHK-910-948- 779-621	19.9	3.0	19.2	2.6	19.331	4.315	19.5
133	517	KHK-911-949- 780-622	14.0	1.3	12.6	1.0	13.083	3.238	13.2
134	518	KHK-912-950- 781-623	20.4	1.1	18.3	1.3	21.258	3.237	20.0
135	519	KHK-913-951- 782-624	23.3	0.9	23.6	1.2	28.036	3.803	25.0
136	520	KHK-914-952- 783-625	70.2	6.9	69.6	6.1	65.824	7.388	68.5
137	521	KHK-939-977	26.7	4.5	28.7	3.9	22.079	3.952	25.8
138	522	KHK-940-978	14.8	2.5	18.1	3.2	11.124	3.4	14.7
139	523	KHK-941-979	31.0	2.1	35.9	2.4	26.216	2.217	31.1
140	524	KHK-942-980	106.5	6.3	93.3	6.2	55.665	9.171	85.2
141	525	KHK-943-981	15.6	1.6	14.3	1.3	14.943	2.853	14.9
142	526	KHK-944-982	68.2	2.2	64.0	3.2	71.816	5.94	68.0
143	527	KHK-945-983	44.6	1.4	42.6	2.1	60.527	7.442	49.2
144	528	KHK-946-984	42.2	2.1	43.0	2.0	44.669	6.993	43.3
145	529	KHK-947-985	21.0	1.1	22.3	1.9	18.992	1.862	20.8
146	530	KHK-948-986- 817	12.7	1.7	13.3	2.9	11.454	2.967	12.5
147	531	KHK-949-987- 818	9.1	0.5	9.8	0.8	16.011	13.037	11.7
148	532	KHK-950-988- 819	9.6	1.2	8.5	0.8	12.475	3.586	10.2

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
149	533	KHK-951-989-820	23.5	2.2	25.3	1.9	23.247	6.755	24.0
150	534	KHK-952-990-821	14.5	0.8	18.3	1.6	15.126	4.553	16.0
151	535	KHK-953-991-822	23.0	1.5	25.9	2.2	25.674	5.773	24.9
152	536	KHK-954-992-823	14.1	1.5	16.9	2.7	17.22	2.41	16.1
153	537	KHK-955-993-824	13.0	2.4	14.4	2.5	10.614	3.054	12.7
154	538	KHK-956-994	11.8	2.7	11.9	3.0	17.221	5.593	13.6
155	539	KHK-957-995	6.1	2.1	10.2	1.7	14.207	1.553	10.2
156	540	KHK-958-996	17.4	3.2	17.9	1.0	26.913	3.733	20.7
157	541	KHK-978-1016	43.0	3.9	50.1	4.1	41.716	3.912	45.0
158	542	KHK-982-1020	51.8	2.6	69.1	5.3	67.745	3.674	62.9
159	543	KHK-983-1021	57.0	6.9	60.3	7.5	60.141	8.62	59.2
160	544	KHK-984-1022	15.4	2.1	16.8	2.1	17.339	3.931	16.5
161	545	KHK-985-1023	17.4	2.3	22.7	7.7	16.976	8.222	19.0
162	546	KHK-991-1029	21.4	2.9	22.7	3.9	27.54	9.397	23.9
163	547	KHK-992-1030	11.2	1.3	11.7	1.4	18.836	2.724	13.9
164	548	KHK-993-1031	32.3	5.5	26.5	4.5	19.635	5.352	26.1
165	549	KHK-999-1037	20.8	1.8	24.4	1.8	26.652	2.248	24.0
166	550	KHK-1000-1038	15.3	0.8	20.9	2.4	15.57	2.369	17.3
167	551	KHK-1019-1057	29.8	4.4	29.5	4.4	36.461	4.748	31.9
168	552	KHK-1054-1092	17.3	2.7	14.9	1.9	19.554	3.963	17.2
169	553	KHK-1055-1093	21.0	1.7	22.2	2.4	20.314	4.35	21.2
170	554	KHK-1057-1095	8.8	1.5	8.0	1.4	12.267	1.962	9.7
171	555	KHK-1058-1096	51.6	3.0	52.5	4.1	54.022	5.889	52.7
172	556	KHK-1059-1097	22.0	2.3	13.9	1.9	23.814	3.884	19.9

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
173	557	KHK-1060-1098	14.7	0.7	10.4	0.8	26.531	6.527	17.2
174	558	KHK-1061-1099	28.3	1.7	22.1	1.5	40.784	3.797	30.4
175	559	KHK-1062-1100	11.6	0.7	12.0	1.1	20.499	2.193	14.7
176	560	KHK-1063-1101	12.6	0.8	9.8	1.2	15.613	1.439	12.7
177	561	KHK-1064-1102	12.7	2.2	9.7	2.5	18.761	3.098	13.7
178	562	KHK-1065-1103	15.2	2.3	13.0	2.0	29.056	2.117	19.1
179	563	KHK-1066-1104	14.0	1.4	13.8	2.9	16.23	2.914	14.7
180	564	KHK-1067-1105	13.7	1.2	10.0	1.2	8.155	3.486	10.6
181	565	KHK-1068-1106	14.0	0.8	11.4	1.1	28.373	4.283	17.9
182	566	KHK-1069-1107	11.8	0.6	9.8	0.7	17.654	3.053	13.1
183	567	KHK-1070-1108	20.2	2.0	14.4	2.7	30.393	6.07	21.7
184	568	KHK-1071-1109	30.0	3.2	22.0	1.5	39.098	8.12	30.4
185	569	KHK-1072-1110	14.5	0.7	12.9	0.8	41.196	15.367	22.8
186	570	KHK-1073-1111	17.7	1.3	14.6	1.7	23.629	3.262	18.6
187	571	KHK-1074- 1112-943-785	25.1	2.1	23.0	2.4	34.784	6.555	27.6
188	572	KHK-1075- 1113-944-786	12.4	2.5	8.4	1.9	9.594	2.863	10.1
189	573	KHK-1076- 1114-945-787	9.8	1.0	7.5	1.0	11.44	3.242	9.6
190	574	KHK-1077- 1115-946-788	13.8	1.6	11.9	1.4	19.983	4.226	15.2
191	575	KHK-1078- 1116-947-789	12.2	1.4	10.2	1.5	19.236	3.613	13.9
192	576	KHK-1079- 1117-948-790	23.0	1.6	20.2	1.4	36.758	3.387	26.6
193	577	KHK-1080- 1118-949-791	12.4	0.7	10.3	0.9	23.489	2.532	15.4
194	578	KHK-1081- 1119-950-792	19.0	2.8	15.4	1.4	35.094	5.069	23.2

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
195	579	KHK-1082-1120-951-793	51.6	12.7	36.2	7.1	79.445	13.29	55.8
196	580	KHK-1083-1121-952-794	12.4	0.9	7.6	1.6	29.815	4.341	16.6
197	581	KHK-1084-1122-953-795	17.8	1.5	15.4	1.3	34.538	5.134	22.6
198	582	KHK-1085-1123-954-796	20.4	2.5	19.1	2.4	28.082	3.898	22.5
199	583	KHK-1086-1124-955-797	9.8	1.4	9.1	1.9	22.862	5.973	13.9
200	584	KHK-1087-1125-956-798	25.1	2.4	26.2	5.9	60.678	13	37.3
201	585	KHK-1090-1128	15.7	2.5	14.2	4.3	47.765	6.748	25.9
202	586	KHK-1091-1129	17.1	1.5	16.0	1.2	47.935	10.554	27.0
203	587	KHK-1092-1130	59.1	13.1	81.9	15.1	116.084	17.529	85.7
204	588	KHK-1093-1131	68.9	6.5	72.1	6.2	135.298	14.786	92.1
205	589	KHK-1095-1133	39.3	2.2	34.2	2.9	49.369	9.398	41.0
206	590	KHK-1096-1134	54.0	3.8	58.2	5.6	107.545	13.331	73.2
207	591	KHK-1097-1135	26.5	3.4	22.1	3.0	39.738	6.746	29.5
208	592	KHK-1099-1137	19.4	2.2	21.9	2.9	37.312	8.866	26.2
209	593	KHK-1100-1138	31.5	3.9	31.8	4.6	86.882	29.059	50.1
210	594	KHK-1101-1139	60.8	5.1	65.8	3.9	89.898	14.227	72.2
211	595	KHK-1102-1140	29.8	1.9	25.1	2.9	49.962	4.639	34.9
212	596	KHK-1103-1141	9.9	1.3	5.7	0.9	14.357	4.377	10.0
213	597	KHK-1104-1142	7.9	0.5	5.3	0.7	14.498	2.508	9.2
214	598	KHK-1106-1144	12.0	2.1	6.8	2.4	17.615	5.575	12.1
215	599	KHK-1107-1145	7.6	1.5	3.5	1.2	12.097	3.884	7.7
216	600	KHK-1135-1173	9.8	2.7	6.3	2.1	20.368	5.935	12.2
217	601	KHK-1136-1174	55.0	8.2	57.6	8.7	51.67	14.619	54.8
218	602	KHK-1137-1175	6.9	1.5	5.5	0.9	14.082	4.459	8.8

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
219	603	KHK-1138-1176	3.4	1.2	2.7	1.0	20.618	4.034	8.9
220	604	KHK-1139-1177	14.2	4.2	10.3	2.6	45.243	8.325	23.2
221	605	KHK-1140-1178	22.3	7.0	14.9	4.7	58.511	10.307	31.9
222	606	KHK-1141-1179	16.8	4.6	18.2	4.1	34.609	7.425	23.2
223	607	KHK-1142-1180	10.0	4.1	8.0	2.3	33.362	7.336	17.1
224	608	KHK-1143-1181	13.7	2.2	12.5	4.2	28.204	4.236	18.1
225	609	KHK-1144-1182	11.7	2.1	14.6	4.6	49.769	18.354	25.3
226	610	KHK-1145-1183	19.0	6.3	22.7	6.7	51.464	20.568	31.1
227	611	KHK-1146-1184	16.8	4.7	14.7	5.5	71.937	37.067	34.5
228	612	KHK-1147-1185	9.0	1.6	9.1	1.1	11.22	4.674	9.7
229	613	KHK-1148-1186	8.8	1.7	6.0	1.8	18.481	8.166	11.1
230	614	KHK-1149-1187	20.1	3.1	18.3	2.8	36.481	11.397	24.9
231	615	KHK-1153-1191	24.4	3.7	20.5	3.0	29.434	6.394	24.8
232	616	KHK-1154-1192	11.9	2.5	8.9	2.2	22.093	6.996	14.3
233	617	KHK-1157-1195	14.5	2.2	11.9	2.2	26.024	4.864	17.5
234	618	KHK-1158-1196	9.3	1.4	5.0	1.5	8.547	5.09	7.6
235	619	KHK-1159-1197	7.3	1.3	11.6	1.3	18.971	4.052	12.6
236	620	KHK-1161-1199	9.9	1.0	4.8	0.7	16.083	3.57	10.3
237	621	KHK-1163-1201	13.7	1.3	11.9	1.4	28.564	6.393	18.0
238	622	KHK-1164-1202	14.6	2.9	10.0	2.5	17.654	4.993	14.1
239	623	KHK-1232-1270	12.0	2.4	13.2	2.6	29.824	4.644	18.4
240	624	KHK-1278- 1316-1147-989	14.0	2.6	8.5	3.2	16.096	5.812	12.9
241	625	KHK-1279- 1317-1148-990	9.4	2.2	8.2	2.0	23.969	10.352	13.9
242	626	KHK-1280- 1318-1149-991	4.5	1.4	5.3	1.2	11.007	1.786	6.9
243	627	KHK-1281- 1319-1150-992	4.0	1.3	7.4	2.3	30.368	6.698	13.9

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
244	628	KHK-1282-1320-1151-993	10.0	1.5	9.4	2.9	10.4	2.173	10.0
245	629	KHK-1283-1321	23.7	3.6	25.9	5.1	20.361	6.111	23.3
246	630	KHK-1284-1322	17.5	1.2	15.1	1.9	23.591	3.59	18.8
247	631	KHK-1285-1323	15.8	1.4	19.5	1.2	13.69	2.902	16.3
248	632	KHK-1286-1324	17.7	2.8	18.7	2.8	18.507	3.994	18.3
249	633	KHK-1287-1325	9.2	3.3	7.7	3.0	10.381	3.571	9.1
250	634	KHK-1288-1326	8.4	2.9	3.8	1.7	11.461	3.398	7.9
251	635	KHK-1289-1327	8.4	2.9	6.4	4.6	11.992	3.025	8.9
252	636	KHK-1290-1328	8.7	1.5	6.7	1.2	8.926	3.258	8.1
253	637	KHK-1291-1329	6.9	0.7	3.8	1.0	7.55	2.469	6.1
254	638	KHK-1292-1330	17.7	1.1	12.8	1.2	30.785	7.501	20.5
255	639	KHK-1293-1331	11.6	1.3	9.7	1.6	15.795	2.45	12.4
256	640	KHK-1294-1332	25.7	1.4	34.2	2.2	33.058	7.279	31.0
257	641	KHK-1295-1333	13.1	1.5	12.2	2.1	15.793	3.001	13.7
258	642	KHK-1297-1335	21.1	1.3	21.8	1.5	24.699	4.755	22.5
259	643	KHK-1323-1361	49.4	8.1	57.3	8.3	44.887	11.548	50.5
260	644	KHK-1325-1363	38.7	2.6	32.1	3.3	28.739	4.127	33.2
261	645	KHK-1326-1364	10.7	0.8	8.2	0.9	20.863	2.809	13.3
262	646	KHK-1327-1365	54.1	2.2	52.2	3.4	94.086	19.883	66.8
263	647	KHK-1328-1366	40.5	1.7	45.3	3.8	44.867	7.194	43.5
264	648	KHK-1329-1367	17.2	1.4	14.4	1.0	32.257	2.561	21.3
265	649	KHK-1330-1368	15.6	1.2	18.9	1.9	19.171	3.863	17.9
266	650	KHK-1331-1369	15.4	1.6	12.9	2.0	42.066	5.461	23.4
267	651	KHK-1332-1370	12.0	0.8	8.5	0.9	10.488	3.467	10.3
268	652	KHK-1333-1371	7.2	0.9	3.7	0.9	8.179	2.058	6.3
269	653	KHK-1334-1372	8.7	1.5	6.5	1.0	7.49	0.985	7.6
270	654	KHK-1335-1373	9.7	0.6	5.2	1.1	9.403	1.153	8.1

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
271	655	KHK-1336-1374	10.0	1.8	5.2	1.4	14.512	2.647	9.9
272	656	KHK-1385-1423	47.5	3.5	49.0	4.8	44.122	7.678	46.9
273	657	KHK-1387-1425	14.4	2.1	15.9	3.0	22.666	4.122	17.7
274	658	KHK-1388-1426	27.0	2.9	28.2	3.3	34.575	4.985	29.9
275	659	KHK-1389-1427	25.1	3.0	29.5	2.8	18.759	3.577	24.5
276	660	KHK-1538-1588	81.1	15.3	73.7	17.3	71.289	16.403	75.3
277	661	KHK-1540-1590	46.8	4.2	35.5	4.6	23.533	8.593	35.3
278	662	KHK-1542-1592	80.6	4.7	89.1	3.3	85.445	7.942	85.0
279	663	KHK-1665-1708	84.8	4.3	86.6	8.9	116.186	21.343	95.8
280	664	KHK-1666-1709	97.0	2.5	99.6	3.9	115.899	10.593	104.2
281	665	KHK-1667-1710	99.5	4.4	109.4	5.7	123.463	8.991	110.8
282	666	KHK-1707-1750	91.1	3.5	107.3	6.3	123.75	26.01	107.4
283	667	KHK-1708-1751	72.5	5.7	85.8	8.2	76.118	10.985	78.1
284	668	KHK-1709-1752	136.2	5.8	114.5	5.9	75.202	14.025	108.7
285	669	KHK-1869-1918	118.1	21.1	111.2	20.6	97.088	18.195	108.8
286	670	KHK-1870-1919	90.2	8.7	83.2	11.2	87.62	22.519	87.0
287	671	KHK-1871-1920	81.7	4.6	80.6	4.6	119.805	13.019	94.1
288	672	KHK-1872-1921	94.5	4.4	87.4	5.7	74.492	13.782	85.4
289	673	KHK-1873-1922	93.2	5.4	90.9	4.6	88.62	13.98	90.9
290	674	KHK-1874-1923	93.2	6.3	90.7	4.9	74.793	8.913	86.2
291	675	KHK-1875-1924	86.5	8.5	76.3	8.2	45.965	7.621	69.6
292	676	KHK-1876-1925	73.7	9.7	61.1	8.7	34.813	6.807	56.6
293	677	KHK-1877-1926	72.7	3.9	51.0	5.3	45.122	9.468	56.3
294	678	KHK-1878-1927	75.8	4.8	79.7	8.0	54.716	8.031	70.1
295	679	KHK-1879-1928	90.6	8.4	77.0	9.0	86.62	13.219	84.7
296	680	KHK-1880-1929	100.4	8.5	84.5	9.8	85.501	13.022	90.1
297	681	KHK-1900-1949	104.9	12.1	96.5	15.3	70.712	8.039	90.7

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
298	682	KHK-1905-1954	71.4	17.0	71.0	22.1	35.273	14.001	59.2
299	683	KHK-1971-2025	77.5	25.4	128.3	28.3	34.399	9.559	80.1
300	684	KHK-1974-2028	74.2	6.0	64.4	7.7	50.763	6.122	63.1
301	685	KHK-1975-2029	80.8	7.8	80.5	7.1	55.779	10.606	72.3
302	686	KHK-1976-2030	69.2	6.8	73.5	8.5	53.873	16.663	65.5
303	687	KHK-1978-2032	73.7	10.3	73.6	10.0	57.334	7.876	68.2
304	688	KHK-1979-2033	81.2	9.5	95.1	13.6	43.016	8.767	73.1
305	689	KHK-2032-2086	94.2	6.3	124.6	9.4	99.842	10.374	106.2
306	690	KHK-2035-2089	66.5	6.2	72.2	14.5	47.134	6.316	61.9
307	691	KHK-2036-2090	82.4	9.1	110.4	15.5	56.532	12.458	83.1
308	692	KHK-2037-2091	88.9	8.1	72.5	7.9	48.451	10.859	70.0
309	693	KHK-2038-2092	74.2	3.6	58.7	4.7	44.437	4.32	59.1
310	694	KHK-2039-2093	75.1	5.3	76.3	8.1	51.597	6.117	67.7
311	695	KHK-2040-2094	75.9	8.5	70.0	11.2	57.499	6.477	67.8
312	696	KHK-2041-2095	80.5	4.1	78.1	3.5	78.593	10.192	79.1
313	697	KHK-2042-2096	79.1	5.2	84.7	4.0	88.699	8.352	84.2
314	698	KHK-2043-2097	72.0	3.8	70.0	2.7	83.791	8.891	75.3
315	699	KHK-2044-2098	37.6	12.9	32.3	13.4	30.83	15.258	33.6
316	700	KHK-2045-2099	101.3	8.7	87.4	11.3	54.839	12.261	81.2
317	701	KHK-2067-2121	88.2	5.1	78.4	2.6	75.916	8.438	80.8
318	702	KHK-2069-2123	83.1	3.7	84.9	5.2	63.679	10.343	77.2
319	703	KHK-2091-2145	83.8	5.4	87.1	8.9	53.463	10.34	74.8
320	704	KHK-2092-2146	85.4	6.2	89.7	7.8	68.656	5.01	81.3
321	705	KHK-2093-2147	102.7	21.4	65.4	19.9	71.693	14.857	79.9
322	706	KHK-2094-2148	88.8	6.4	94.1	6.7	53.85	10.392	78.9
323	707	KHK-2095-2149	76.2	21.4	97.2	25.9	47.372	14.735	73.6
324	708	KHK-2096-2150	87.9	16.4	78.6	13.2	49.454	14.398	72.0

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
325	709	KHK-2105	92.1	7.7	90.8	11.5	97.683	10.156	93.5
326	710	KHK-2148-2197	86.5	5.8	79.3	16.0	76.198	8.142	80.7
327	711	KHK-2149-2198	71.3	3.7	73.8	4.2	55.558	6.731	66.9
328	712	KHK-2150-2199	92.1	7.1	97.5	4.9	75.703	6.126	88.4
329	713	KHK-2151-2200	96.2	3.7	108.0	10.3	91.908	5.852	98.7
330	714	KHK-2152-2201	78.7	6.5	74.7	9.6	42.766	6.332	65.4
331	715	KHK-2153-2202	95.2	14.8	73.9	13.1	47.169	10.902	72.1
332	716	KHK-2154-2203	114.1	11.9	92.3	7.2	61.728	10.943	89.4
333	717	KHK-2155-2204	92.1	8.4	83.1	3.8	119.537	11.18	98.2
334	718	KHK-2156-2205	104.7	5.4	91.6	4.7	148.445	15.208	114.9
335	719	KHK-2157-2206	94.2	8.4	92.0	10.4	68.735	7.132	85.0
336	720	KHK-2159-2208	85.4	4.5	78.4	6.2	62.397	10.642	75.4
337	721	KHK-2160-2209	72.7	1.9	81.8	5.3	56.483	11.255	70.3
338	722	KHK-2161-2210	93.7	14.6	74.3	10.9	18.252	5.102	62.1
339	723	KHK-2162-2211	106.7	11.3	127.3	17.9	53.455	15.254	95.8
340	724	KHK-2163-2212	79.5	8.2	91.6	6.4	49.199	6.236	73.5
341	725	KHK-2164-2213	101.1	13.4	115.2	20.4	84.893	29.662	100.4
342	726	KHK-2165-2214	97.0	10.8	102.1	9.9	76.079	10.525	91.7
343	727	KHK-2166-2215	91.6	20.4	89.3	22.7	55.353	11.894	78.8
344	728	KHK-2170-2219	75.9	4.5	89.7	4.6	68.461	8.991	78.0
345	729	KHK-2196-2245	60.3	2.9	65.1	4.4	43.35	5.951	56.3
346	730	KHK-2197-2246	85.4	8.4	98.9	9.4	65.81	6.865	83.4
347	731	KHK-2198-2247	89.4	15.0	108.1	10.3	44.371	7.323	80.6
348	732	KHK-2199-2248	97.2	14.8	91.3	16.1	49.493	8.874	79.3
349	733	KHK-2200-2249	104.7	10.7	111.8	13.5	47.327	5.488	87.9
350	734	KHK-2201-2250	100.3	11.7	102.7	13.8	52.984	11.652	85.3
351	735	KHK-2205	96.9	17.0	88.0	10.9	55.021	8.208	80.0

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			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
352	736	KHK-2238	89.1	8.0	99.6	8.2	113.917	11.636	100.9
353	737	KHK-2260-2309	111.5	13.2	110.2	11.9	95.452	20.407	105.7
354	738	KHK-2261-2310	103.6	9.1	106.9	12.4	97.581	15.894	102.7
355	739	KHK-2262-2311	141.3	14.6	132.9	11.8	112.052	19.366	128.7
356	740	KHK-2263-2312	104.0	10.5	80.5	11.4	59.852	7.342	81.4
357	741	KHK-2264-2313	100.7	17.1	88.6	15.5	53.023	12.056	80.8
358	742	KHK-2265-2314	103.2	11.2	103.8	11.9	60.929	8.309	89.3
359	743	KHK-2266-2315	119.8	8.9	110.3	8.5	66.846	9.19	99.0
360	744	KHK-2299	77.7	3.2	72.0	5.9	69.804	11.442	73.2
361	745	KHK-2317-2366	81.2	3.0	84.4	7.7	66.04	7.299	77.2
362	746	KHK-2318-2367	86.6	3.7	97.0	5.2	66.519	4.573	83.4
363	747	KHK-2319-2368	127.5	12.5	102.9	8.9	82.338	11.524	104.2
364	748	KHK-2320-2369	98.9	11.1	94.2	15.6	59.154	17.115	84.1
365	749	KHK-2321-2370	127.6	13.8	127.6	16.5	81.979	19.313	112.4
366	750	KHK-2322-2371	83.3	9.1	68.5	8.6	78.252	14.344	76.7
367	751	KHK-2323-2372	83.2	7.3	79.8	7.7	57.202	9.062	73.4
368	752	KHK-2324-2373	95.0	3.0	101.4	5.2	118.194	16.285	104.9
369	753	KHK-2325-2374	123.0	15.6	153.7	23.1	188.498	24.768	155.1
370	754	KHK-2326-2375	94.5	12.0	101.2	8.2	110.056	29.627	101.9
371	755	KHK-2332	96.2	11.9	122.2	10.2	120.096	15.829	112.8
372	756	KHK-2333	97.9	12.7	73.0	9.9	50.041	16.617	73.7
373	757	KHK-2335	104.4	9.0	81.2	7.5	33.77	6.814	73.1
374	758	KHK-2340	64.4	14.3	45.7	12.3	34.661	10.468	48.2
375	759	KHK-2341	61.9	10.6	53.7	6.9	43.579	8.14	53.1
376	760	KHK-2346	104.5	9.2	92.5	12.6	104.386	32.315	100.4
377	761	KHK-2352	78.5	6.7	83.6	8.0	97.544	18.168	86.6
378	762	KHK-2358	78.8	7.0	75.7	9.9	64.974	13.327	73.1

			KHK-F495		KHK-F1026		KHK-825		
SEQ ID NO (Sense Strand)	SEQ ID NO (Anti-sense Strand)	DsiRNA name	% remain- ing	SEM	% remain- ing	SEM	% remain- ing	SEM	% average of all assays
379	763	KHK-2359	89.5	9.0	91.8	8.2	71.314	7.358	84.2
380	764	KHK-2360	132.4	26.2	82.8	8.7	159.973	15.729	125.0
381	765	KHK-2361	110.4	8.5	87.7	7.8	87.634	7.799	95.3
382	766	KHK-2362	92.5	12.8	72.7	7.2	84.427	12.833	83.2
383	767	KHK-2363	100.4	9.2	76.1	14.4	52.066	18.068	76.2
384	768	KHK-2364	116.4	9.8	88.5	8.3	120.931	26.855	108.6
385	769	KHK-2365	100.5	5.7	92.9	5.2	132.668	7.14	108.7
386	770	KHK-2366	129.3	7.2	113.5	5.7	135.163	16.2	126.0
387	771	KHK-2367	123.3	9.0	105.9	9.2	136.356	9.025	121.9

Example 3: RNAi Oligonucleotide Inhibition of Both KHK Isoforms *In Vivo*

[0350] The *in vitro* screening assay in **Example 2** validated the ability of KHK DsiRNA to knock-down both isoforms of KHK (KHK-All). To confirm the ability of the RNAi oligonucleotides to knockdown both KHK-A and KHK-C isoforms, a side-by-side HDI mouse model was used. First, the nucleotide sequences comprising a subset of the 384 DsiRNAs identified in **Example 2**, and that recognize human/NHP-conserved *KHK*, were used to generate corresponding double-stranded RNAi oligonucleotides comprising a nicked tetraloop GalNAc-conjugated structure (referred to herein as “GalNAc-conjugated *KHK* oligonucleotides” or “GalNAc-*KHK* constructs”) having a 36-mer passenger strand and a 22-mer guide strand (**Table 3**). Specifically, to generate the 22-mer guide strand, the 19-mer core antisense strand sequences used in **Example 2** (e.g., SEQ ID NOs: 948-953) were modified to have a phosphorylated uracil at the 5' end and two guanines at the 3' end. To generate the 36-mer passenger strand, an adenine corresponding to the phosphorylated uracil in the antisense strand and a 16-mer stem loop (SEQ ID NO: 871) were added to the 3' end of the 19-mer core sense strand sequences used in **Example 2** (e.g., SEQ ID NOs: 942-947). Further, the nucleotide sequences comprising the passenger strand and guide strand of the GalNAc-conjugated *KHK* oligonucleotides have a distinct pattern of modified nucleotides and phosphorothioate linkages (e.g., see **FIG. 2A**, **FIG. 2B** and **Table 3** for schematics of the generic structure and key of chemical modifications; referred to herein as Low-2'-Fluoro (3PS) and Low-2'-Fluoro (2PS), respectively, together as the Low-2'-Fluoro pattern for GalNAc-conjugated *KHK* oligonucleotides). The three adenosine nucleotides comprising the tetraloop are each conjugated to a GalNAc moiety (CAS#: 14131-60-3). The modification pattern is represented below in two interchangeable modification keys.

Low-2'-Fluoro (3PS) Modification Pattern for GalNAc-KHK Constructs (5' Antisense 3PS)

Sense Strand: 5'-mX-S-mX-mX-mX-mX-mX-mX-fX-fX-fX-fX-mX-mX-mX-mX-mX-mX-mX-mX-

mX-mX-mX-mX-mX-mX-[ademA-GalNAc]- [ademA-GalNAc]- [ademA-GalNAc]-mX-mX-mX-mX-mX- 3'.

Hybridized to:

Antisense Strand: 5'-[MePhosphonate-4O-mX]-S-fX-S-fX-S-fX-fX-mX-fX-mX-mX-fX-mX-

5 mX-mX-mX-mX-mX-S-mX-S-mX-3'

(Modification key: **Table 3**).

Or, represented as:

Sense Strand: [mXs][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX]

10 [mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mX][mX][mX][mX][mX]

Hybridized to:

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fXs][fX][fX][mX][fX][mX][mX][fX]

15 [mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

(Modification key: **Table 3**).

Low-2'Fluoro (2PS) Modification Pattern for GalNAc-KHK Constructs (5' Antisense 2PS)

Sense Strand: 5'-mX-S-mX-mX-mX-mX-mX-fX-fX-fX-fX-mX-mX-mX-mX-mX-mX-mX-mX-

20 mX-mX-mX-mX-mX-[ademA-GalNAc]- [ademA-GalNAc]- [ademA-GalNAc]-mX-mX-mX-mX-mX- 3'.

Hybridized to:

Antisense Strand: 5'-[MePhosphonate-4O-mX]-S-fX-S-fX-fX-fX-mX-fX-mX-mX-fX-mX-mX-mX-mX-mX-S-mX-S-mX-3'

25

(Modification key: **Table 3**).

Or, represented as:

Sense Strand: [mXs][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX]

30 [mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mX][mX][mX][mX][mX]

Hybridized to:

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fX][fX][fX][mX][fX][mX][mX][fX]

35 [mX][mX][mX][fX][mX][mX][mX][mX][mXs][mXs][mX]

Table 3. Modification Key

Symbol	Modification/linkage
Key 1	
mX	2'-O-methyl modified nucleotide
fX	2'- fluoro modified nucleotide
-S-	phosphorothioate linkage
-	phosphodiester linkage
[MePhosphonate-4O-mX]	5'-methoxyphosphonate-4'-oxy modified nucleotide
ademA-GalNAc	GalNAc attached to an adenine nucleotide
Key 2	
[mXs]	2'-O-methyl modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[fXs]	2'- fluoro modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[mX]	2'-O-methyl modified nucleotide with phosphodiester linkages to neighboring nucleotides
[fX]	2'- fluoro modified nucleotide with phosphodiester linkages to neighboring nucleotides

[0351] The GalNAc-KHK constructs were then used to evaluate inhibition efficacy in mice. Specifically, 6-8-week-old female CD-1 mice (n = 5) were subcutaneously administered the indicated GalNAc-conjugated *KHK* oligonucleotides (**Table 4**) at a dose of 2mg/kg formulated in PBS. A control group of mice (n = 5) were administered only PBS. Three days later (72 hours), the mice were hydrodynamically injected (HDI) either with a DNA plasmid (pCMV6-KHK-C, Cat#: RC223488, OriGene) encoding the full human *KHK* gene (NM_006488.3) (25µg) or plasmid (pCMV6-KHK-A, Cat#:RC202424, OriGene) encoding the full human *KHK-A* gene (NM_000221) under control of a ubiquitous cytomegalovirus (CMV) promoter sequence. One day after introduction of the DNA plasmid, liver samples from HDI mice were collected. The values were normalized for transfection efficiency using the NeoR gene included on the DNA plasmid.

[0352] Total RNA isolated from mouse livers were used to assess relative *KHK* mRNA expressions by qRT-PCR. The TaqMan RT-qPCR probes from Life Technologies were used to evaluate [3' assay (Forward-1026; TGGAGGTGGAGAAGCCA (SEQ ID NO: 865), Reverse-1157; GACCATACAAGCCCCTCAAG (SEQ ID NO:866), Probe-1080; TGGTGTTCAGCAAAGATGTGGC (SEQ ID NO:867)) and a 5' assay (Forward-496; AGGAAGCTCTGGGAGTA (SEQ ID NO: 868), Reverse-596; CCTCCTTAGGGTACTTGTC (SEQ ID NO: 869), Probe-518; ATGGAAGAGAAGCAGATCCTGTGCG (SEQ ID NO: 870))]. The values were normalized for transfection efficiency using the NeoR gene included on the DNA plasmid. HDI mice were generated as described above but using a human *KHK-A* plasmid or a human *KHK-C* plasmid. The mice were treated in groups of 5 with the GalNAc-*KHK* constructs in **Table 4** (with the Low-2'-Fluoro modification pattern). Livers were collected and mRNA measured using primer pairs recognizing *KHK-AII*, *KHK-C*, or *KHK-A*. The results confirmed that GalNAc-*KHK* constructs designed to target all *KHK* transcripts demonstrate successful knockdown in both the human *KHK-A* and *KHK-C* HDI mouse models (**FIG. 3**).

Table 4. GalNAc-KHK Constructs Evaluated In *KHK-C* and *KHK-A* HDI Mouse Models

together and used as a positive control for inhibition. Both modification patterns resulted in inhibition of *KHK* mRNA in mice (**FIG. 4B-4E**). These results demonstrate that both modification patterns provided knockdown of the target mRNA.

Table 5: GalNAc-*KHK* Constructs for Modification Pattern Assay

Name	Modification pattern	Sense Strand Unmodified SEQ ID NO	Anti-sense Strand Unmodified SEQ ID NO	Sense Strand Modified SEQ ID NO	Anti-sense Strand Modified SEQ ID NO
KHK-861	Low-2'F	100	484	778	823
KHK-861	Med-2'F	100	484	808	853
KHK-865	Low-2'F	102	486	779	824
KHK-865	Med-2'F	102	486	809	854
KHK-882	Low-2'F	104	488	780	820
KHK-882	Med-2'F	104	488	810	855
KHK-883	Low-2'F	105	489	781	826
KHK-883	Med-2'F	105	489	811	856
KHK-885	Low-2'F	107	491	782	827
KHK-885	Med-2'F	107	491	812	857
KHK-1288	Low-2'F	250	634	787	832
KHK-1288	Med-2'F	250	634	816	861
KHK-1290	Low-2'F	252	636	788	833
KHK-1290	Med-2'F	252	636	817	862
KHK-1334	Low-2'F	269	653	804	849
KHK-1334	Med-2'F	269	653	818	863
KHK-516	Med-2'F	39	423	805	850
KHK-804	Med-2'F	N/A	N/A	806	851
KHK-829	Med-2'F	92	476	807	852
KHK-1076	Med-2'F	189	573	814	859
KHK-1078	Med-2'F	191	575	815	860

5

Example 5: RNAi Oligonucleotide Inhibition of *KHK* Expression *In Vivo*

Mouse HDI *KHK* knockdown screening studies

[0355] The GalNAc-conjugated *KHK* oligonucleotides listed in **Table 6** were evaluated in HDI mice as described in **Example 3**. GalNAc-*KHK* construct treatment effectively reduced *KHK*-All mRNA (**FIG. 5**). When using primers specific for the *KHK*-C isoform, the GalNAc-*KHK* constructs were still effective at reducing mRNA (**FIG. 5**).

10

Table 6. GalNAc-*KHK* Constructs Assayed in HDI Model

Name	Sense Strand Modified SEQ ID NO	Antisense Strand Modified SEQ ID NO
------	---------------------------------	-------------------------------------

KHK-885	782	827
KHK-869	795	840
KHK-873	796	841
KHK-879	797	842
KHK-881	798	843
KHK-896	799	844
KHK-1064	800	845
KHK-1075	784	829
KHK-1077	801	846
KHK-1080	802	847
KHK-1106	803	848
KHK-1147	794	839
KHK-1148	789	834
KHK-1152	790	835
KHK-1154	791	836
KHK-1155	792	837
KHK-1277	793	838

[0356] Additional constructs (**Table 7**) were assayed using the same methods and found effective knock-down for KHK-All and KHK-C (**FIG. 6A** and **6B**). Similarly, endogenous mouse KHK was reduced by GalNAc-KHK constructs which align with mouse KHK mRNA (**FIG. 6C**). Overall, both HDI studies identified GalNAc-KHK constructs effective at reducing *KHK* mRNA *in vivo*.

Table 7. GalNAc-KHK Constructs Assayed in HDI Model

Name	Sense Strand Modified SEQ ID NO	Antisense Strand Modified SEQ ID NO
KHK-1054	783	828
KHK-510	774	819
KHK-516	775	820
KHK-829	776	821
KHK-860	777	822
KHK-861	778	823
KHK-865	779	824
KHK-882	780	825
KHK-883	781	826
KHK-885	782	827
KHK-1075	784	829
KHK-1078	785	830
KHK-1281	786	831
KHK-1288	787	832
KHK-1290	788	833
KHK-1334	804	849

Example 6: RNAi Oligonucleotide Inhibition of KHK Expression and Studies in Non-human Primates

10 Single-dose Non-Human Primate (NHP) Studies

[0357] Effective GalNAc-KHK constructs identified in the HDI mouse studies were assayed for targeting efficiency in non-human primates. Specifically, GalNAc-conjugated KHK oligonucleotides listed in **Table 8** were evaluated in non-naïve cynomolgus monkeys (*Macaca fascicularis*). In this study, the monkeys were grouped so that their mean body weights (about 5.4 kg) were comparable between the control and experimental groups. Each cohort contained at least two female and at least two male subjects. The GalNAc-conjugated KHK oligonucleotides were administered subcutaneously at a dose of 6 mg/kg on Study Day 0. Blood samples were collected one week prior to dosing (Day -7), on the dosing date (Day 0) and days 28, 56 and 84 after dosing. Ultrasound-guided core needle liver biopsies were collected on Study Days -7, 28, 56 and 84. At each time point, total RNA derived from the liver biopsy samples was subjected to qRT-PCR analysis to measure KHK mRNA in oligonucleotide-treated monkeys relative to those treated with a comparable volume of PBS. To normalize the data, the measurements were made relative to the geometric mean of two reference genes, PPIB and 18S rRNA. The following TaqMan qPCR probes purchased from Life Technologies, Inc, were used to evaluate gene expressions: Forward – TGCCTTCATGGGCTCAATG (SEQ ID NO: 772); Reverse – TCGGCCACCAGGAAGTCA (SEQ ID NO: 773); Fam probe- CCCTGGCCATGTTG (SEQ ID NO: 864)). As shown in **FIG. 7A** (Day 28), treating NHPs with the GalNAc-conjugated KHK oligonucleotides listed in **Table 8** inhibited KHK expression in the liver, as determined by a reduced amount of KHK mRNA in liver samples from oligonucleotide-treated NHPs relative to NHPs treated with PBS. The mean percent reduction of KHK mRNA in the liver samples of treated NHPs is indicated above the set of data points for each treatment group. Days 56 and 84 were also measured (**FIG. 7B and 7C**) and a plot of the mean values over each time point is shown in **FIG. 7D**. For all time points evaluated, almost all the tested GalNAc-conjugated KHK oligonucleotides significantly inhibited KHK mRNA expression. In the same samples, KHK protein levels were detected using rabbit anti-Ketohexokinase (Abcam, AB197593) and anti-rabbit Detection Module for Sally Sue (Protein Simple, cat#DM-001). As shown in **FIGs. 8A-8C**, at the 28-day timepoint, GalNAc-KHK constructs inhibit KHK protein expression, as normalized to the vinculin control and slowly increases by Day 86. These results demonstrate that treating NHPs with the GalNAc-conjugated KHK oligonucleotides reduces the amount of KHK mRNA in the liver and concomitantly reduces the amount of KHK protein in the liver. However, this correlation is reduced over time after the initial dose (**FIGs. 9A-9C**).

[0358] Taken together, these results show that GalNAc-conjugated KHK oligonucleotides designed to target human total KHK mRNA inhibit total KHK expression *in vivo* (as determined by the reduction of the amount of KHK mRNA and protein).

Table 8. Single-dose GalNAc-KHK Constructs for NHP Study

Name	Sense strand SEQ ID NO	Anti-sense strand SEQ ID NO
KHK-516	775	820
KHK-865	779	824
KHK-882	780	825
KHK-885	782	827
KHK-1078	785	830
KHK-1334	804	849

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SEQUENCE LISTING

Name	Description Species (Hs-Mf-Ms- Rn (rat))	Strand	Sequence	SEQ ID NO
Human (Hs) KHK nucleotide sequence NM_006488. 3	Human (Hs)	N/A	AGGCAGGGCTGCAGATGCGAGGCCAGCTGTACCT CGCGTGTCCCGGGTCGGGAGTCGGAGACGCAGGT GCAGGAGAGTGCGGGGCAAGTAGCGCATTTTCTCT TTGCATTCTCGAGATCGCTTAGCCGCGCTTTAAAAA GGTTTGCATCAGCTGTGAGTCCATCTGACAAGCGAG GAACTAAGGCTGAGAAAGTGGGAGGCGTTGCCATC TGCAGGCCAGGCAACCTGCTACGGGAAGACCGGG GACCAAGACCTCTGGGTTGGCTTTCTAGACCCGCT CGGGTCTTCGGGTGTGCGGAGGAAGGGCCCTGCTC CTTCGTTCCCTGCACCCCTGGCCGCTGCAGGTGG CTCCCTGGAGGAGGAGCTCCACGCGGAGGAGGA GCCAGGGCAGCTGGGAGCGGGGACACCATCCTCCT GGATAAGAGGCAGAGGCCGGGAGGAACCCCGTCA GCCGGGCGGGCAGGAAGCTCTGGGAGTAGCCTCAT GGAAGAGAAGCAGATCCTGTGCGTGGGGCTAGTGG TGCTGGACGTCATCAGCCTGGTGGACAAGTACCCTA AGGAGGACTCGGAGATAAGGTGTTTGTCCCAGAGA TGGCAGCGCGGAGGCAACGCGTCCAACCTGCAC CGTTCTCTCCCTGCTCGGAGCCCCCTGTGCCTTCAT GGGCTCAATGGCTCCTGGCCATGTTGCTGACTTCCT GGTGGCCGACTTCAGGCGGCGGGGCGTGGACGTG TCTCAGGTGGCCTGGCAGAGCAAGGGGGACACCCC CAGCTCCTGCTGCATCATCAACAACCTCCAATGGCAA CCGTACCATTGTGCTCCATGACACGAGCCTGCCAGA TGTGTCTGCTACAGACTTTGAGAAGGTTGATCTGAC CCAGTTCAAGTGGATCCACATTGAGGGCCGGAACG CATCGGAGCAGGTGAAGATGCTGCAGCGGATAGAC GCACACAACACCAGGCAGCCTCCAGAGCAGAAGAT CCGGGTGTCCGTGGAGGTGGAGAAGCCACGAGAG GAGCTCTTCAGCTGTTTGGCTACGGAGACGTGGT GTTTGTGAGCAAAGATGTGGCCAAGCACTTGGGGTT CCAGTCAGCAGAGGAAGCCTTGAGGGGCTTGATG GTCGTGTGAGGAAAGGGGCTGTGCTTGCTGTGCC TGGGCTGAGGAGGGCGCCGACGCCCTGGGCCCTG ATGGCAAATTGCTCCACTCGGATGCTTTCCCGCCAC CCCGCGTGGTGGATACACTGGGAGCTGGAGACACC TTCAATGCCTCCGTCATCTTCAGCCTCTCCAGGGG AGGAGCGTGCAGGAAGCACTGAGATTCGGGTGCCA GGTGGCCGCAAGAAGTGTGGCCTGCAGGGCTTTG ATGGCATCGTGTGAGAGCAGGTGCCGGCTCCTCAC ACACCATGGAGACTACCATTGCGGCTGCATCGCCTT CTCCCTCCATCCAGCCTGGCGTCCAGGTTGCCCT GTTAGGGGACAGATGCAAGCTGTGGGGAGGACTC TGCCTGTGCTCTGTGTTCCCCACAGGGAGAGGCTC TGGGGGGATGGCTGGGGGATGCAGAGCCTCAGAG	1

			CAAATAAATCTTCCTCAGAGCCAGCTTCTCCTCTCAA TGTCTGAACTGCTCTGGCTGGGCATTCTGAGGCTC TGACTCTTCGATCCTCCCTCTTTGTGTCCATTCCCCA AATTAACCTCTCCGCCCAGGCCAGAGGAGGGGCT GCCTGGGCTAGAGCAGCGAGAAAGTCCCCTGGGCTT GCCACCAGCTCTGCCCTGGCTGGGGAGGACACTCG GTGCCCCACACCCAGTGAACCTGCCAAAGAAACCG TGAGAGCTCTTCGGGGCCCTGCGTTGTGCAGACTC TATTCCACAGCTCAGAAGCTGGGAGTCCACACCG CTGAGCTGAACTGACAGGCCAGTGGGGGGCAGGG GTGCGCCTCCTCTGCCCTGCCACCAGCCTGTGAT TTGATGGGGTCTTCATTGTCCAGAAATACCTCCTCC CGCTGACTGCCCCAGAGCCTGAAAGTCTCACCCCTT GGAGCCCACCTTGGAATTAAGGGCGTGCCTCAGCC ACAAATGTGACCCAGGATACAGAGTGTTGCTGTCT CAGGGAGGTCCGATCTGGAACACATATTGGAATTGG GGCCAACCTCAATATAGGGTGGGTAAGGCCCTTATAA TGTAAGAGCATATAATGTAAAGGGCTTTAGAGTGA GACAGACCTGGATTAAATCTGCCATTTAATTAGCTG CATATCACCTTAGGGTACAGCACTTAACGCAATCTG CCTCAATTTCTCATCTGTCAAATGGAACCAATTCTG CTTGGCTACAGAATTATTGTGAGGATAAAATCATATA TAAATGCCCAGCATGATGCCTGATGTGTA	
Cynomolgus monkey (Mf) KHK nucleotide sequence XM_0055763 22.2	Cynomolgu s monkey (Mf)	N/A	GGGGCCGGGCAGCCGCGACACGGTCTTCAGGCA GGGCTGCAGATGCAGGCCAGCTCTACCTCGCGGG TCCAGGGTCCGGAGTCCGAGACGCAGGTGCAGCA GAGGGCGGGGCACGTAGCGCATTTCCAGCGCATTT TCTCTTTGCATTCTCGAGATCGCTTAGCCGCGCTTT AGAAGGGTTTGCATCAGCTCCGAGTCCATCTGACAA GCGAGGAAACTGAGGCTGAGAAGTGGGAGGCGTTG CCATCTGCAGGCCCAGGCAACCTGCTACGGGAAGA CCGGGGGCCAAGACCTCCGGGTGGCTTTCCAGG CCAGCTTGGGTCTTCGGGTGTCCGGAGCAAAGGCC CAGCTCCTTTTCGTTTCCTGCACCCCTCGCCGCTGCA GGTGGCTCCCCGGAGGAGGAGTCCCACGCGGAG GAGGAGCCAGGGCAGCTGGGAGCGAGGACACCAT CCTCCTGGATAACAGGCAGAGGCCGGGAGGAACCC GTCAGTCGGGCGGGCAGGAAGCTCTGGGATCAGCC TCATGGAAGAGAAGCAGATCCTGTGCGTGGGGCTA GTGGTGTGACGTCATCAGCCTGGTGGACAAGTA CCCTAAGGAGGACTCAGAGATAAGGTGCTTGTCCCA GAGATGGCAACGCGGAGGCAACGCGTCCAACCTCT GCACCGTTCTCTCCCTGCTCGGAGCCCCCTGTGCC TTCATGGGCTCAATGGCCCCTGGCCATGTTGCTGAC TTCCTGGTGGCCGACTTCAGGCGGCGGGGTGTGGA CGTGTCTCAGGTGGCCTGGCAGAGCAAGGGGGACA CCCCCAGCTCCTGCTGCATCATCAACAACCTCCAATG GCAACCGTACCATTGTGCTCCATGACACGAGCCTGC CAGATGTGTCTGCTACGGACTTTGAGAAGGTTGATC TGACCCAGTTCAAGTGGATCCACATTGAGGGCCGG AATGCATCGGAGCAGGTGAAGATGCTGCAGCGGAT AGACGCGCACAAACACCAGGCAGCCTCCAGAGCAGA	2

			AGATCCGGGTGTCCGTGGAGGTGGAGAAGCCACAA GAGGAGCTCTTTCAGCTGTTTGGCTACGGAGACGT GGTGTTCGTGTCAGCAAAGATGTGGCCAAGCACTTGG GGTTCCAGTCAGCAGGGGAAGCCCTGAGGGGCTTG TATGGTCGTGTGAGGAAAGGGGCTGTGCTTGTCTGT GCCTGGGCTGAGGAGGGCGCCGACGCCCTGGGCC CTGATGGCAAAGTATCCACTCGGATGCTTTCCCGC CACCCGCGTGGTGGATACCCTGGGGGCTGGAGAC ACCTTCAATGCCTCCGTCATCTTCAGCCTCTCCCAG GGGAGGAGCGTGCAGGAAGCACTGAGATTCGGATG CCAGGTGGCCGGCAAGAAGTGTGGCCAGCAGGGC TTTGATGGCATCGTGTGAGAGCCGGTGCGGTAGGA GGTGCCGGCTCCCCGCACACTATGGAGGCTGACAT TGCGGCTGCATCGCCTTCTCCCCTCCATCCAGCCTG GCATCCAGGTTGCCCTGCTCAGGGGACAGATGCAG GCTGTGGGAGGACTCCGCTGTGTCCTGTGTTCC CCACACGTCTCTCCCTGCAGAGCCTCAGAGCGAATA AATCTTCCTCGGAGCCAGCTTCCCCTGGCAGCTTCT GTCCTCGATGTCTGAACTGCTCTGGCTGGGCATTCC TGAGGCTCTGACTCTCCAGTCCTCCCTCCTCGTGTG CATTCCCCAAATTAACCTCTCCACCCAGGCCCAGAG GAGGGGCTGCCTGGGCTATAGCAGCAAGAAGTGCC CCAGGCTTGCCGCCAGCTCTGCCCTGGCTGGGGAG GACACTAGTGCCCCATACCCAGCGAACCTGCCAA AGAACCAGAAGCCATGAGAGCTCTTTGGGGCCCTG CGTTGTGCAGACTCTATTCCCATAGCTCAGAAGCTG GGAGTCCACACGGCTGAGCCAAAGTACAGGCCAG TGGGGGGCGAGGGGGTGGGGCGCCTCCTCTGCCC TGCCCCACAGCCTGTGATTTGGTGGCGTCTTTGTTG TCCAAAAATATCTCTCCCGCTGACTGCCCCAGAGC CTGAAAGTCTACCCGTGGAGCCACCTTGAATTA AGGGGATGCCTCAGCCACAAATGTGACCCAAGATA GAGTGTTGTCTCAGGGAGGTGGATCTGGAACAC ATATTGGAATTGGGGCCAACTCCAATATAGAGTGGA TAAGGCCTTATAATGTAAAGAGCACATAAGGTAAAG GGCTTTAGAGTCAGACAGACCTAGATTCAAATCTGC CATTTAATTAGCTGCATGTCACCTGAGGGTACAGCG CTTAACACAATCCGCCTCAATTTCTTCATCTGTCAA TGGAGCCAATTCTGCCTGGCTACAGAATTATTGCGA GGATAAAATCATGTA	
Mouse (Mm) KHK nucleotide sequence NM_008439. 4	Mouse (Mm)	N/A	GAGGGAGAGAACGCTTGCTTCTGTGCTCCGCCTGC GAAGGCGAAGTTTCTGTTGCCAGACTGTGCTAGTCC GGGTGGTCCAGGGTCTGCAGCAGGCGCAGAGGGA TCGGAAAGGCGATGCATTACTAGTGCGCTTTGCTT TGACAGCTGAGGCGGAAAAGTGAAGAGGGCCTGCCA TTGGCCGGGCTAGGTAACCCACCTTGCAAAGCAG AAAGCTCCCTGCGGGAGGAGTTCTGCACGCAGAGG AGGAGCCAAGGTAGCCAGTGAGAAAGTTGGGACACG GTCCTCCAGTAGATAAGAGGCAGAGCCCAGCAGGA ACCCCTCTGCTTGCGGGTAGGAAGCTTGGGGAGC AGCCTCATGGAAGAGAAGCAGATCCTGTGCGTGGG GCTGGTGGTGTGCTGGACATCATCAATGTGGTGGACA	3

			AATACCCAGAGGAAGACACGGATCGCAGGTGCCTG TCCCAGAGATGGCAGCGTGGAGGCAACGCATCCAA CTCCTGCACTGTCCTTTCTTGCTTGGAGCCCCGCTG TGCCTTCATGGGCTCTTTGGCCCCCTGGCCACGTTGC CGACTTCCTGGTGGCTGACTTCAGGCAGAGGGGCG TGGATGTGTCTCAAGTGACTTGGCAGAGCCAGGGA GATACCCCTTGCTCTTGCTGCATCGTCAACAACCTCC AATGGCTCCCGTACCATTATACTCTACGACACGAAC CTGCCAGATGTGTCTGCTAAGGACTTTGAGAAGGTC GATCTGACCCGGTTCAAGTGGATCCACATTGAGGG CCGGAATGCATCGGAACAGGTGAAGATGCTGCAGC GGATAGAGGAGCACAATGCCAAGCAGCCTCTGCCA CAGAAGGTCCGGGTGTCGGTGGAGATAGAGAAGCC CCGTGAGGAGCTCTCCAGTTGTTAGCTATGGTGA GGTGGTGTGTTGTCAGCAAAGATGTGGCCAAGCACCT GGGGTTCCAGTCAGCAGTGGAGGCCCTGAGGGGCT TGTACAGTCGAGTGAAGAAAGGGGCTACGCTTGTCT GTGCCTGGGCTGAGGAGGGTGCCGATGCCCTGGG CCCCGATGGTCAGCTGCTCCACTCAGATGCCTTCCC ACCGCCCCGAGTAGTAGACACTCTTGGGGCTGGAG ACACCTTCAATGCCTCTGTCATCTTCAGCCTCTCGA AGGGAAACAGCATGCAAGAGGCCCTGAGATTCGGG TGCCAGGTGGCTGGCAAGAAGTGTGGCTTGACAGG GTTTGATGGCATTGTGTGAGAGGCAAGCGGCACCA GCTCGATACCTCAGAGGCTGGCACCATGCCTGCCA CTGCCTTCTCTACTTCCTCCAGCTTAGCATCCAGCT GCCATTCCCCGGCAGGTGTGGGATGTGGGACAGCC TCTGTCTGTGTCTGCGTCTCTGTATACCTATCTCCTC TCTGCAGATACCTGGAGCAAATAAATCTTCCCCTGA GCCAGC	
KHK-115-154	Hs-Mf commons	25 mer Sense Strand	AGCGCAUUUUCUCUUUGCAUUCUCG	4
KHK-116-155	Hs-Mf commons	25 mer Sense Strand	GCGCAUUUUCUCUUUGCAUUCUCGA	5
KHK-117-156	Hs-Mf commons	25 mer Sense Strand	CGCAUUUUCUCUUUGCAUUCUCGAG	6
KHK-118-157	Hs-Mf commons	25 mer Sense Strand	GCAUUUUCUCUUUGCAUUCUCGAGA	7
KHK-119-158	Hs-Mf commons	25 mer Sense Strand	CAUUUUCUCUUUGCAUUCUCGAGAT	8
KHK-120-159	Hs-Mf commons	25 mer Sense Strand	AUUUUCUCUUUGCAUUCUCGAGATC	9
KHK-121-160	Hs-Mf commons	25 mer Sense Strand	UUUUCUCUUUGCAUUCUCGAGAUCG	10

KHK-122-161	Hs-Mf commons	25 mer Sense Strand	UUUCUCUUUGCAUUCUCGAGAU CGC	11
KHK-123-162	Hs-Mf commons	25 mer Sense Strand	UUCUCUUUGCAUUCUCGAGAU CGCT	12
KHK-124-163	Hs-Mf commons	25 mer Sense Strand	UCUCUUUGCAUUCUCGAGAU CGCTT	13
KHK-125-164	Hs-Mf commons	25 mer Sense Strand	CUCUUUGCAUUCUCGAGAU CGCUTA	14
KHK-126-165	Hs-Mf commons	25 mer Sense Strand	UCUUUGCAUUCUCGAGAU CGCUUAG	15
KHK-127-166	Hs-Mf commons	25 mer Sense Strand	CUUUGCAUUCUCGAGAU CGCUUAGC	16
KHK-128-167	Hs-Mf commons	25 mer Sense Strand	UUUGCAUUCUCGAGAU CGCUUAGCC	17
KHK-179	Hs unique	25 mer Sense Strand	GUGAGUCCAUCUGACAAGCGAGGAA	18
KHK-181-220	Hs-Mf commons	25 mer Sense Strand	GAGUCCAUCUGACAAGCGAGGAAAC	19
KHK-182-221	Hs-Mf commons	25 mer Sense Strand	AGUCCAUCUGACAAGCGAGGAAACT	20
KHK-183-222	Hs-Mf commons	25 mer Sense Strand	GUCCAUCUGACAAGCGAGGAAACTA	21
KHK-184-223	Hs-Mf commons	25 mer Sense Strand	UCCAUCUGACAAGCGAGGAAACUAA	22
KHK-185-224	Hs-Mf commons	25 mer Sense Strand	CCAUCUGACAAGCGAGGAAACUAAG	23
KHK-186-225	Hs-Mf commons	25 mer Sense Strand	CAUCUGACAAGCGAGGAAACUAAGG	24
KHK-187-226	Hs-Mf commons	25 mer Sense Strand	AUCUGACAAGCGAGGAAACUAAGGC	25
KHK-188-227	Hs-Mf commons	25 mer Sense Strand	UCUGACAAGCGAGGAAACUAAGGCT	26
KHK-431-470	Hs-Mf commons	25 mer Sense Strand	GGACACCAUCCUCCUGGAUAAGAGG	27

KHK-432-471	Hs-Mf commons	25 mer Sense Strand	GACACCAUCCUCCUGGAUAAGAGGC	28
KHK-433-472	Hs-Mf commons	25 mer Sense Strand	ACACCAUCCUCCUGGAUAAGAGGCA	29
KHK-507- 545-376-218	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	AGCCUCAUGGAAGAGAAGCAGAUCC	30
KHK-508- 546-377-219	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	GCCUCAUGGAAGAGAAGCAGAUCCCT	31
KHK-509- 547-378-220	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	CCUCAUGGAAGAGAAGCAGAUCCCTG	32
KHK-510- 548-379-221	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	CUCAUGGAAGAGAAGCAGAUCCUGT	33
KHK-511- 549-380-222	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	UCAUGGAAGAGAAGCAGAUCCUGTG	34
KHK-512- 550-381-223	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	CAUGGAAGAGAAGCAGAUCCUGUGC	35
KHK-513- 551-382-224	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	AUGGAAGAGAAGCAGAUCCUGUGCG	36
KHK-514- 552-383-225	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	UGGAAGAGAAGCAGAUCCUGUGCGT	37
KHK-515- 553-384-226	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	GGAAGAGAAGCAGAUCCUGUGCGTG	38
KHK-516- 554-385-227	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	GAAGAGAAGCAGAUCCUGUGCGUGG	39
KHK-517- 555-386-228	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	AAGAGAAGCAGAUCCUGUGCGUGGG	40
KHK-518- 556-387-229	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	AGAGAAGCAGAUCCUGUGCGUGGGG	41
KHK-520- 558-389-231	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	AGAAGCAGAUCCUGUGCGUGGGGCT	42
KHK-521- 559-390-232	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	GAAGCAGAUCCUGUGCGUGGGGCTA	43
KHK-522- 560-391-233	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	AAGCAGAUCCUGUGCGUGGGGCUAG	44

KHK-541-579	Hs-Mf commons	25 mer Sense Strand	GGCUAGUGGUGCUGGACGUCAUCAG	45
KHK-544-582	Hs-Mf commons	25 mer Sense Strand	UAGUGGUGCUGGACGUCAUCAGCCT	46
KHK-546-584	Hs-Mf commons	25 mer Sense Strand	GUGGUGCUGGACGUCAUCAGCCUGG	47
KHK-547-585	Hs-Mf commons	25 mer Sense Strand	UGGUGCUGGACGUCAUCAGCCUGGT	48
KHK-548-586	Hs-Mf commons	25 mer Sense Strand	GGUGCUGGACGUCAUCAGCCUGGTG	49
KHK-549-587	Hs-Mf commons	25 mer Sense Strand	GUGCUGGACGUCAUCAGCCUGGUGG	50
KHK-550-588	Hs-Mf commons	25 mer Sense Strand	UGCUGGACGUCAUCAGCCUGGUGGA	51
KHK-551-589	Hs-Mf commons	25 mer Sense Strand	GCUGGACGUCAUCAGCCUGGUGGAC	52
KHK-552-590	Hs-Mf commons	25 mer Sense Strand	CUGGACGUCAUCAGCCUGGUGGACA	53
KHK-553-591	Hs-Mf commons	25 mer Sense Strand	UGGACGUCAUCAGCCUGGUGGACAA	54
KHK-554-592	Hs-Mf commons	25 mer Sense Strand	GGACGUCAUCAGCCUGGUGGACAAG	55
KHK-555-593	Hs-Mf commons	25 mer Sense Strand	GACGUCAUCAGCCUGGUGGACAAGT	56
KHK-556-594	Hs-Mf commons	25 mer Sense Strand	ACGUCAUCAGCCUGGUGGACAAGTA	57
KHK-557-595	Hs-Mf commons	25 mer Sense Strand	CGUCAUCAGCCUGGUGGACAAGUAC	58
KHK-558-596	Hs-Mf commons	25 mer Sense Strand	GUCAUCAGCCUGGUGGACAAGUACC	59
KHK-559-597	Hs-Mf commons	25 mer Sense Strand	UCAUCAGCCUGGUGGACAAGUACCC	60
KHK-560-598	Hs-Mf commons	25 mer Sense Strand	CAUCAGCCUGGUGGACAAGUACCCT	61

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KHK-561-599	Hs-Mf commons	25 mer Sense Strand	AUCAGCCUGGUGGACAAGUACCCTA	62
KHK-562-600	Hs-Mf commons	25 mer Sense Strand	UCAGCCUGGUGGACAAGUACCCUAA	63
KHK-563-601	Hs-Mf commons	25 mer Sense Strand	CAGCCUGGUGGACAAGUACCCUAAG	64
KHK-564-602	Hs-Mf commons	25 mer Sense Strand	AGCCUGGUGGACAAGUACCCUAAGG	65
KHK-565-603	Hs-Mf commons	25 mer Sense Strand	GCCUGGUGGACAAGUACCCUAAGGA	66
KHK-566-604	Hs-Mf commons	25 mer Sense Strand	CCUGGUGGACAAGUACCCUAAGGAG	67
KHK-567-605	Hs-Mf commons	25 mer Sense Strand	CUGGUGGACAAGUACCCUAAGGAGG	68
KHK-568-606	Hs-Mf commons	25 mer Sense Strand	UGGUGGACAAGUACCCUAAGGAGGA	69
KHK-569-607	Hs-Mf commons	25 mer Sense Strand	GGUGGACAAGUACCCUAAGGAGGAC	70
KHK-570-608	Hs-Mf commons	25 mer Sense Strand	GUGGACAAGUACCCUAAGGAGGACT	71
KHK-571-609	Hs-Mf commons	25 mer Sense Strand	UGGACAAGUACCCUAAGGAGGACTC	72
KHK-572-610	Hs-Mf commons	25 mer Sense Strand	GGACAAGUACCCUAAGGAGGACUCG	73
KHK-573-611	Hs-Mf commons	25 mer Sense Strand	GACAAGUACCCUAAGGAGGACUCGG	74
KHK-574-612	Hs-Mf commons	25 mer Sense Strand	ACAAGUACCCUAAGGAGGACUCGGA	75
KHK-575-613	Hs-Mf commons	25 mer Sense Strand	CAAGUACCCUAAGGAGGACUCGGAG	76
KHK-576-614	Hs-Mf commons	25 mer Sense Strand	AAGUACCCUAAGGAGGACUCGGAGA	77
KHK-577-615	Hs-Mf commons	25 mer Sense Strand	AGUACCCUAAGGAGGACUCGGAGAT	78

KHK-638-676	Hs-Mf commons	25 mer Sense Strand	CGCGUCCAACUCCUGCACCGUUCTC	79
KHK-641-679	Hs-Mf commons	25 mer Sense Strand	GUCCAACUCCUGCACCGUUCUCUCC	80
KHK-642-680	Hs-Mf commons	25 mer Sense Strand	UCCAACUCCUGCACCGUUCUCUCCC	81
KHK-643-681	Hs-Mf commons	25 mer Sense Strand	CCAACUCCUGCACCGUUCUCUCCT	82
KHK-644-682	Hs-Mf commons	25 mer Sense Strand	CAACUCCUGCACCGUUCUCUCCTG	83
KHK-645-683	Hs-Mf commons	25 mer Sense Strand	AACUCCUGCACCGUUCUCUCCCUGC	84
KHK-646-684	Hs-Mf commons	25 mer Sense Strand	ACUCCUGCACCGUUCUCUCCCUGCT	85
KHK-647-685	Hs-Mf commons	25 mer Sense Strand	CUCCUGCACCGUUCUCUCCCUGCTC	86
KHK-650-688	Hs-Mf commons	25 mer Sense Strand	CUGCACCGUUCUCUCCCUGCUCGGA	87
KHK-676-714	Hs-Mf commons	25 mer Sense Strand	CCCCUGUGCCUUAUGGGCUCAAT	88
KHK-713-722	Hs-Mf commons	25 mer Sense Strand	UGUUGCUGACUCCUGGUGGCGAC	89
KHK-826-835	Hs-Mf commons	25 mer Sense Strand	AUGGCAACCGUACCAUUGUGCUCCA	90
KHK-827-836	Hs-Mf commons	25 mer Sense Strand	UGGCAACCGUACCAUUGUGCUCCAT	91
KHK-829-838	Hs-Mf commons	25 mer Sense Strand	GCAACCGUACCAUUGUGCUCCAUGA	92
KHK-830-839	Hs-Mf commons	25 mer Sense Strand	CAACCGUACCAUUGUGCUCCAUGAC	93
KHK-831-840	Hs-Mf commons	25 mer Sense Strand	AACCGUACCAUUGUGCUCCAUGACA	94
KHK-832-841	Hs-Mf commons	25 mer Sense Strand	ACCGUACCAUUGUGCUCCAUGACAC	95

KHK-857-895	Hs-Mf commons	25 mer Sense Strand	GAGCCUGCCAGAUGUGUCUGCUACA	96
KHK-858-896	Hs-Mf commons	25 mer Sense Strand	AGCCUGCCAGAUGUGUCUGCUACAG	97
KHK-859-897	Hs-Mf commons	25 mer Sense Strand	GCCUGCCAGAUGUGUCUGCUACAGA	98
KHK-860- 898-729-571	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	CCUGCCAGAUGUGUCUGCUACAGAC	99
KHK-861- 899-730-572	Hs-Mf-Mm- Rn commons	25 mer Sense Strand	CUGCCAGAUGUGUCUGCUACAGACT	100
KHK-862-900	Hs-Mf commons	25 mer Sense Strand	UGCCAGAUGUGUCUGCUACAGACTT	101
KHK-865	Hs unique	25 mer Sense Strand	CAGAUGUGUCUGCUACAGACUUUGA	102
KHK-880	Hs unique	25 mer Sense Strand	CAGACUUUGAGAAGGUUGAUCUGAC	103
KHK-882-920	Hs-Mf commons	25 mer Sense Strand	GACUUUGAGAAGGUUGAUCUGACCC	104
KHK-883-921	Hs-Mf commons	25 mer Sense Strand	ACUUUGAGAAGGUUGAUCUGACCCA	105
KHK-884-922	Hs-Mf commons	25 mer Sense Strand	CUUUGAGAAGGUUGAUCUGACCCAG	106
KHK-885-923	Hs-Mf commons	25 mer Sense Strand	UUUGAGAAGGUUGAUCUGACCCAGT	107
KHK-886-924	Hs-Mf commons	25 mer Sense Strand	UUGAGAAGGUUGAUCUGACCCAGTT	108
KHK-887-925	Hs-Mf commons	25 mer Sense Strand	UGAGAAGGUUGAUCUGACCCAGUTC	109
KHK-888-926	Hs-Mf commons	25 mer Sense Strand	GAGAAGGUUGAUCUGACCCAGUUCA	110
KHK-889-927	Hs-Mf commons	25 mer Sense Strand	AGAAGGUUGAUCUGACCCAGUUCAA	111
KHK-890-928	Hs-Mf commons	25 mer Sense Strand	GAAGGUUGAUCUGACCCAGUUCAAG	112

KHK-891-929	Hs-Mf commons	25 mer Sense Strand	AAGGUUGAUCUGACCCAGUUCAAGT	113
KHK-892-930	Hs-Mf commons	25 mer Sense Strand	AGGUUGAUCUGACCCAGUUCAAGTG	114
KHK-893-931	Hs-Mf commons	25 mer Sense Strand	GGUUGAUCUGACCCAGUUCAAGUGG	115
KHK-894-932	Hs-Mf commons	25 mer Sense Strand	GUUGAUCUGACCCAGUUCAAGUGGA	116
KHK-895-933	Hs-Mf commons	25 mer Sense Strand	UUGAUCUGACCCAGUUCAAGUGGAT	117
KHK-896-934	Hs-Mf commons	25 mer Sense Strand	UGAUCUGACCCAGUUCAAGUGGATC	118
KHK-897-935	Hs-Mf commons	25 mer Sense Strand	GAUCUGACCCAGUUCAAGUGGAUCC	119
KHK-898-936	Hs-Mf commons	25 mer Sense Strand	AUCUGACCCAGUUCAAGUGGAUCCA	120
KHK-899-937	Hs-Mf commons	25 mer Sense Strand	UCUGACCCAGUUCAAGUGGAUCCAC	121
KHK-900-938	Hs-Mf commons	25 mer Sense Strand	CUGACCCAGUUCAAGUGGAUCCACA	122
KHK-901-939	Hs-Mf commons	25 mer Sense Strand	UGACCCAGUUCAAGUGGAUCCACAT	123
KHK-902-940	Hs-Mf commons	25 mer Sense Strand	GACCCAGUUCAAGUGGAUCCACATT	124
KHK-903-941	Hs-Mf commons	25 mer Sense Strand	ACCCAGUUCAAGUGGAUCCACAUTG	125
KHK-904-942	Hs-Mf commons	25 mer Sense Strand	CCCAGUUCAAGUGGAUCCACAUUGA	126
KHK-905-943	Hs-Mf commons	25 mer Sense Strand	CCAGUUCAAGUGGAUCCACAUUGAG	127
KHK-906-944	Hs-Mf commons	25 mer Sense Strand	CAGUUCAAGUGGAUCCACAUUGAGG	128
KHK-907-945	Hs-Mf commons	25 mer Sense Strand	AGUUCAAGUGGAUCCACAUUGAGGG	129

KHK-908-946-777-619	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GUUCAAGUGGAUCCACAUUGAGGGC	130
KHK-909-947-778-620	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	UUCAAGUGGAUCCACAUUGAGGGCC	131
KHK-910-948-779-621	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	UCAAGUGGAUCCACAUUGAGGGCCG	132
KHK-911-949-780-622	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	CAAGUGGAUCCACAUUGAGGGCCGG	133
KHK-912-950-781-623	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	AAGUGGAUCCACAUUGAGGGCCGGA	134
KHK-913-951-782-624	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	AGUGGAUCCACAUUGAGGGCCGGAA	135
KHK-914-952-783-625	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GUGGAUCCACAUUGAGGGCCGGAAC	136
KHK-939-977	Hs-Mf commons	25 mer Sense Strand	GCAUCGGAGCAGGUGAAGAUGCUGC	137
KHK-940-978	Hs-Mf commons	25 mer Sense Strand	CAUCGGAGCAGGUGAAGAUGCUGCA	138
KHK-941-979	Hs-Mf commons	25 mer Sense Strand	AUCGGAGCAGGUGAAGAUGCUGCAG	139
KHK-942-980	Hs-Mf commons	25 mer Sense Strand	UCGGAGCAGGUGAAGAUGCUGCAGC	140
KHK-943-981	Hs-Mf commons	25 mer Sense Strand	CGGAGCAGGUGAAGAUGCUGCAGCG	141
KHK-944-982	Hs-Mf commons	25 mer Sense Strand	GGAGCAGGUGAAGAUGCUGCAGCGG	142
KHK-945-983	Hs-Mf commons	25 mer Sense Strand	GAGCAGGUGAAGAUGCUGCAGCGGA	143
KHK-946-984	Hs-Mf commons	25 mer Sense Strand	AGCAGGUGAAGAUGCUGCAGCGGAT	144
KHK-947-985	Hs-Mf commons	25 mer Sense Strand	GCAGGUGAAGAUGCUGCAGCGGATA	145
KHK-948-986-817	Hs-Mf-Mm commons	25 mer Sense Strand	CAGGUGAAGAUGCUGCAGCGGAUAG	146

KHK-949-987-818	Hs-Mf-Mm commons	25 mer Sense Strand	AGGUGAAGAUGCUGCAGCGGAUAGA	147
KHK-950-988-819	Hs-Mf-Mm commons	25 mer Sense Strand	GGUGAAGAUGCUGCAGCGGAUAGAC	148
KHK-951-989-820	Hs-Mf-Mm commons	25 mer Sense Strand	GUGAAGAUGCUGCAGCGGAUAGACG	149
KHK-952-990-821	Hs-Mf-Mm commons	25 mer Sense Strand	UGAAGAUGCUGCAGCGGAUAGACGC	150
KHK-953-991-822	Hs-Mf-Mm commons	25 mer Sense Strand	GAAGAUGCUGCAGCGGAUAGACGCA	151
KHK-954-992-823	Hs-Mf-Mm commons	25 mer Sense Strand	AAGAUGCUGCAGCGGAUAGACGCAC	152
KHK-955-993-824	Hs-Mf-Mm commons	25 mer Sense Strand	AGAUGCUGCAGCGGAUAGACGCACA	153
KHK-956-994	Hs-Mf commons	25 mer Sense Strand	GAUGCUGCAGCGGAUAGACGCACAC	154
KHK-957-995	Hs-Mf commons	25 mer Sense Strand	AUGCUGCAGCGGAUAGACGCACACA	155
KHK-958-996	Hs-Mf commons	25 mer Sense Strand	UGCUGCAGCGGAUAGACGCACACAA	156
KHK-978-1016	Hs-Mf commons	25 mer Sense Strand	CACAACACCAGGCAGCCUCCAGAGC	157
KHK-982-1020	Hs-Mf commons	25 mer Sense Strand	ACACCAGGCAGCCUCCAGAGCAGAA	158
KHK-983-1021	Hs-Mf commons	25 mer Sense Strand	CACCAGGCAGCCUCCAGAGCAGAAG	159
KHK-984-1022	Hs-Mf commons	25 mer Sense Strand	ACCAGGCAGCCUCCAGAGCAGAAGA	160
KHK-985-1023	Hs-Mf commons	25 mer Sense Strand	CCAGGCAGCCUCCAGAGCAGAAGAT	161
KHK-991-1029	Hs-Mf commons	25 mer Sense Strand	AGCCUCCAGAGCAGAAGAUCCGGGT	162
KHK-992-1030	Hs-Mf commons	25 mer Sense Strand	GCCUCCAGAGCAGAAGAUCCGGGTG	163

KHK-993-1031	Hs-Mf commons	25 mer Sense Strand	CCUCCAGAGCAGAAGAUCCGGGUGT	164
KHK-999-1037	Hs-Mf commons	25 mer Sense Strand	GAGCAGAAGAUCCGGGUGUCCGUGG	165
KHK-1000-1038	Hs-Mf commons	25 mer Sense Strand	AGCAGAAGAUCCGGGUGUCCGUGGA	166
KHK-1019-1057	Hs-Mf commons	25 mer Sense Strand	CGUGGAGGUGGAGAAGCCACGAGAG	167
KHK-1054-1092	Hs-Mf commons	25 mer Sense Strand	AGCUGUUUGGCUACGGAGACGUGGT	168
KHK-1055-1093	Hs-Mf commons	25 mer Sense Strand	GCUGUUUGGCUACGGAGACGUGGTG	169
KHK-1057-1095	Hs-Mf commons	25 mer Sense Strand	UGUUUGGCUACGGAGACGUGGUGTT	170
KHK-1058-1096	Hs-Mf commons	25 mer Sense Strand	GUUUGGCUACGGAGACGUGGUGUTT	171
KHK-1059-1097	Hs-Mf commons	25 mer Sense Strand	UUUGGCUACGGAGACGUGGUGUUTG	172
KHK-1060-1098	Hs-Mf commons	25 mer Sense Strand	UUGGCUACGGAGACGUGGUGUUUGT	173
KHK-1061-1099	Hs-Mf commons	25 mer Sense Strand	UGGCUACGGAGACGUGGUGUUUGTC	174
KHK-1062-1100	Hs-Mf commons	25 mer Sense Strand	GGCUACGGAGACGUGGUGUUUGUCA	175
KHK-1063-1101	Hs-Mf commons	25 mer Sense Strand	GCUACGGAGACGUGGUGUUUGUCAG	176
KHK-1064-1102	Hs-Mf commons	25 mer Sense Strand	CUACGGAGACGUGGUGUUUGUCAGC	177
KHK-1065-1103	Hs-Mf commons	25 mer Sense Strand	UACGGAGACGUGGUGUUUGUCAGCA	178
KHK-1066-1104	Hs-Mf commons	25 mer Sense Strand	ACGGAGACGUGGUGUUUGUCAGCAA	179
KHK-1067-1105	Hs-Mf commons	25 mer Sense Strand	CGGAGACGUGGUGUUUGUCAGCAAA	180

KHK-1068-1106	Hs-Mf commons	25 mer Sense Strand	GGAGACGUGGUGUUUGUCAGCAAAG	181
KHK-1069-1107	Hs-Mf commons	25 mer Sense Strand	GAGACGUGGUGUUUGUCAGCAAAGA	182
KHK-1070-1108	Hs-Mf commons	25 mer Sense Strand	AGACGUGGUGUUUGUCAGCAAAGAT	183
KHK-1071-1109	Hs-Mf commons	25 mer Sense Strand	GACGUGGUGUUUGUCAGCAAAGATG	184
KHK-1072-1110	Hs-Mf commons	25 mer Sense Strand	ACGUGGUGUUUGUCAGCAAAGAUGT	185
KHK-1073-1111	Hs-Mf commons	25 mer Sense Strand	CGUGGUGUUUGUCAGCAAAGAUGTG	186
KHK-1074-1112-943-785	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GUGGUGUUUGUCAGCAAAGAUGUGG	187
KHK-1075-1113-944-786	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	UGGUGUUUGUCAGCAAAGAUGUGGC	188
KHK-1076-1114-945-787	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GGUGUUUGUCAGCAAAGAUGUGGCC	189
KHK-1077-1115-946-788	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GUGUUUGUCAGCAAAGAUGUGGCCA	190
KHK-1078-1116-947-789	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	UGUUUGUCAGCAAAGAUGUGGCCAA	191
KHK-1079-1117-948-790	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GUUUGUCAGCAAAGAUGUGGCCAAG	192
KHK-1080-1118-949-791	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	UUUGUCAGCAAAGAUGUGGCCAAGC	193
KHK-1081-1119-950-792	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	UUGUCAGCAAAGAUGUGGCCAAGCA	194
KHK-1082-1120-951-793	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	UGUCAGCAAAGAUGUGGCCAAGCAC	195
KHK-1083-1121-952-794	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GUCAGCAAAGAUGUGGCCAAGCACT	196
KHK-1084-1122-953-795	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	UCAGCAAAGAUGUGGCCAAGCACTT	197

KHK-1085-1123-954-796	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	CAGCAAAGAUGUGGCCAAGCACUTG	198
KHK-1086-1124-955-797	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	AGCAAAGAUGUGGCCAAGCACUUGG	199
KHK-1087-1125-956-798	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GCAAAGAUGUGGCCAAGCACUUGGG	200
KHK-1090-1128	Hs-Mf commons	25 mer Sense Strand	AAGAUGUGGCCAAGCACUUGGGGTT	201
KHK-1091-1129	Hs-Mf commons	25 mer Sense Strand	AGAUGUGGCCAAGCACUUGGGGUTC	202
KHK-1092-1130	Hs-Mf commons	25 mer Sense Strand	GAUGUGGCCAAGCACUUGGGGUUCC	203
KHK-1093-1131	Hs-Mf commons	25 mer Sense Strand	AUGUGGCCAAGCACUUGGGGUUCCA	204
KHK-1095-1133	Hs-Mf commons	25 mer Sense Strand	GUGGCCAAGCACUUGGGGUUCCAGT	205
KHK-1096-1134	Hs-Mf commons	25 mer Sense Strand	UGGCCAAGCACUUGGGGUUCCAGTC	206
KHK-1097-1135	Hs-Mf commons	25 mer Sense Strand	GGCCAAGCACUUGGGGUUCCAGUCA	207
KHK-1099-1137	Hs-Mf commons	25 mer Sense Strand	CCAAGCACUUGGGGUUCCAGUCAGC	208
KHK-1100-1138	Hs-Mf commons	25 mer Sense Strand	CAAGCACUUGGGGUUCCAGUCAGCA	209
KHK-1101-1139	Hs-Mf commons	25 mer Sense Strand	AAGCACUUGGGGUUCCAGUCAGCAG	210
KHK-1102-1140	Hs-Mf commons	25 mer Sense Strand	AGCACUUGGGGUUCCAGUCAGCAGA	211
KHK-1103-1141	Hs-Mf commons	25 mer Sense Strand	GCACUUGGGGUUCCAGUCAGCAGAG	212
KHK-1104-1142	Hs-Mf commons	25 mer Sense Strand	CACUUGGGGUUCCAGUCAGCAGAGG	213
KHK-1106-1144	Hs-Mf commons	25 mer Sense Strand	CUUGGGGUUCCAGUCAGCAGAGGAA	214

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KHK-1107-1145	Hs-Mf commons	25 mer Sense Strand	UUGGGGUUCCAGUCAGCAGAGGAAG	215
KHK-1135-1173	Hs-Mf commons	25 mer Sense Strand	UGAGGGGCUUGUAUGGUCGUGUGAG	216
KHK-1136-1174	Hs-Mf commons	25 mer Sense Strand	GAGGGGCUUGUAUGGUCGUGUGAGG	217
KHK-1137-1175	Hs-Mf commons	25 mer Sense Strand	AGGGGCUUGUAUGGUCGUGUGAGGA	218
KHK-1138-1176	Hs-Mf commons	25 mer Sense Strand	GGGGCUUGUAUGGUCGUGUGAGGAA	219
KHK-1139-1177	Hs-Mf commons	25 mer Sense Strand	GGGCUUGUAUGGUCGUGUGAGGAAA	220
KHK-1140-1178	Hs-Mf commons	25 mer Sense Strand	GGCUUGUAUGGUCGUGUGAGGAAAG	221
KHK-1141-1179	Hs-Mf commons	25 mer Sense Strand	GCUUGUAUGGUCGUGUGAGGAAAGG	222
KHK-1142-1180	Hs-Mf commons	25 mer Sense Strand	CUUGUAUGGUCGUGUGAGGAAAGGG	223
KHK-1143-1181	Hs-Mf commons	25 mer Sense Strand	UUGUAUGGUCGUGUGAGGAAAGGGG	224
KHK-1144-1182	Hs-Mf commons	25 mer Sense Strand	UGUAUGGUCGUGUGAGGAAAGGGGC	225
KHK-1145-1183	Hs-Mf commons	25 mer Sense Strand	GUAUGGUCGUGUGAGGAAAGGGGCT	226
KHK-1146-1184	Hs-Mf commons	25 mer Sense Strand	UAUGGUCGUGUGAGGAAAGGGGCTG	227
KHK-1147-1185	Hs-Mf commons	25 mer Sense Strand	AUGGUCGUGUGAGGAAAGGGGCUGT	228
KHK-1148-1186	Hs-Mf commons	25 mer Sense Strand	UGGUCGUGUGAGGAAAGGGGCUGTG	229
KHK-1149-1187	Hs-Mf commons	25 mer Sense Strand	GGUCGUGUGAGGAAAGGGGCUGUGC	230
KHK-1153-1191	Hs-Mf commons	25 mer Sense Strand	GUGUGAGGAAAGGGGCUGUGCUUGT	231

KHK-1154-1192	Hs-Mf commons	25 mer Sense Strand	UGUGAGGAAAGGGGCUGUGCUUGTC	232
KHK-1157-1195	Hs-Mf commons	25 mer Sense Strand	GAGGAAAGGGGCUGUGCUUGUCUGT	233
KHK-1158-1196	Hs-Mf commons	25 mer Sense Strand	AGGAAAGGGGCUGUGCUUGUCUGTG	234
KHK-1159-1197	Hs-Mf commons	25 mer Sense Strand	GGAAAGGGGCUGUGCUUGUCUGUGC	235
KHK-1161-1199	Hs-Mf commons	25 mer Sense Strand	AAAGGGGCUGUGCUUGUCUGUGCCT	236
KHK-1163-1201	Hs-Mf commons	25 mer Sense Strand	AGGGGCUGUGCUUGUCUGUGCCUGG	237
KHK-1164-1202	Hs-Mf commons	25 mer Sense Strand	GGGGCUGUGCUUGUCUGUGCCUGGG	238
KHK-1232-1270	Hs-Mf commons	25 mer Sense Strand	CCACUCGGAUGCUUUCCCCGCCACCC	239
KHK-1278-1316-1147-989	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GCUGGAGACACCUUCA AUGCCUCCG	240
KHK-1279-1317-1148-990	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	CUGGAGACACCUUCA AUGCCUCCGT	241
KHK-1280-1318-1149-991	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	UGGAGACACCUUCA AUGCCUCCGTC	242
KHK-1281-1319-1150-992	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GGAGACACCUUCA AUGCCUCCGUCA	243
KHK-1282-1320-1151-993	Hs-Mf-Mm-Rn commons	25 mer Sense Strand	GAGACACCUUCA AUGCCUCCGUCAT	244
KHK-1283-1321	Hs-Mf commons	25 mer Sense Strand	AGACACCUUCA AUGCCUCCGUCATC	245
KHK-1284-1322	Hs-Mf commons	25 mer Sense Strand	GACACCUUCA AUGCCUCCGUCAUCT	246
KHK-1285-1323	Hs-Mf commons	25 mer Sense Strand	ACACCUUCA AUGCCUCCGUCAUCTT	247
KHK-1286-1324	Hs-Mf commons	25 mer Sense Strand	CACCUUCA AUGCCUCCGUCAUCUTC	248

KHK-1287-1325	Hs-Mf commons	25 mer Sense Strand	ACCUUCAAUGCCUCCGUCAUCUUCA	249
KHK-1288-1326	Hs-Mf commons	25 mer Sense Strand	CCUUCAAUGCCUCCGUCAUCUUCAG	250
KHK-1289-1327	Hs-Mf commons	25 mer Sense Strand	CUUCAAUGCCUCCGUCAUCUUCAGC	251
KHK-1290-1328	Hs-Mf commons	25 mer Sense Strand	UUCAAUGCCUCCGUCAUCUUCAGCC	252
KHK-1291-1329	Hs-Mf commons	25 mer Sense Strand	UCAAUGCCUCCGUCAUCUUCAGCCT	253
KHK-1292-1330	Hs-Mf commons	25 mer Sense Strand	CAAUGCCUCCGUCAUCUUCAGCCTC	254
KHK-1293-1331	Hs-Mf commons	25 mer Sense Strand	AAUGCCUCCGUCAUCUUCAGCCUCT	255
KHK-1294-1332	Hs-Mf commons	25 mer Sense Strand	AUGCCUCCGUCAUCUUCAGCCUCTC	256
KHK-1295-1333	Hs-Mf commons	25 mer Sense Strand	UGCCUCCGUCAUCUUCAGCCUCUCC	257
KHK-1297-1335	Hs-Mf commons	25 mer Sense Strand	CCUCCGUCAUCUUCAGCCUCUCCCA	258
KHK-1323-1361	Hs-Mf commons	25 mer Sense Strand	GGGAGGAGCGUGCAGGAAGCACUGA	259
KHK-1325-1363	Hs-Mf commons	25 mer Sense Strand	GAGGAGCGUGCAGGAAGCACUGAGA	260
KHK-1326-1364	Hs-Mf commons	25 mer Sense Strand	AGGAGCGUGCAGGAAGCACUGAGAT	261
KHK-1327-1365	Hs-Mf commons	25 mer Sense Strand	GGAGCGUGCAGGAAGCACUGAGATT	262
KHK-1328-1366	Hs-Mf commons	25 mer Sense Strand	GAGCGUGCAGGAAGCACUGAGAUTC	263
KHK-1329-1367	Hs-Mf commons	25 mer Sense Strand	AGCGUGCAGGAAGCACUGAGAUUCG	264
KHK-1330-1368	Hs-Mf commons	25 mer Sense Strand	GCGUGCAGGAAGCACUGAGAUUCGG	265

KHK-1331-1369	Hs-Mf commons	25 mer Sense Strand	CGUGCAGGAAGCACUGAGAUUCGGG	266
KHK-1332-1370	Hs-Mf commons	25 mer Sense Strand	GUGCAGGAAGCACUGAGAUUCGGGT	267
KHK-1333-1371	Hs-Mf commons	25 mer Sense Strand	UGCAGGAAGCACUGAGAUUCGGGTG	268
KHK-1334-1372	Hs-Mf commons	25 mer Sense Strand	GCAGGAAGCACUGAGAUUCGGGUGC	269
KHK-1335-1373	Hs-Mf commons	25 mer Sense Strand	CAGGAAGCACUGAGAUUCGGGUGCC	270
KHK-1336-1374	Hs-Mf commons	25 mer Sense Strand	AGGAAGCACUGAGAUUCGGGUGCCA	271
KHK-1385-1423	Hs-Mf commons	25 mer Sense Strand	GCAGGGCUUUGAUGGCAUCGUGUGA	272
KHK-1387-1425	Hs-Mf commons	25 mer Sense Strand	AGGGCUUUGAUGGCAUCGUGUGAGA	273
KHK-1388-1426	Hs-Mf commons	25 mer Sense Strand	GGGCUUUGAUGGCAUCGUGUGAGAG	274
KHK-1389-1427	Hs-Mf commons	25 mer Sense Strand	GGCUUUGAUGGCAUCGUGUGAGAGC	275
KHK-1538-1588	Hs-Mf commons	25 mer Sense Strand	GCCUGUGUCCUGUGUUCCCCACAGG	276
KHK-1540-1590	Hs-Mf commons	25 mer Sense Strand	CUGUGUCCUGUGUUCCCCACAGGGA	277
KHK-1542-1592	Hs-Mf commons	25 mer Sense Strand	GUGUCCUGUGUUCCCCACAGGGAGA	278
KHK-1665-1708	Hs-Mf commons	25 mer Sense Strand	CAUUCCUGAGGCUCUGACUCUUCGA	279
KHK-1666-1709	Hs-Mf commons	25 mer Sense Strand	AUUCCUGAGGCUCUGACUCUUCGAT	280
KHK-1667-1710	Hs-Mf commons	25 mer Sense Strand	UUCCUGAGGCUCUGACUCUUCGATC	281
KHK-1707-1750	Hs-Mf commons	25 mer Sense Strand	CAUUCCCCAAAUUAACCUCUCCGCC	282

KHK-1708-1751	Hs-Mf commons	25 mer Sense Strand	AUUCCCCAAAUUAACCUCUCCGCC	283
KHK-1709-1752	Hs-Mf commons	25 mer Sense Strand	UUCCCCAAAUUAACCUCUCCGCCCA	284
KHK-1869-1918	Hs-Mf commons	25 mer Sense Strand	GGGCCUGCGUUGUGCAGACUCUAT	285
KHK-1870-1919	Hs-Mf commons	25 mer Sense Strand	GGCCCUGCGUUGUGCAGACUCUATT	286
KHK-1871-1920	Hs-Mf commons	25 mer Sense Strand	GCCCUGCGUUGUGCAGACUCUAUTC	287
KHK-1872-1921	Hs-Mf commons	25 mer Sense Strand	CCCUGCGUUGUGCAGACUCUAUUC	288
KHK-1873-1922	Hs-Mf commons	25 mer Sense Strand	CCUGCGUUGUGCAGACUCUAUUCCC	289
KHK-1874-1923	Hs-Mf commons	25 mer Sense Strand	CUGCGUUGUGCAGACUCUAUUCCCA	290
KHK-1875-1924	Hs-Mf commons	25 mer Sense Strand	UGCGUUGUGCAGACUCUAUUCCCAC	291
KHK-1876-1925	Hs-Mf commons	25 mer Sense Strand	GCGUUGUGCAGACUCUAUUCCCACA	292
KHK-1877-1926	Hs-Mf commons	25 mer Sense Strand	CGUUGUGCAGACUCUAUUCCCACAG	293
KHK-1878-1927	Hs-Mf commons	25 mer Sense Strand	GUUGUGCAGACUCUAUUCCCACAGC	294
KHK-1879-1928	Hs-Mf commons	25 mer Sense Strand	UUGUGCAGACUCUAUUCCCACAGCT	295
KHK-1880-1929	Hs-Mf commons	25 mer Sense Strand	UGUGCAGACUCUAUUCCCACAGCTC	296
KHK-1900-1949	Hs-Mf commons	25 mer Sense Strand	AGCUCAGAAGCUGGGAGUCCACACC	297
KHK-1905-1954	Hs-Mf commons	25 mer Sense Strand	AGAAGCUGGGAGUCCACACCGCUGA	298
KHK-1971-2025	Hs-Mf commons	25 mer Sense Strand	CUGCCCUGCCCACCAGCCUGUGATT	299

KHK-1974-2028	Hs-Mf commons	25 mer Sense Strand	CCCUGCCCACCAGCCUGUGAUUUUGA	300
KHK-1975-2029	Hs-Mf commons	25 mer Sense Strand	CCUGCCCACCAGCCUGUGAUUUUGAT	301
KHK-1976-2030	Hs-Mf commons	25 mer Sense Strand	CUGCCCACCAGCCUGUGAUUUUGATG	302
KHK-1978-2032	Hs-Mf commons	25 mer Sense Strand	GCCCACCAGCCUGUGAUUUUGAUGGG	303
KHK-1979-2033	Hs-Mf commons	25 mer Sense Strand	CCCACCAGCCUGUGAUUUUGAUGGGG	304
KHK-2032-2086	Hs-Mf commons	25 mer Sense Strand	GCUGACUGCCCCAGAGCCUGAAAGT	305
KHK-2035-2089	Hs-Mf commons	25 mer Sense Strand	GACUGCCCCAGAGCCUGAAAGUCTC	306
KHK-2036-2090	Hs-Mf commons	25 mer Sense Strand	ACUGCCCCAGAGCCUGAAAGUCUCA	307
KHK-2037-2091	Hs-Mf commons	25 mer Sense Strand	CUGCCCCAGAGCCUGAAAGUCUCAC	308
KHK-2038-2092	Hs-Mf commons	25 mer Sense Strand	UGCCCCAGAGCCUGAAAGUCUCACC	309
KHK-2039-2093	Hs-Mf commons	25 mer Sense Strand	GCCCCAGAGCCUGAAAGUCUCACCC	310
KHK-2040-2094	Hs-Mf commons	25 mer Sense Strand	CCCCAGAGCCUGAAAGUCUCACCCT	311
KHK-2041-2095	Hs-Mf commons	25 mer Sense Strand	CCCAGAGCCUGAAAGUCUCACCCTT	312
KHK-2042-2096	Hs-Mf commons	25 mer Sense Strand	CCAGAGCCUGAAAGUCUCACCCUTG	313
KHK-2043-2097	Hs-Mf commons	25 mer Sense Strand	CAGAGCCUGAAAGUCUCACCCUUGG	314
KHK-2044-2098	Hs-Mf commons	25 mer Sense Strand	AGAGCCUGAAAGUCUCACCCUUGGA	315
KHK-2045-2099	Hs-Mf commons	25 mer Sense Strand	GAGCCUGAAAGUCUCACCCUUGGAG	316

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KHK-2067-2121	Hs-Mf commons	25 mer Sense Strand	GAGCCCACCUUGGAAUUAAGGGCGT	317
KHK-2069-2123	Hs-Mf commons	25 mer Sense Strand	GCCCACCUUGGAAUUAAGGGCGUGC	318
KHK-2091-2145	Hs-Mf commons	25 mer Sense Strand	UGCCUCAGCCACAAAUGUGACCCAG	319
KHK-2092-2146	Hs-Mf commons	25 mer Sense Strand	GCCUCAGCCACAAAUGUGACCCAGG	320
KHK-2093-2147	Hs-Mf commons	25 mer Sense Strand	CCUCAGCCACAAAUGUGACCCAGGA	321
KHK-2094-2148	Hs-Mf commons	25 mer Sense Strand	CUCAGCCACAAAUGUGACCCAGGAT	322
KHK-2095-2149	Hs-Mf commons	25 mer Sense Strand	UCAGCCACAAAUGUGACCCAGGATA	323
KHK-2096-2150	Hs-Mf commons	25 mer Sense Strand	CAGCCACAAAUGUGACCCAGGAUAC	324
KHK-2105	Hs unique	25 mer Sense Strand	AUGUGACCCAGGAUACAGAGUGUTG	325
KHK-2148-2197	Hs-Mf commons	25 mer Sense Strand	GAUCUGGAACACAUAUUGGAAUUGG	326
KHK-2149-2198	Hs-Mf commons	25 mer Sense Strand	AUCUGGAACACAUAUUGGAAUUGGG	327
KHK-2150-2199	Hs-Mf commons	25 mer Sense Strand	UCUGGAACACAUAUUGGAAUUGGGG	328
KHK-2151-2200	Hs-Mf commons	25 mer Sense Strand	CUGGAACACAUAUUGGAAUUGGGGC	329
KHK-2152-2201	Hs-Mf commons	25 mer Sense Strand	UGGAACACAUAUUGGAAUUGGGGCC	330
KHK-2153-2202	Hs-Mf commons	25 mer Sense Strand	GGAACACAUAUUGGAAUUGGGGCCA	331
KHK-2154-2203	Hs-Mf commons	25 mer Sense Strand	GAACACAUAUUGGAAUUGGGGCCAA	332
KHK-2155-2204	Hs-Mf commons	25 mer Sense Strand	AACACAUAUUGGAAUUGGGGCCAAC	333

KHK-2156-2205	Hs-Mf commons	25 mer Sense Strand	ACACAUUUUGGAAUUGGGGCCAACT	334
KHK-2157-2206	Hs-Mf commons	25 mer Sense Strand	CACAUUUUGGAAUUGGGGCCAACTC	335
KHK-2159-2208	Hs-Mf commons	25 mer Sense Strand	CAUAAUUGGAAUUGGGGCCAACUCCA	336
KHK-2160-2209	Hs-Mf commons	25 mer Sense Strand	AUAAUUGGAAUUGGGGCCAACUCCAA	337
KHK-2161-2210	Hs-Mf commons	25 mer Sense Strand	UAUUGGAAUUGGGGCCAACUCCAAT	338
KHK-2162-2211	Hs-Mf commons	25 mer Sense Strand	AUUGGAAUUGGGGCCAACUCCAATA	339
KHK-2163-2212	Hs-Mf commons	25 mer Sense Strand	UUGGAAUUGGGGCCAACUCCAAUAT	340
KHK-2164-2213	Hs-Mf commons	25 mer Sense Strand	UGGAAUUGGGGCCAACUCCAAUATA	341
KHK-2165-2214	Hs-Mf commons	25 mer Sense Strand	GGAAUUGGGGCCAACUCCAAUUAUAG	342
KHK-2166-2215	Hs-Mf commons	25 mer Sense Strand	GAAUUGGGGCCAACUCCAAUUAUAGG	343
KHK-2170-2219	Hs-Mf commons	25 mer Sense Strand	UGGGGCCAACUCCAAUUAUAGGGUGG	344
KHK-2196-2245	Hs-Mf commons	25 mer Sense Strand	UAAGGCCUUAUAAUGUAAAGAGCAT	345
KHK-2197-2246	Hs-Mf commons	25 mer Sense Strand	AAGGCCUUAUAAUGUAAAGAGCATA	346
KHK-2198-2247	Hs-Mf commons	25 mer Sense Strand	AGGCCUUAUAAUGUAAAGAGCAUAT	347
KHK-2199-2248	Hs-Mf commons	25 mer Sense Strand	GGCCUUAUAAUGUAAAGAGCAUATA	348
KHK-2200-2249	Hs-Mf commons	25 mer Sense Strand	GCCUUAUAAUGUAAAGAGCAUUAUA	349
KHK-2201-2250	Hs-Mf commons	25 mer Sense Strand	CCUUAUAAUGUAAAGAGCAUUAUAAT	350

KHK-2205	Hs unique	25 mer Sense Strand	AUAAUGUAAAGAGCAUAAUAAUGUAA	351
KHK-2238	Hs unique	25 mer Sense Strand	AGAGUGAGACAGACCUGGAUUAAAA	352
KHK-2260- 2309	Hs-Mf commons	25 mer Sense Strand	AAAUCUGCCAUUUAAUUAGCUGCAT	353
KHK-2261- 2310	Hs-Mf commons	25 mer Sense Strand	AAUCUGCCAUUUAAUUAGCUGCATA	354
KHK-2262- 2311	Hs-Mf commons	25 mer Sense Strand	AUCUGCCAUUUAAUUAGCUGCAUAT	355
KHK-2263- 2312	Hs-Mf commons	25 mer Sense Strand	UCUGCCAUUUAAUUAGCUGCAUATC	356
KHK-2264- 2313	Hs-Mf commons	25 mer Sense Strand	CUGCCAUUUAAUUAGCUGCAUAUCA	357
KHK-2265- 2314	Hs-Mf commons	25 mer Sense Strand	UGCCAUUUAAUUAGCUGCAUAUCAC	358
KHK-2266- 2315	Hs-Mf commons	25 mer Sense Strand	GCCAUUUAAUUAGCUGCAUAUCACC	359
KHK-2299	Hs unique	25 mer Sense Strand	CAGCACUUAACGCAAUCUGCCUCA	360
KHK-2317- 2366	Hs-Mf commons	25 mer Sense Strand	GCCUCAUUUCUUCAUCUGUCAAAAT	361
KHK-2318- 2367	Hs-Mf commons	25 mer Sense Strand	CCUCAUUUCUUCAUCUGUCAAAATG	362
KHK-2319- 2368	Hs-Mf commons	25 mer Sense Strand	CUCAUUUCUUCAUCUGUCAAAUGG	363
KHK-2320- 2369	Hs-Mf commons	25 mer Sense Strand	UCAUUUCUUCAUCUGUCAAAUGGA	364
KHK-2321- 2370	Hs-Mf commons	25 mer Sense Strand	CAUUUCUUCAUCUGUCAAAUGGAA	365
KHK-2322- 2371	Hs-Mf commons	25 mer Sense Strand	AAUUUCUUCAUCUGUCAAAUGGAAC	366
KHK-2323- 2372	Hs-Mf commons	25 mer Sense Strand	AUUUCUUCAUCUGUCAAAUGGAACC	367

KHK-2324-2373	Hs-Mf commons	25 mer Sense Strand	UUUCUUCaucugucAAAUGGAACCA	368
KHK-2325-2374	Hs-Mf commons	25 mer Sense Strand	UUCUUCaucugucAAAUGGAACCAA	369
KHK-2326-2375	Hs-Mf commons	25 mer Sense Strand	UCUUCaucugucAAAUGGAACCAAT	370
KHK-2332	Hs unique	25 mer Sense Strand	UCUGUCAAAUGGAACCAAUUCUGCT	371
KHK-2333	Hs unique	25 mer Sense Strand	CUGUCAAAUGGAACCAAUUCUGCTT	372
KHK-2335	Hs unique	25 mer Sense Strand	GUCAAAUGGAACCAAUUCUGCUUGG	373
KHK-2340	Hs unique	25 mer Sense Strand	AUGGAACCAAUUCUGCUUGGCUACA	374
KHK-2341	Hs unique	25 mer Sense Strand	UGGAACCAAUUCUGCUUGGCUACAG	375
KHK-2346	Hs unique	25 mer Sense Strand	CCAAUUCUGCUUGGCUACAGAAUTA	376
KHK-2352	Hs unique	25 mer Sense Strand	CUGCUUGGCUACAGAAUUAUUGUGA	377
KHK-2358	Hs unique	25 mer Sense Strand	GGCUACAGAAUUAUUGUGAGGAUAA	378
KHK-2359	Hs unique	25 mer Sense Strand	GCUACAGAAUUAUUGUGAGGAUAAA	379
KHK-2360	Hs unique	25 mer Sense Strand	CUACAGAAUUAUUGUGAGGAUAAAA	380
KHK-2361	Hs unique	25 mer Sense Strand	UACAGAAUUAUUGUGAGGAUAAAAT	381
KHK-2362	Hs unique	25 mer Sense Strand	ACAGAAUUAUUGUGAGGAUAAAATC	382
KHK-2363	Hs unique	25 mer Sense Strand	CAGAAUUAUUGUGAGGAUAAAAUCA	383
KHK-2364	Hs unique	25 mer Sense Strand	AGAAUUAUUGUGAGGAUAAAAUCAT	384

KHK-2365	Hs unique	25 mer Sense Strand	GAAUUAUUGUGAGGAUAAAAUCATA	385
KHK-2366	Hs unique	25 mer Sense Strand	AAUUAUUGUGAGGAUAAAAUCAUAT	386
KHK-2367	Hs unique	25 mer Sense Strand	AUUAUUGUGAGGAUAAAAUCAUATA	387
KHK-115-154	Hs-Mf commons	27mer Anti- sense Strand	CGAGAAUGCAAAGAGAAAAUGCGCUAC	388
KHK-116-155	Hs-Mf commons	27mer Anti- sense Strand	UCGAGAAUGCAAAGAGAAAAUGCGCUA	389
KHK-117-156	Hs-Mf commons	27mer Anti- sense Strand	CUCGAGAAUGCAAAGAGAAAAUGCGCU	390
KHK-118-157	Hs-Mf commons	27mer Anti- sense Strand	UCUCGAGAAUGCAAAGAGAAAAUGCGC	391
KHK-119-158	Hs-Mf commons	27mer Anti- sense Strand	AUCUCGAGAAUGCAAAGAGAAAAUGCG	392
KHK-120-159	Hs-Mf commons	27mer Anti- sense Strand	GAUCUCGAGAAUGCAAAGAGAAAAUGC	393
KHK-121-160	Hs-Mf commons	27mer Anti- sense Strand	CGAUCUCGAGAAUGCAAAGAGAAAAUG	394
KHK-122-161	Hs-Mf commons	27mer Anti- sense Strand	GCGAUCUCGAGAAUGCAAAGAGAAAAU	395
KHK-123-162	Hs-Mf commons	27mer Anti- sense Strand	AGCGAUCUCGAGAAUGCAAAGAGAAAA	396
KHK-124-163	Hs-Mf commons	27mer Anti- sense Strand	AAGCGAUCUCGAGAAUGCAAAGAGAAA	397
KHK-125-164	Hs-Mf commons	27mer Anti- sense Strand	UAAGCGAUCUCGAGAAUGCAAAGAGAA	398
KHK-126-165	Hs-Mf commons	27mer Anti- sense Strand	CUAAGCGAUCUCGAGAAUGCAAAGAGA	399
KHK-127-166	Hs-Mf commons	27mer Anti- sense Strand	GCUAAGCGAUCUCGAGAAUGCAAAGAG	400
KHK-128-167	Hs-Mf commons	27mer Anti- sense Strand	GGCUAAGCGAUCUCGAGAAUGCAAAGA	401

KHK-179	Hs unique	27mer sense Strand	Anti-	UUCCUCGCUUGUCAGAUGGACUCACAG	402
KHK-181-220	Hs-Mf commons	27mer sense Strand	Anti-	GUUUCCUCGCUUGUCAGAUGGACUCAC	403
KHK-182-221	Hs-Mf commons	27mer sense Strand	Anti-	AGUUUCCUCGCUUGUCAGAUGGACUCA	404
KHK-183-222	Hs-Mf commons	27mer sense Strand	Anti-	UAGUUUCCUCGCUUGUCAGAUGGACUC	405
KHK-184-223	Hs-Mf commons	27mer sense Strand	Anti-	UUAGUUUCCUCGCUUGUCAGAUGGACU	406
KHK-185-224	Hs-Mf commons	27mer sense Strand	Anti-	CUUAGUUUCCUCGCUUGUCAGAUGGAC	407
KHK-186-225	Hs-Mf commons	27mer sense Strand	Anti-	CCUAGUUUCCUCGCUUGUCAGAUGGA	408
KHK-187-226	Hs-Mf commons	27mer sense Strand	Anti-	GCCUAGUUUCCUCGCUUGUCAGAUGG	409
KHK-188-227	Hs-Mf commons	27mer sense Strand	Anti-	AGCCUAGUUUCCUCGCUUGUCAGAUG	410
KHK-431-470	Hs-Mf commons	27mer sense Strand	Anti-	CCUCUUAUCCAGGAGGAUGGUGUCCCC	411
KHK-432-471	Hs-Mf commons	27mer sense Strand	Anti-	GCCUCUUAUCCAGGAGGAUGGUGUCCC	412
KHK-433-472	Hs-Mf commons	27mer sense Strand	Anti-	UGCCUCUUAUCCAGGAGGAUGGUGUCC	413
KHK-507- 545-376-218	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	GGAUCUGCUUCUCUCCAUGAGGCUAC	414
KHK-508- 546-377-219	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	AGGAUCUGCUUCUCUCCAUGAGGCUA	415
KHK-509- 547-378-220	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	CAGGAUCUGCUUCUCUCCAUGAGGCU	416
KHK-510- 548-379-221	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	ACAGGAUCUGCUUCUCUCCAUGAGGC	417
KHK-511- 549-380-222	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	CACAGGAUCUGCUUCUCUCCAUGAGG	418

KHK-512-550-381-223	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	GCACAGGAUCUGCUUCUCUCCAUGAG	419
KHK-513-551-382-224	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CGCACAGGAUCUGCUUCUCUCCAUGA	420
KHK-514-552-383-225	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	ACGCACAGGAUCUGCUUCUCUCCAUG	421
KHK-515-553-384-226	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CACGCACAGGAUCUGCUUCUCUCCAU	422
KHK-516-554-385-227	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CCACGCACAGGAUCUGCUUCUCUCCA	423
KHK-517-555-386-228	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CCCACGCACAGGAUCUGCUUCUCUCC	424
KHK-518-556-387-229	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CCCCACGCACAGGAUCUGCUUCUCUUC	425
KHK-520-558-389-231	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	AGCCCCACGCACAGGAUCUGCUUCUCU	426
KHK-521-559-390-232	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	UAGCCCCACGCACAGGAUCUGCUUCUC	427
KHK-522-560-391-233	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CUAGCCCCACGCACAGGAUCUGCUUCU	428
KHK-541-579	Hs-Mf commons	27mer sense Strand	Anti-	CUGAUGACGUCCAGCACCACUAGCCCC	429
KHK-544-582	Hs-Mf commons	27mer sense Strand	Anti-	AGGCUGAUGACGUCCAGCACCACUAGC	430
KHK-546-584	Hs-Mf commons	27mer sense Strand	Anti-	CCAGGCUGAUGACGUCCAGCACCACUA	431
KHK-547-585	Hs-Mf commons	27mer sense Strand	Anti-	ACCAGGCUGAUGACGUCCAGCACCACU	432
KHK-548-586	Hs-Mf commons	27mer sense Strand	Anti-	CACCAGGCUGAUGACGUCCAGCACCAC	433
KHK-549-587	Hs-Mf commons	27mer sense Strand	Anti-	CCACCAGGCUGAUGACGUCCAGCACCA	434
KHK-550-588	Hs-Mf commons	27mer sense Strand	Anti-	UCCACCAGGCUGAUGACGUCCAGCACC	435

KHK-551-589	Hs-Mf commons	27mer sense Strand	Anti-	GUCCACCAGGCUGAUGACGUCCAGCAC	436
KHK-552-590	Hs-Mf commons	27mer sense Strand	Anti-	UGUCCACCAGGCUGAUGACGUCCAGCA	437
KHK-553-591	Hs-Mf commons	27mer sense Strand	Anti-	UUGUCCACCAGGCUGAUGACGUCCAGC	438
KHK-554-592	Hs-Mf commons	27mer sense Strand	Anti-	CUUGUCCACCAGGCUGAUGACGUCCAG	439
KHK-555-593	Hs-Mf commons	27mer sense Strand	Anti-	ACUUGUCCACCAGGCUGAUGACGUCCA	440
KHK-556-594	Hs-Mf commons	27mer sense Strand	Anti-	UACUUGUCCACCAGGCUGAUGACGUCC	441
KHK-557-595	Hs-Mf commons	27mer sense Strand	Anti-	GUACUUGUCCACCAGGCUGAUGACGUC	442
KHK-558-596	Hs-Mf commons	27mer sense Strand	Anti-	GGUACUUGUCCACCAGGCUGAUGACGU	443
KHK-559-597	Hs-Mf commons	27mer sense Strand	Anti-	GGGUACUUGUCCACCAGGCUGAUGACG	444
KHK-560-598	Hs-Mf commons	27mer sense Strand	Anti-	AGGGUACUUGUCCACCAGGCUGAUGAC	445
KHK-561-599	Hs-Mf commons	27mer sense Strand	Anti-	UAGGGUACUUGUCCACCAGGCUGAUGA	446
KHK-562-600	Hs-Mf commons	27mer sense Strand	Anti-	UUAGGGUACUUGUCCACCAGGCUGAUG	447
KHK-563-601	Hs-Mf commons	27mer sense Strand	Anti-	CUUAGGGUACUUGUCCACCAGGCUGAU	448
KHK-564-602	Hs-Mf commons	27mer sense Strand	Anti-	CCUUAGGGUACUUGUCCACCAGGCUGA	449
KHK-565-603	Hs-Mf commons	27mer sense Strand	Anti-	UCCUUAGGGUACUUGUCCACCAGGCUG	450
KHK-566-604	Hs-Mf commons	27mer sense Strand	Anti-	CUCCUUAGGGUACUUGUCCACCAGGCU	451
KHK-567-605	Hs-Mf commons	27mer sense Strand	Anti-	CCUCCUUAGGGUACUUGUCCACCAGGC	452

KHK-568-606	Hs-Mf commons	27mer sense Strand	Anti-	UCCUCCUUAGGGUACUUGUCCACCAGG	453
KHK-569-607	Hs-Mf commons	27mer sense Strand	Anti-	GUCCUCCUUAGGGUACUUGUCCACCAG	454
KHK-570-608	Hs-Mf commons	27mer sense Strand	Anti-	AGUCCUCCUUAGGGUACUUGUCCACCA	455
KHK-571-609	Hs-Mf commons	27mer sense Strand	Anti-	GAGUCCUCCUUAGGGUACUUGUCCACC	456
KHK-572-610	Hs-Mf commons	27mer sense Strand	Anti-	CGAGUCCUCCUUAGGGUACUUGUCCAC	457
KHK-573-611	Hs-Mf commons	27mer sense Strand	Anti-	CCGAGUCCUCCUUAGGGUACUUGUCCA	458
KHK-574-612	Hs-Mf commons	27mer sense Strand	Anti-	UCCGAGUCCUCCUUAGGGUACUUGUCC	459
KHK-575-613	Hs-Mf commons	27mer sense Strand	Anti-	CUCCGAGUCCUCCUUAGGGUACUUGUC	460
KHK-576-614	Hs-Mf commons	27mer sense Strand	Anti-	UCUCCGAGUCCUCCUUAGGGUACUUGU	461
KHK-577-615	Hs-Mf commons	27mer sense Strand	Anti-	AUCUCCGAGUCCUCCUUAGGGUACUUG	462
KHK-638-676	Hs-Mf commons	27mer sense Strand	Anti-	GAGAACGGUGCAGGAGUUGGACGCGUU	463
KHK-641-679	Hs-Mf commons	27mer sense Strand	Anti-	GGAGAGAACGGUGCAGGAGUUGGACGC	464
KHK-642-680	Hs-Mf commons	27mer sense Strand	Anti-	GGGAGAGAACGGUGCAGGAGUUGGACG	465
KHK-643-681	Hs-Mf commons	27mer sense Strand	Anti-	AGGGAGAGAACGGUGCAGGAGUUGGAC	466
KHK-644-682	Hs-Mf commons	27mer sense Strand	Anti-	CAGGGAGAGAACGGUGCAGGAGUUGGA	467
KHK-645-683	Hs-Mf commons	27mer sense Strand	Anti-	GCAGGGAGAGAACGGUGCAGGAGUUGG	468
KHK-646-684	Hs-Mf commons	27mer sense Strand	Anti-	AGCAGGGAGAGAACGGUGCAGGAGUUG	469

KHK-647-685	Hs-Mf commons	27mer sense Strand	Anti-	GAGCAGGGAGAGAACGGUGCAGGAGUU	470
KHK-650-688	Hs-Mf commons	27mer sense Strand	Anti-	UCCGAGCAGGGAGAGAACGGUGCAGGA	471
KHK-676-714	Hs-Mf commons	27mer sense Strand	Anti-	AUUGAGCCCAUGAAGGCACAGGGGGCU	472
KHK-713-722	Hs-Mf commons	27mer sense Strand	Anti-	GUCGGCCACCAGGAAGUCAGCAACAUG	473
KHK-826-835	Hs-Mf commons	27mer sense Strand	Anti-	UGGAGCACAAUGGUACGGUUGCCAUUG	474
KHK-827-836	Hs-Mf commons	27mer sense Strand	Anti-	AUGGAGCACAAUGGUACGGUUGCCAUU	475
KHK-829-838	Hs-Mf commons	27mer sense Strand	Anti-	UCAUGGAGCACAAUGGUACGGUUGCCA	476
KHK-830-839	Hs-Mf commons	27mer sense Strand	Anti-	GUCAUGGAGCACAAUGGUACGGUUGCC	477
KHK-831-840	Hs-Mf commons	27mer sense Strand	Anti-	UGUCAUGGAGCACAAUGGUACGGUUGC	478
KHK-832-841	Hs-Mf commons	27mer sense Strand	Anti-	GUGUCAUGGAGCACAAUGGUACGGUUG	479
KHK-857-895	Hs-Mf commons	27mer sense Strand	Anti-	UGUAGCAGACACAUCUGGCAGGCUCGU	480
KHK-858-896	Hs-Mf commons	27mer sense Strand	Anti-	CUGUAGCAGACACAUCUGGCAGGCUCG	481
KHK-859-897	Hs-Mf commons	27mer sense Strand	Anti-	UCUGUAGCAGACACAUCUGGCAGGCUC	482
KHK-860- 898-729-571	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	GUCUGUAGCAGACACAUCUGGCAGGCU	483
KHK-861- 899-730-572	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	AGUCUGUAGCAGACACAUCUGGCAGGC	484
KHK-862-900	Hs-Mf commons	27mer sense Strand	Anti-	AAGUCUGUAGCAGACACAUCUGGCAGG	485
KHK-865	Hs unique	27mer sense Strand	Anti-	UCAAAGUCUGUAGCAGACACAUCUGGC	486

KHK-880	Hs unique	27mer sense Strand	Anti-	GUCAGAUCAACCUUCUCAAGUCUGUA	487
KHK-882-920	Hs-Mf commons	27mer sense Strand	Anti-	GGGUCAGAUCAACCUUCUCAAGUCUG	488
KHK-883-921	Hs-Mf commons	27mer sense Strand	Anti-	UGGGUCAGAUCAACCUUCUCAAGUCU	489
KHK-884-922	Hs-Mf commons	27mer sense Strand	Anti-	CUGGGUCAGAUCAACCUUCUCAAGUC	490
KHK-885-923	Hs-Mf commons	27mer sense Strand	Anti-	ACUGGGUCAGAUCAACCUUCUCAAGU	491
KHK-886-924	Hs-Mf commons	27mer sense Strand	Anti-	AACUGGGUCAGAUCAACCUUCUCAAG	492
KHK-887-925	Hs-Mf commons	27mer sense Strand	Anti-	GAACUGGGUCAGAUCAACCUUCUCAA	493
KHK-888-926	Hs-Mf commons	27mer sense Strand	Anti-	UGAACUGGGUCAGAUCAACCUUCUCAA	494
KHK-889-927	Hs-Mf commons	27mer sense Strand	Anti-	UUGAACUGGGUCAGAUCAACCUUCUCA	495
KHK-890-928	Hs-Mf commons	27mer sense Strand	Anti-	CUUGAACUGGGUCAGAUCAACCUUCUC	496
KHK-891-929	Hs-Mf commons	27mer sense Strand	Anti-	ACUUGAACUGGGUCAGAUCAACCUUCU	497
KHK-892-930	Hs-Mf commons	27mer sense Strand	Anti-	CACUUGAACUGGGUCAGAUCAACCUUC	498
KHK-893-931	Hs-Mf commons	27mer sense Strand	Anti-	CCACUUGAACUGGGUCAGAUCAACCUU	499
KHK-894-932	Hs-Mf commons	27mer sense Strand	Anti-	UCCACUUGAACUGGGUCAGAUCAACCU	500
KHK-895-933	Hs-Mf commons	27mer sense Strand	Anti-	AUCCACUUGAACUGGGUCAGAUCAACC	501
KHK-896-934	Hs-Mf commons	27mer sense Strand	Anti-	GAUCCACUUGAACUGGGUCAGAUCAAC	502
KHK-897-935	Hs-Mf commons	27mer sense Strand	Anti-	GGAUCCACUUGAACUGGGUCAGAUCAA	503

KHK-898-936	Hs-Mf commons	27mer sense Strand	Anti-	UGGAUCCACUUGAACUGGGUCAGAUCA	504
KHK-899-937	Hs-Mf commons	27mer sense Strand	Anti-	GUGGAUCCACUUGAACUGGGUCAGAU	505
KHK-900-938	Hs-Mf commons	27mer sense Strand	Anti-	UGUGGAUCCACUUGAACUGGGUCAGAU	506
KHK-901-939	Hs-Mf commons	27mer sense Strand	Anti-	AUGUGGAUCCACUUGAACUGGGUCAGA	507
KHK-902-940	Hs-Mf commons	27mer sense Strand	Anti-	AAUGUGGAUCCACUUGAACUGGGUCAG	508
KHK-903-941	Hs-Mf commons	27mer sense Strand	Anti-	CAAUGUGGAUCCACUUGAACUGGGUCA	509
KHK-904-942	Hs-Mf commons	27mer sense Strand	Anti-	UCAUGUGGAUCCACUUGAACUGGGUC	510
KHK-905-943	Hs-Mf commons	27mer sense Strand	Anti-	CUCAAUGUGGAUCCACUUGAACUGGGU	511
KHK-906-944	Hs-Mf commons	27mer sense Strand	Anti-	CCUCAAUGUGGAUCCACUUGAACUGGG	512
KHK-907-945	Hs-Mf commons	27mer sense Strand	Anti-	CCCUCAAUGUGGAUCCACUUGAACUGG	513
KHK-908- 946-777-619	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	GCCCUCAAUGUGGAUCCACUUGAACUG	514
KHK-909- 947-778-620	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	GGCCCUCAAUGUGGAUCCACUUGAACU	515
KHK-910- 948-779-621	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	CGGCCCUCAAUGUGGAUCCACUUGAAC	516
KHK-911- 949-780-622	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	CCGGCCCUCAAUGUGGAUCCACUUGAA	517
KHK-912- 950-781-623	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	UCCGGCCCUCAAUGUGGAUCCACUUGA	518
KHK-913- 951-782-624	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	UUCGGCCCUCAAUGUGGAUCCACUUG	519
KHK-914- 952-783-625	Hs-Mf-Mm- Rn commons	27mer sense Strand	Anti-	GUUCGGCCCUCAAUGUGGAUCCACUU	520

KHK-939-977	Hs-Mf commons	27mer sense Strand	Anti-	GCAGCAUCUUCACCUGCUCCGAUGCGU	521
KHK-940-978	Hs-Mf commons	27mer sense Strand	Anti-	UGCAGCAUCUUCACCUGCUCCGAUGCG	522
KHK-941-979	Hs-Mf commons	27mer sense Strand	Anti-	CUGCAGCAUCUUCACCUGCUCCGAUGC	523
KHK-942-980	Hs-Mf commons	27mer sense Strand	Anti-	GCUGCAGCAUCUUCACCUGCUCCGAUG	524
KHK-943-981	Hs-Mf commons	27mer sense Strand	Anti-	CGCUGCAGCAUCUUCACCUGCUCCGAU	525
KHK-944-982	Hs-Mf commons	27mer sense Strand	Anti-	CCGCUGCAGCAUCUUCACCUGCUCCGA	526
KHK-945-983	Hs-Mf commons	27mer sense Strand	Anti-	UCCGCUGCAGCAUCUUCACCUGCUCCG	527
KHK-946-984	Hs-Mf commons	27mer sense Strand	Anti-	AUCCGCUGCAGCAUCUUCACCUGCUCC	528
KHK-947-985	Hs-Mf commons	27mer sense Strand	Anti-	UAUCCGCUGCAGCAUCUUCACCUGCUC	529
KHK-948- 986-817	Hs-Mf-Mm commons	27mer sense Strand	Anti-	CUAUCCGCUGCAGCAUCUUCACCUGCU	530
KHK-949- 987-818	Hs-Mf-Mm commons	27mer sense Strand	Anti-	UCUAUCCGCUGCAGCAUCUUCACCUGC	531
KHK-950- 988-819	Hs-Mf-Mm commons	27mer sense Strand	Anti-	GUCUAUCCGCUGCAGCAUCUUCACCUG	532
KHK-951- 989-820	Hs-Mf-Mm commons	27mer sense Strand	Anti-	CGUCUAUCCGCUGCAGCAUCUUCACCU	533
KHK-952- 990-821	Hs-Mf-Mm commons	27mer sense Strand	Anti-	GCGUCUAUCCGCUGCAGCAUCUUCACC	534
KHK-953- 991-822	Hs-Mf-Mm commons	27mer sense Strand	Anti-	UGCGUCUAUCCGCUGCAGCAUCUUCAC	535
KHK-954- 992-823	Hs-Mf-Mm commons	27mer sense Strand	Anti-	GUGCGUCUAUCCGCUGCAGCAUCUUCA	536
KHK-955- 993-824	Hs-Mf-Mm commons	27mer sense Strand	Anti-	UGUGCGUCUAUCCGCUGCAGCAUCUUC	537

KHK-956-994	Hs-Mf commons	27mer sense Strand	Anti-	GUGUGCGUCUAUCCGCUGCAGCAUCUU	538
KHK-957-995	Hs-Mf commons	27mer sense Strand	Anti-	UGUGUGCGUCUAUCCGCUGCAGCAUCU	539
KHK-958-996	Hs-Mf commons	27mer sense Strand	Anti-	UUGUGUGCGUCUAUCCGCUGCAGCAUC	540
KHK-978-1016	Hs-Mf commons	27mer sense Strand	Anti-	GCUCUGGAGGCUGCCUGGUGUUGUGUG	541
KHK-982-1020	Hs-Mf commons	27mer sense Strand	Anti-	UUCUGCUCUGGAGGCUGCCUGGUGUUG	542
KHK-983-1021	Hs-Mf commons	27mer sense Strand	Anti-	CUUCUGCUCUGGAGGCUGCCUGGUGUU	543
KHK-984-1022	Hs-Mf commons	27mer sense Strand	Anti-	UCUUCUGCUCUGGAGGCUGCCUGGUGU	544
KHK-985-1023	Hs-Mf commons	27mer sense Strand	Anti-	AUCUUCUGCUCUGGAGGCUGCCUGGUG	545
KHK-991-1029	Hs-Mf commons	27mer sense Strand	Anti-	ACCCGGAUCUUCUGCUCUGGAGGCUGC	546
KHK-992-1030	Hs-Mf commons	27mer sense Strand	Anti-	CACCCGGAUCUUCUGCUCUGGAGGCUG	547
KHK-993-1031	Hs-Mf commons	27mer sense Strand	Anti-	ACACCCGGAUCUUCUGCUCUGGAGGCU	548
KHK-999-1037	Hs-Mf commons	27mer sense Strand	Anti-	CCACGGACACCCGGAUCUUCUGCUCUG	549
KHK-1000-1038	Hs-Mf commons	27mer sense Strand	Anti-	UCCACGGACACCCGGAUCUUCUGCUCU	550
KHK-1019-1057	Hs-Mf commons	27mer sense Strand	Anti-	CUCUCGUGGCUUCUCCACCUCCACGGA	551
KHK-1054-1092	Hs-Mf commons	27mer sense Strand	Anti-	ACCACGUCUCCGUAGCCAAACAGCUGG	552
KHK-1055-1093	Hs-Mf commons	27mer sense Strand	Anti-	CACCACGUCUCCGUAGCCAAACAGCUG	553
KHK-1057-1095	Hs-Mf commons	27mer sense Strand	Anti-	AACACCACGUCUCCGUAGCCAAACAGC	554

KHK-1058-1096	Hs-Mf commons	27mer sense Strand	Anti-	AAACACCACGUCUCCGUAGCCAAACAG	555
KHK-1059-1097	Hs-Mf commons	27mer sense Strand	Anti-	CAAACACCACGUCUCCGUAGCCAAACA	556
KHK-1060-1098	Hs-Mf commons	27mer sense Strand	Anti-	ACAAACACCACGUCUCCGUAGCCAAAC	557
KHK-1061-1099	Hs-Mf commons	27mer sense Strand	Anti-	GACAAACACCACGUCUCCGUAGCCAAA	558
KHK-1062-1100	Hs-Mf commons	27mer sense Strand	Anti-	UGACAAACACCACGUCUCCGUAGCCAA	559
KHK-1063-1101	Hs-Mf commons	27mer sense Strand	Anti-	CUGACAAACACCACGUCUCCGUAGCCA	560
KHK-1064-1102	Hs-Mf commons	27mer sense Strand	Anti-	GCUGACAAACACCACGUCUCCGUAGCC	561
KHK-1065-1103	Hs-Mf commons	27mer sense Strand	Anti-	UGCUGACAAACACCACGUCUCCGUAGC	562
KHK-1066-1104	Hs-Mf commons	27mer sense Strand	Anti-	UUGCUGACAAACACCACGUCUCCGUAG	563
KHK-1067-1105	Hs-Mf commons	27mer sense Strand	Anti-	UUUGCUGACAAACACCACGUCUCCGUA	564
KHK-1068-1106	Hs-Mf commons	27mer sense Strand	Anti-	CUUUGCUGACAAACACCACGUCUCCGU	565
KHK-1069-1107	Hs-Mf commons	27mer sense Strand	Anti-	UCUUUGCUGACAAACACCACGUCUCCG	566
KHK-1070-1108	Hs-Mf commons	27mer sense Strand	Anti-	AUCUUUGCUGACAAACACCACGUCUCC	567
KHK-1071-1109	Hs-Mf commons	27mer sense Strand	Anti-	CAUCUUUGCUGACAAACACCACGUCUC	568
KHK-1072-1110	Hs-Mf commons	27mer sense Strand	Anti-	ACAUCUUUGCUGACAAACACCACGUCU	569
KHK-1073-1111	Hs-Mf commons	27mer sense Strand	Anti-	CACAUCUUUGCUGACAAACACCACGUC	570
KHK-1074-1112-943-785	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CCACAUCUUUGCUGACAAACACCACGU	571

KHK-1075-1113-944-786	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	GCCACAUCUUUGCUGACAAACACCACG	572
KHK-1076-1114-945-787	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	GGCCACAUCUUUGCUGACAAACACCAC	573
KHK-1077-1115-946-788	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	UGGCCACAUCUUUGCUGACAAACACCA	574
KHK-1078-1116-947-789	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	UUGGCCACAUCUUUGCUGACAAACACC	575
KHK-1079-1117-948-790	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CUUGGCCACAUCUUUGCUGACAAACAC	576
KHK-1080-1118-949-791	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	GCUUGGCCACAUCUUUGCUGACAAACA	577
KHK-1081-1119-950-792	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	UGCUUGGCCACAUCUUUGCUGACAAAC	578
KHK-1082-1120-951-793	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	GUGCUUGGCCACAUCUUUGCUGACAAA	579
KHK-1083-1121-952-794	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	AGUGCUUGGCCACAUCUUUGCUGACAA	580
KHK-1084-1122-953-795	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	AAGUGCUUGGCCACAUCUUUGCUGACA	581
KHK-1085-1123-954-796	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CAAGUGCUUGGCCACAUCUUUGCUGAC	582
KHK-1086-1124-955-797	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CCAAGUGCUUGGCCACAUCUUUGCUGA	583
KHK-1087-1125-956-798	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CCAAGUGCUUGGCCACAUCUUUGCUG	584
KHK-1090-1128	Hs-Mf commons	27mer sense Strand	Anti-	AACCCCAAGUGCUUGGCCACAUCUUUG	585
KHK-1091-1129	Hs-Mf commons	27mer sense Strand	Anti-	GAACCCCAAGUGCUUGGCCACAUCUUU	586
KHK-1092-1130	Hs-Mf commons	27mer sense Strand	Anti-	GGAACCCCAAGUGCUUGGCCACAUCUU	587
KHK-1093-1131	Hs-Mf commons	27mer sense Strand	Anti-	UGGAACCCCAAGUGCUUGGCCACAUCU	588

KHK-1095-1133	Hs-Mf commons	27mer sense Strand	Anti-	ACUGGAACCCCAAGUGCUUGGCCACAU	589
KHK-1096-1134	Hs-Mf commons	27mer sense Strand	Anti-	GACUGGAACCCCAAGUGCUUGGCCACA	590
KHK-1097-1135	Hs-Mf commons	27mer sense Strand	Anti-	UGACUGGAACCCCAAGUGCUUGGCCAC	591
KHK-1099-1137	Hs-Mf commons	27mer sense Strand	Anti-	GCUGACUGGAACCCCAAGUGCUUGGCC	592
KHK-1100-1138	Hs-Mf commons	27mer sense Strand	Anti-	UGCUGACUGGAACCCCAAGUGCUUGGC	593
KHK-1101-1139	Hs-Mf commons	27mer sense Strand	Anti-	CUGCUGACUGGAACCCCAAGUGCUUGG	594
KHK-1102-1140	Hs-Mf commons	27mer sense Strand	Anti-	UCUGCUGACUGGAACCCCAAGUGCUUG	595
KHK-1103-1141	Hs-Mf commons	27mer sense Strand	Anti-	CUCUGCUGACUGGAACCCCAAGUGCUU	596
KHK-1104-1142	Hs-Mf commons	27mer sense Strand	Anti-	CCUCUGCUGACUGGAACCCCAAGUGCU	597
KHK-1106-1144	Hs-Mf commons	27mer sense Strand	Anti-	UUCCUCUGCUGACUGGAACCCCAAGUG	598
KHK-1107-1145	Hs-Mf commons	27mer sense Strand	Anti-	CUUCCUCUGCUGACUGGAACCCCAAGU	599
KHK-1135-1173	Hs-Mf commons	27mer sense Strand	Anti-	CUCACACGACCAUACAAGCCCCUCAAG	600
KHK-1136-1174	Hs-Mf commons	27mer sense Strand	Anti-	CCUCACACGACCAUACAAGCCCCUCAA	601
KHK-1137-1175	Hs-Mf commons	27mer sense Strand	Anti-	UCCUCACACGACCAUACAAGCCCCUCA	602
KHK-1138-1176	Hs-Mf commons	27mer sense Strand	Anti-	UUCCUCACACGACCAUACAAGCCCCUC	603
KHK-1139-1177	Hs-Mf commons	27mer sense Strand	Anti-	UUUCCUCACACGACCAUACAAGCCCCU	604
KHK-1140-1178	Hs-Mf commons	27mer sense Strand	Anti-	CUUCCUCACACGACCAUACAAGCCCC	605

KHK-1141-1179	Hs-Mf commons	27mer sense Strand	Anti-	CCUUUCCUCACACGACCAUACAAGCCC	606
KHK-1142-1180	Hs-Mf commons	27mer sense Strand	Anti-	CCCUUCCUCACACGACCAUACAAGCC	607
KHK-1143-1181	Hs-Mf commons	27mer sense Strand	Anti-	CCCCUUUCCUCACACGACCAUACAAGC	608
KHK-1144-1182	Hs-Mf commons	27mer sense Strand	Anti-	GCCCCUUUCCUCACACGACCAUACAAG	609
KHK-1145-1183	Hs-Mf commons	27mer sense Strand	Anti-	AGCCCCUUUCCUCACACGACCAUACAA	610
KHK-1146-1184	Hs-Mf commons	27mer sense Strand	Anti-	CAGCCCCUUUCCUCACACGACCAUACA	611
KHK-1147-1185	Hs-Mf commons	27mer sense Strand	Anti-	ACAGCCCCUUUCCUCACACGACCAUAC	612
KHK-1148-1186	Hs-Mf commons	27mer sense Strand	Anti-	CACAGCCCCUUUCCUCACACGACCAUA	613
KHK-1149-1187	Hs-Mf commons	27mer sense Strand	Anti-	GCACAGCCCCUUUCCUCACACGACCAU	614
KHK-1153-1191	Hs-Mf commons	27mer sense Strand	Anti-	ACAAGCACAGCCCCUUUCCUCACACGA	615
KHK-1154-1192	Hs-Mf commons	27mer sense Strand	Anti-	GACAAGCACAGCCCCUUUCCUCACACG	616
KHK-1157-1195	Hs-Mf commons	27mer sense Strand	Anti-	ACAGACAAGCACAGCCCCUUUCCUCAC	617
KHK-1158-1196	Hs-Mf commons	27mer sense Strand	Anti-	CACAGACAAGCACAGCCCCUUUCCUCA	618
KHK-1159-1197	Hs-Mf commons	27mer sense Strand	Anti-	GCACAGACAAGCACAGCCCCUUUCCUC	619
KHK-1161-1199	Hs-Mf commons	27mer sense Strand	Anti-	AGGCACAGACAAGCACAGCCCCUUUCC	620
KHK-1163-1201	Hs-Mf commons	27mer sense Strand	Anti-	CCAGGCACAGACAAGCACAGCCCCUUU	621
KHK-1164-1202	Hs-Mf commons	27mer sense Strand	Anti-	CCCAGGCACAGACAAGCACAGCCCCUU	622

KHK-1232-1270	Hs-Mf commons	27mer sense Strand	Anti-	GGGUGGCGGGAAAGCAUCCGAGUGGAG	623
KHK-1278-1316-1147-989	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	CGGAGGCAUUGAAGGUGUCUCCAGCUC	624
KHK-1279-1317-1148-990	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	ACGGAGGCAUUGAAGGUGUCUCCAGCU	625
KHK-1280-1318-1149-991	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	GACGGAGGCAUUGAAGGUGUCUCCAGC	626
KHK-1281-1319-1150-992	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	UGACGGAGGCAUUGAAGGUGUCUCCAG	627
KHK-1282-1320-1151-993	Hs-Mf-Mm-Rn commons	27mer sense Strand	Anti-	AUGACGGAGGCAUUGAAGGUGUCUCCA	628
KHK-1283-1321	Hs-Mf commons	27mer sense Strand	Anti-	GAUGACGGAGGCAUUGAAGGUGUCUCC	629
KHK-1284-1322	Hs-Mf commons	27mer sense Strand	Anti-	AGAUGACGGAGGCAUUGAAGGUGUCUC	630
KHK-1285-1323	Hs-Mf commons	27mer sense Strand	Anti-	AAGAUGACGGAGGCAUUGAAGGUGUCU	631
KHK-1286-1324	Hs-Mf commons	27mer sense Strand	Anti-	GAAGAUGACGGAGGCAUUGAAGGUGUC	632
KHK-1287-1325	Hs-Mf commons	27mer sense Strand	Anti-	UGAAGAUGACGGAGGCAUUGAAGGUGU	633
KHK-1288-1326	Hs-Mf commons	27mer sense Strand	Anti-	CUGAAGAUGACGGAGGCAUUGAAGGUG	634
KHK-1289-1327	Hs-Mf commons	27mer sense Strand	Anti-	GCUGAAGAUGACGGAGGCAUUGAAGGU	635
KHK-1290-1328	Hs-Mf commons	27mer sense Strand	Anti-	GGCUGAAGAUGACGGAGGCAUUGAAGG	636
KHK-1291-1329	Hs-Mf commons	27mer sense Strand	Anti-	AGGCUGAAGAUGACGGAGGCAUUGAAG	637
KHK-1292-1330	Hs-Mf commons	27mer sense Strand	Anti-	GAGGCUGAAGAUGACGGAGGCAUUGAA	638
KHK-1293-1331	Hs-Mf commons	27mer sense Strand	Anti-	AGAGGCUGAAGAUGACGGAGGCAUUGA	639

KHK-1294-1332	Hs-Mf commons	27mer sense Strand	Anti-	GAGAGGCUGAAGAUGACGGAGGCAUUG	640
KHK-1295-1333	Hs-Mf commons	27mer sense Strand	Anti-	GGAGAGGCUGAAGAUGACGGAGGCAUU	641
KHK-1297-1335	Hs-Mf commons	27mer sense Strand	Anti-	UGGGAGAGGCUGAAGAUGACGGAGGCA	642
KHK-1323-1361	Hs-Mf commons	27mer sense Strand	Anti-	UCAGUGCUUCCUGCACGCUCCUCCCCU	643
KHK-1325-1363	Hs-Mf commons	27mer sense Strand	Anti-	UCUCAGUGCUUCCUGCACGCUCCUCCC	644
KHK-1326-1364	Hs-Mf commons	27mer sense Strand	Anti-	AUCUCAGUGCUUCCUGCACGCUCCUCC	645
KHK-1327-1365	Hs-Mf commons	27mer sense Strand	Anti-	AAUCUCAGUGCUUCCUGCACGCUCCUC	646
KHK-1328-1366	Hs-Mf commons	27mer sense Strand	Anti-	GAAUCUCAGUGCUUCCUGCACGCUCCU	647
KHK-1329-1367	Hs-Mf commons	27mer sense Strand	Anti-	CGAAUCUCAGUGCUUCCUGCACGCUCC	648
KHK-1330-1368	Hs-Mf commons	27mer sense Strand	Anti-	CCGAAUCUCAGUGCUUCCUGCACGCUC	649
KHK-1331-1369	Hs-Mf commons	27mer sense Strand	Anti-	CCCgAAUCUCAGUGCUUCCUGCACGCU	650
KHK-1332-1370	Hs-Mf commons	27mer sense Strand	Anti-	ACCCGAAUCUCAGUGCUUCCUGCACGC	651
KHK-1333-1371	Hs-Mf commons	27mer sense Strand	Anti-	CACCCGAAUCUCAGUGCUUCCUGCACG	652
KHK-1334-1372	Hs-Mf commons	27mer sense Strand	Anti-	GCACCCGAAUCUCAGUGCUUCCUGCAC	653
KHK-1335-1373	Hs-Mf commons	27mer sense Strand	Anti-	GGCACCCGAAUCUCAGUGCUUCCUGCA	654
KHK-1336-1374	Hs-Mf commons	27mer sense Strand	Anti-	UGGCACCCGAAUCUCAGUGCUUCCUGC	655
KHK-1385-1423	Hs-Mf commons	27mer sense Strand	Anti-	UCACACGAUGCCAUCAAAGCCCUGCAG	656

KHK-1387-1425	Hs-Mf commons	27mer sense Strand	Anti-	UCUCACACGAUGCCAUCAAAGCCCUGC	657
KHK-1388-1426	Hs-Mf commons	27mer sense Strand	Anti-	CUCUCACACGAUGCCAUCAAAGCCCUG	658
KHK-1389-1427	Hs-Mf commons	27mer sense Strand	Anti-	GCUCUCACACGAUGCCAUCAAAGCCCUC	659
KHK-1538-1588	Hs-Mf commons	27mer sense Strand	Anti-	CCUGUGGGGAACACAGGACACAGGCAG	660
KHK-1540-1590	Hs-Mf commons	27mer sense Strand	Anti-	UCCCUGUGGGGAACACAGGACACAGGC	661
KHK-1542-1592	Hs-Mf commons	27mer sense Strand	Anti-	UCUCCCUGUGGGGAACACAGGACACAG	662
KHK-1665-1708	Hs-Mf commons	27mer sense Strand	Anti-	UCGAAGAGUCAGAGCCUCAGGAAUGCC	663
KHK-1666-1709	Hs-Mf commons	27mer sense Strand	Anti-	AUCGAAGAGUCAGAGCCUCAGGAAUGC	664
KHK-1667-1710	Hs-Mf commons	27mer sense Strand	Anti-	GAUCGAAGAGUCAGAGCCUCAGGAAUG	665
KHK-1707-1750	Hs-Mf commons	27mer sense Strand	Anti-	GGCGGAGAGGUUAAUUUGGGGAUGGA	666
KHK-1708-1751	Hs-Mf commons	27mer sense Strand	Anti-	GGGCGGAGAGGUUAAUUUGGGGAUGG	667
KHK-1709-1752	Hs-Mf commons	27mer sense Strand	Anti-	UGGCGGAGAGGUUAAUUUGGGGAUG	668
KHK-1869-1918	Hs-Mf commons	27mer sense Strand	Anti-	AUAGAGUCUGCACAACGCAGGGCCCCG	669
KHK-1870-1919	Hs-Mf commons	27mer sense Strand	Anti-	AAUAGAGUCUGCACAACGCAGGGCCCC	670
KHK-1871-1920	Hs-Mf commons	27mer sense Strand	Anti-	GAAUAGAGUCUGCACAACGCAGGGCCC	671
KHK-1872-1921	Hs-Mf commons	27mer sense Strand	Anti-	GGAAUAGAGUCUGCACAACGCAGGGCC	672
KHK-1873-1922	Hs-Mf commons	27mer sense Strand	Anti-	GGGAAUAGAGUCUGCACAACGCAGGGC	673

KHK-1874-1923	Hs-Mf commons	27mer sense Strand	Anti-	UGGGAAUAGAGUCUGCACAACGCAGGG	674
KHK-1875-1924	Hs-Mf commons	27mer sense Strand	Anti-	GUGGGAAUAGAGUCUGCACAACGCAGG	675
KHK-1876-1925	Hs-Mf commons	27mer sense Strand	Anti-	UGUGGGAAUAGAGUCUGCACAACGCAG	676
KHK-1877-1926	Hs-Mf commons	27mer sense Strand	Anti-	CUGUGGGAAUAGAGUCUGCACAACGCA	677
KHK-1878-1927	Hs-Mf commons	27mer sense Strand	Anti-	GCUGUGGGAAUAGAGUCUGCACAACGC	678
KHK-1879-1928	Hs-Mf commons	27mer sense Strand	Anti-	AGCUGUGGGAAUAGAGUCUGCACAACG	679
KHK-1880-1929	Hs-Mf commons	27mer sense Strand	Anti-	GAGCUGUGGGAAUAGAGUCUGCACAAC	680
KHK-1900-1949	Hs-Mf commons	27mer sense Strand	Anti-	GGUGUGGACUCCCAGCUUCUGAGCUGU	681
KHK-1905-1954	Hs-Mf commons	27mer sense Strand	Anti-	UCAGCGGUGUGGACUCCCAGCUUCUGA	682
KHK-1971-2025	Hs-Mf commons	27mer sense Strand	Anti-	AAUCACAGGCUGGUGGGCAGGGCAGAG	683
KHK-1974-2028	Hs-Mf commons	27mer sense Strand	Anti-	UCAAUACACAGGCUGGUGGGCAGGGCA	684
KHK-1975-2029	Hs-Mf commons	27mer sense Strand	Anti-	AUCAAUACACAGGCUGGUGGGCAGGGC	685
KHK-1976-2030	Hs-Mf commons	27mer sense Strand	Anti-	CAUCAAUACACAGGCUGGUGGGCAGGG	686
KHK-1978-2032	Hs-Mf commons	27mer sense Strand	Anti-	CCCAUCAAUACACAGGCUGGUGGGCAG	687
KHK-1979-2033	Hs-Mf commons	27mer sense Strand	Anti-	CCCCAUCAAUACACAGGCUGGUGGGCA	688
KHK-2032-2086	Hs-Mf commons	27mer sense Strand	Anti-	ACUUUCAGGCUCUGGGGCAGUCAGCGG	689
KHK-2035-2089	Hs-Mf commons	27mer sense Strand	Anti-	GAGACUUUCAGGCUCUGGGGCAGUCAG	690

KHK-2036-2090	Hs-Mf commons	27mer sense Strand	Anti-	UGAGACUUUCAGGCUCUGGGGCAGUCA	691
KHK-2037-2091	Hs-Mf commons	27mer sense Strand	Anti-	GUGAGACUUUCAGGCUCUGGGGCAGUC	692
KHK-2038-2092	Hs-Mf commons	27mer sense Strand	Anti-	GGUGAGACUUUCAGGCUCUGGGGCAGU	693
KHK-2039-2093	Hs-Mf commons	27mer sense Strand	Anti-	GGGUGAGACUUUCAGGCUCUGGGGCAG	694
KHK-2040-2094	Hs-Mf commons	27mer sense Strand	Anti-	AGGGUGAGACUUUCAGGCUCUGGGGCA	695
KHK-2041-2095	Hs-Mf commons	27mer sense Strand	Anti-	AAGGGUGAGACUUUCAGGCUCUGGGGC	696
KHK-2042-2096	Hs-Mf commons	27mer sense Strand	Anti-	CAAGGGUGAGACUUUCAGGCUCUGGGG	697
KHK-2043-2097	Hs-Mf commons	27mer sense Strand	Anti-	CCAAGGGUGAGACUUUCAGGCUCUGGG	698
KHK-2044-2098	Hs-Mf commons	27mer sense Strand	Anti-	UCCAAGGGUGAGACUUUCAGGCUCUGG	699
KHK-2045-2099	Hs-Mf commons	27mer sense Strand	Anti-	CUCCAAGGGUGAGACUUUCAGGCUCUG	700
KHK-2067-2121	Hs-Mf commons	27mer sense Strand	Anti-	ACGCCC UAAU UCCAAGGUGGGCUCCA	701
KHK-2069-2123	Hs-Mf commons	27mer sense Strand	Anti-	GCACGCCC UAAU UCCAAGGUGGGCUC	702
KHK-2091-2145	Hs-Mf commons	27mer sense Strand	Anti-	CUGGGUCACAUUUGUGGCUGAGGCACG	703
KHK-2092-2146	Hs-Mf commons	27mer sense Strand	Anti-	CCUGGGUCACAUUUGUGGCUGAGGCAC	704
KHK-2093-2147	Hs-Mf commons	27mer sense Strand	Anti-	UCCUGGGUCACAUUUGUGGCUGAGGCA	705
KHK-2094-2148	Hs-Mf commons	27mer sense Strand	Anti-	AUCCUGGGUCACAUUUGUGGCUGAGGC	706
KHK-2095-2149	Hs-Mf commons	27mer sense Strand	Anti-	UAUCCUGGGUCACAUUUGUGGCUGAGG	707

KHK-2096-2150	Hs-Mf commons	27mer sense Strand	Anti-	GUAUCCUGGGUCACAUUUGUGGCUGAG	708
KHK-2105	Hs unique	27mer sense Strand	Anti-	CAACACUCUGUAUCCUGGGUCACAUUU	709
KHK-2148-2197	Hs-Mf commons	27mer sense Strand	Anti-	CCAAUCCAAUAUGUGUCCAGAUCCG	710
KHK-2149-2198	Hs-Mf commons	27mer sense Strand	Anti-	CCCAAUCCAAUAUGUGUCCAGAUCCG	711
KHK-2150-2199	Hs-Mf commons	27mer sense Strand	Anti-	CCCCAAUCCAAUAUGUGUCCAGAUCC	712
KHK-2151-2200	Hs-Mf commons	27mer sense Strand	Anti-	GCCCCAAUCCAAUAUGUGUCCAGAU	713
KHK-2152-2201	Hs-Mf commons	27mer sense Strand	Anti-	GGCCCCAAUCCAAUAUGUGUCCAGAU	714
KHK-2153-2202	Hs-Mf commons	27mer sense Strand	Anti-	UGGCCCCAAUCCAAUAUGUGUCCAGAU	715
KHK-2154-2203	Hs-Mf commons	27mer sense Strand	Anti-	UUGGCCCCAAUCCAAUAUGUGUCCAGAU	716
KHK-2155-2204	Hs-Mf commons	27mer sense Strand	Anti-	GUUGGCCCCAAUCCAAUAUGUGUCCAGAU	717
KHK-2156-2205	Hs-Mf commons	27mer sense Strand	Anti-	AGUUGGCCCCAAUCCAAUAUGUGUCCAGAU	718
KHK-2157-2206	Hs-Mf commons	27mer sense Strand	Anti-	GAGUUGGCCCCAAUCCAAUAUGUGUCCAGAU	719
KHK-2159-2208	Hs-Mf commons	27mer sense Strand	Anti-	UGGAGUUGGCCCCAAUCCAAUAUGUGUCCAGAU	720
KHK-2160-2209	Hs-Mf commons	27mer sense Strand	Anti-	UUGGAGUUGGCCCCAAUCCAAUAUGUGUCCAGAU	721
KHK-2161-2210	Hs-Mf commons	27mer sense Strand	Anti-	AUUGGAGUUGGCCCCAAUCCAAUAUGUGUCCAGAU	722
KHK-2162-2211	Hs-Mf commons	27mer sense Strand	Anti-	UAUUGGAGUUGGCCCCAAUCCAAUAUGUGUCCAGAU	723
KHK-2163-2212	Hs-Mf commons	27mer sense Strand	Anti-	AUAUUGGAGUUGGCCCCAAUCCAAUAUGUGUCCAGAU	724

KHK-2164-2213	Hs-Mf commons	27mer sense Strand	Anti-	UAUUAUUGGAGUUGGCCCCAAUCCAAU	725
KHK-2165-2214	Hs-Mf commons	27mer sense Strand	Anti-	CUAUUAUUGGAGUUGGCCCCAAUCCAA	726
KHK-2166-2215	Hs-Mf commons	27mer sense Strand	Anti-	CCUAUAUUGGAGUUGGCCCCAAUCCA	727
KHK-2170-2219	Hs-Mf commons	27mer sense Strand	Anti-	CCACCCUAUAUUGGAGUUGGCCCCAAU	728
KHK-2196-2245	Hs-Mf commons	27mer sense Strand	Anti-	AUGCUCUUUACAUAUAAGGCCUUAAC	729
KHK-2197-2246	Hs-Mf commons	27mer sense Strand	Anti-	UAUGCUCUUUACAUAUAAGGCCUUAAC	730
KHK-2198-2247	Hs-Mf commons	27mer sense Strand	Anti-	AUAUGCUCUUUACAUAUAAGGCCUUA	731
KHK-2199-2248	Hs-Mf commons	27mer sense Strand	Anti-	UAUAUGCUCUUUACAUAUAAGGCCUU	732
KHK-2200-2249	Hs-Mf commons	27mer sense Strand	Anti-	UUAUAUGCUCUUUACAUAUAAGGCCU	733
KHK-2201-2250	Hs-Mf commons	27mer sense Strand	Anti-	AUAUAUGCUCUUUACAUAUAAGGCC	734
KHK-2205	Hs unique	27mer sense Strand	Anti-	UUACAUAUAUGCUCUUUACAUAUAUA	735
KHK-2238	Hs unique	27mer sense Strand	Anti-	UUUUAAUCCAGGUCUGUCUCACUCUAA	736
KHK-2260-2309	Hs-Mf commons	27mer sense Strand	Anti-	AUGCAGCUAAUUAUAAUGGCAGAUUUUA	737
KHK-2261-2310	Hs-Mf commons	27mer sense Strand	Anti-	UAUGCAGCUAAUUAUAAUGGCAGAUUUU	738
KHK-2262-2311	Hs-Mf commons	27mer sense Strand	Anti-	AUAUGCAGCUAAUUAUAAUGGCAGAUUU	739
KHK-2263-2312	Hs-Mf commons	27mer sense Strand	Anti-	GAUAUGCAGCUAAUUAUAAUGGCAGAUU	740
KHK-2264-2313	Hs-Mf commons	27mer sense Strand	Anti-	UGAUAUGCAGCUAAUUAUAAUGGCAGAU	741

KHK-2265-2314	Hs-Mf commons	27mer sense Strand	Anti-	GUGAU AUGCAGCUAAUUAAAUGGCAGA	742
KHK-2266-2315	Hs-Mf commons	27mer sense Strand	Anti-	GGUGAU AUGCAGCUAAUUAAAUGGCAG	743
KHK-2299	Hs unique	27mer sense Strand	Anti-	UUGAGGCAGAUUGCGUUAAGUGCUGUA	744
KHK-2317-2366	Hs-Mf commons	27mer sense Strand	Anti-	AUUUGACAGAUGAAGAAAUUGAGGCAG	745
KHK-2318-2367	Hs-Mf commons	27mer sense Strand	Anti-	CAUUUGACAGAUGAAGAAAUUGAGGCA	746
KHK-2319-2368	Hs-Mf commons	27mer sense Strand	Anti-	CCAUUUGACAGAUGAAGAAAUUGAGGC	747
KHK-2320-2369	Hs-Mf commons	27mer sense Strand	Anti-	UCCAUUUGACAGAUGAAGAAAUUGAGG	748
KHK-2321-2370	Hs-Mf commons	27mer sense Strand	Anti-	UUCCAUUUGACAGAUGAAGAAAUUGAG	749
KHK-2322-2371	Hs-Mf commons	27mer sense Strand	Anti-	GUUCCAUUUGACAGAUGAAGAAAUUGA	750
KHK-2323-2372	Hs-Mf commons	27mer sense Strand	Anti-	GGUCCAUUUGACAGAUGAAGAAAUUG	751
KHK-2324-2373	Hs-Mf commons	27mer sense Strand	Anti-	UGGUCCAUUUGACAGAUGAAGAAAUU	752
KHK-2325-2374	Hs-Mf commons	27mer sense Strand	Anti-	UUGGUCCAUUUGACAGAUGAAGAAAU	753
KHK-2326-2375	Hs-Mf commons	27mer sense Strand	Anti-	AUUGGUCCAUUUGACAGAUGAAGAAA	754
KHK-2332	Hs unique	27mer sense Strand	Anti-	AGCAGAAUUGGUCCAUUUGACAGAUG	755
KHK-2333	Hs unique	27mer sense Strand	Anti-	AAGCAGAAUUGGUCCAUUUGACAGAU	756
KHK-2335	Hs unique	27mer sense Strand	Anti-	CCAAGCAGAAUUGGUCCAUUUGACAG	757
KHK-2340	Hs unique	27mer sense Strand	Anti-	UGUAGCCAAGCAGAAUUGGUCCAUUU	758

KHK-2341	Hs unique	27mer sense Strand	Anti-	CUGUAGCCAAGCAGAAUUGGUUCCAUU	759
KHK-2346	Hs unique	27mer sense Strand	Anti-	UAAUUCUGUAGCCAAGCAGAAUUGGUU	760
KHK-2352	Hs unique	27mer sense Strand	Anti-	UCACAAUAAUUCUGUAGCCAAGCAGAA	761
KHK-2358	Hs unique	27mer sense Strand	Anti-	UUAUCCUCACAAUAAUUCUGUAGCCAA	762
KHK-2359	Hs unique	27mer sense Strand	Anti-	UUUAUCCUCACAAUAAUUCUGUAGCCA	763
KHK-2360	Hs unique	27mer sense Strand	Anti-	UUUUAUCCUCACAAUAAUUCUGUAGCC	764
KHK-2361	Hs unique	27mer sense Strand	Anti-	AUUUUAUCCUCACAAUAAUUCUGUAGC	765
KHK-2362	Hs unique	27mer sense Strand	Anti-	GAUUUUAUCCUCACAAUAAUUCUGUAG	766
KHK-2363	Hs unique	27mer sense Strand	Anti-	UGAUUUUAUCCUCACAAUAAUUCUGUA	767
KHK-2364	Hs unique	27mer sense Strand	Anti-	AUGAUUUUAUCCUCACAAUAAUUCUGU	768
KHK-2365	Hs unique	27mer sense Strand	Anti-	UAUGAUUUUAUCCUCACAAUAAUUCUG	769
KHK-2366	Hs unique	27mer sense Strand	Anti-	AUAUGAUUUUAUCCUCACAAUAAUUCU	770
KHK-2367	Hs unique	27mer sense Strand	Anti-	UAUAUGAUUUUAUCCUCACAAUAAUUC	771
Forward Primer	NHP KHK	N/A		TGCCTTCATGGGCTCAATG	772
Reverse Primer	NHP KHK	N/A		TCGGCCACCAGGAAGTCA	773
KHK-510- 548-379-221	Hs-Mf-Mm- Rn commons	Low-2'- Fluoro Pattern Modified Sense Strand		[mCs][mU][mC][mA][mU][mG][mG][fA][fA][fG][fA][mG][mA][mA][mG][mC][mA][mG][mA][mG][mC][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	774
KHK-516- 554-385-227	Hs-Mf-Mm- Rn	Low-2'- Fluoro		[mGs][mA][mA][mG][mA][mG][mA][fA][fG][fC][fA][mG][mA][mU][mC][mC][mU][mG][mU][mA][mG][mC][mA][mG][	775

	commons	Pattern Modified Sense Strand	mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
KHK-829-838	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mGs][mC][mA][mA][mC][mC][mG][fU][fA][fC][fC][mA][mU][mU][mG][mU][mG][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	776
KHK-860-898-729-571	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mCs][mC][mU][mG][mC][mC][mA][fG][fA][fU][fG][mU][mG][mU][mC][mU][mG][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	777
KHK-861-899-730-572	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mCs][mU][mG][mC][mC][mA][mG][fA][fU][fG][fU][mG][mU][mC][mU][mG][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	778
KHK-865	Hs unique	Low-2'-Fluoro Pattern Modified Sense Strand	[mCs][mA][mG][mA][mU][mG][mU][fG][fU][fC][fU][mG][mC][mU][mA][mC][mA][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	779
KHK-882-920	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mGs][mA][mC][mU][mU][mU][mG][fA][fG][fA][fA][mG][mG][mU][mU][mG][mA][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	780
KHK-883-921	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mAs][mC][mU][mU][mU][mG][mA][fG][fA][fA][fG][mG][mU][mU][mG][mA][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	781
KHK-885-923	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mU][mU][mG][mA][mG][mA][fA][fG][fG][fU][mU][mG][mA][mU][mC][mU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	782
KHK-1054-1092	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense	[mAs][mG][fC][mU][mG][mU][mU][fU][fG][fG][mC][fU][fA][mC][mG][mG][fA][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	783

		Strand		
KHK-1075-1113-944-786	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mG][mG][mU][mG][mU][fU][fG][fU][fC][mA][mG][mC][mA][mA][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	784
KHK-1078-1116-947-789	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mG][mU][mU][mU][mG][mU][fC][fA][fG][fC][mA][mA][mA][mG][mA][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	785
KHK-1281-1319-1150-992	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mGs][mG][mA][mG][mA][mC][mA][fC][fC][fU][fU][mC][mA][mA][mU][mG][mC][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	786
KHK-1288-1326	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mCs][mC][mU][mU][mC][mA][mA][fU][fG][fC][fC][mU][mC][mC][mG][mU][mC][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	787
KHK-1290-1328	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mU][mC][mA][mA][mU][mG][fC][fC][fU][fC][mC][mG][mU][mC][mA][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	788
KHK-1148-1186	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mG][mG][mU][mC][mG][mU][fG][fU][fG][fA][mG][mG][mA][mA][mA][mG][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	789
KHK-1152-1190	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mCs][mG][mU][mG][mU][mG][mA][fG][fG][fA][fA][mA][mG][mG][mG][mG][mC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	790
KHK-1154-1192	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mG][mU][mG][mA][mG][mG][fA][fA][fA][fG][mG][mG][mG][mC][mU][mG][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	791
KHK-1155-1193	Hs-Mf commons	Low-2'-Fluoro	[mGs][mU][mG][mA][mG][mG][mA][fA][fA][fG][fG][mG][mG][mC][mU][mG][mU][mG][mC][mA][mG][mC][mA][mG][	792

		Pattern Modified Sense Strand	mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
KHK-1277	Hs unique	Low-2'-Fluoro Pattern Modified Sense Strand	[mAs][mG][mC][mU][mG][mG][mA][fG][fA][fC][fA][mC][mC][mU][mU][mC][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	793
KHK-1147-1185	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mAs][mU][mG][mG][mU][mC][mG][fU][fG][fU][fG][mA][mG][mG][mA][mA][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	794
KHK-869-934	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mG][mU][mG][mU][mC][mU][fG][fC][fU][fA][mC][mA][mG][mA][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	795
KHK-873	Hs unique	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mC][mU][mG][mC][mU][mA][fC][fA][fG][fA][mC][mU][mU][mU][mG][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	796
KHK-879	Hs unique	Low-2'-Fluoro Pattern Modified Sense Strand	[mAs][mC][mA][mG][mA][mC][mU][fU][fU][fG][fA][mG][mA][mA][mG][mG][mU][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	797
KHK-881	Hs unique	Low-2'-Fluoro Pattern Modified Sense Strand	[mAs][mG][mA][mC][mU][mU][mU][fG][fA][fG][fA][mA][mG][mG][mU][mU][mG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	798
KHK-896-934	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mG][mA][mU][mC][mU][mG][fA][fC][fC][fC][mA][mG][mU][mU][mC][mA][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	799
KHK-1064-1102	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense	[mCs][mU][mA][mC][mG][mG][mA][fG][fA][fC][fG][mU][mG][mG][mU][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	800

		Strand		
KHK-1077-1115-946-788	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mGs][mU][mG][mU][mU][mU][mG][fU][fC][fA][fG][mC][mA][mA][mA][mG][mA][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	801
KHK-1080-1118-949-791	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mUs][mU][mU][mG][mU][mC][mA][fG][fC][fA][fA][mA][mG][mA][mU][mG][mU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	802
KHK-1106-1144	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mCs][mU][mU][mG][mG][mG][mG][fU][fU][fC][fC][mA][mG][mU][mC][mA][mG][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	803
KHK-1334-1372	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Sense Strand	[mGs][mC][mA][mG][mG][mA][mA][fG][fC][fA][fC][mU][mG][mA][mG][mA][mU][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	804
KHK-516-554-385-227	Hs-Mf-Mm-Rn commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mGs][mA][fA][mG][mA][mG][mA][fA][fG][fC][mA][fG][fA][mU][mC][mC][fU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	805
KHK-804	Hs unique	Med-2'-Fluoro Pattern Modified Sense Strand	[mUs][mG][fC][mU][mG][mC][mA][fU][fC][fA][mU][fC][fA][mA][mC][mA][fA][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	806
KHK-829-838	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mGs][mC][fA][mA][mC][mC][mG][fU][fA][fC][mC][fA][fU][mU][mG][mU][fG][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	807
KHK-861-899-730-572	Hs-Mf-Mm-Rn commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mCs][mU][fG][mC][mC][mA][mG][fA][fU][fG][mU][fG][fU][mC][mU][mG][fC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	808
KHK-865	Hs unique	Med-2'-Fluoro	[mCs][mA][fG][mA][mU][mG][mU][fG][fU][fC][mU][fG][fC][mU][mA][mC][fA][mG][mA][mA][mG][mC][mA][mG][mC][	809

		Pattern Modified Sense Strand	mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
KHK-882-920	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mGs][mA][fC][mU][mU][mU][mG][fA][fG][fA][mA][fG][fG][mU][mU][mG][fA][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	810
KHK-883-921	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mAs][mC][fU][mU][mU][mG][mA][fG][fA][fA][mG][fG][fU][mU][mG][mA][fU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	811
KHK-885-923	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mUs][mU][fU][mG][mA][mG][mA][fA][fG][fG][mU][fU][fG][mA][mU][mC][fU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	812
KHK-1054-1092	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mAs][mG][fC][mU][mG][mU][mU][fU][fG][fG][mC][fU][fA][mC][mG][mG][fA][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	813
KHK-1076-1114-945-787	Hs-Mf-Mm-Rn commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mGs][mG][fU][mG][mU][mU][mU][fG][fU][fC][mA][fG][fC][mA][mA][mA][fG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	814
KHK-1078-1116-947-789	Hs-Mf-Mm-Rn commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mUs][mG][fU][mU][mU][mG][mU][fC][fA][fG][mC][fA][fA][mA][mG][mA][fU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	815
KHK-1288-1326	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mCs][mC][fU][mU][mC][mA][mA][fU][fG][fC][mC][fU][fC][mC][mG][mU][fC][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	816
KHK-1290-1328	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Sense	[mUs][mU][fC][mA][mA][mU][mG][fC][fC][fU][mC][fC][fG][mU][mC][mA][fU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	817

		Strand		
KHK-1334-1372	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Sense Strand	[mGs][mC][fA][mG][mG][mA][mA][fG][fC][fA][mC][fU][fG][mA][mG][mA][fU][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	818
KHK-510-548-379-221	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fCs][fU][fG][mC][fU][mU][mC][fU][mC][mU][mU][fC][mC][mA][mU][mG][mA][mGs][mGs][mG]	819
KHK-516-554-385-227	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fC][fA][fG][mG][fA][mU][mC][fU][mG][mC][mU][fU][mC][mU][mC][mU][mU][mCs][mGs][mG]	820
KHK-829-838	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fG][fC][fA][mC][fA][mA][mU][fG][mG][mU][mA][fC][mG][mG][mU][mU][mG][mCs][mGs][mG]	821
KHK-860-898-729-571	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fGs][fC][fA][mG][fA][mC][mA][fC][mA][mU][mC][fU][mG][mG][mC][mA][mG][mGs][mGs][mG]	822
KHK-861-899-730-572	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fAs][fG][fC][mA][fG][mA][mC][fA][mC][mA][mU][fC][mU][mG][mG][mC][mA][mGs][mGs][mG]	823
KHK-865	Hs unique	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fCs][fU][fG][mU][fA][mG][mC][fA][mG][mA][mC][fA][mC][mA][mU][mC][mU][mGs][mGs][mG]	824
KHK-882-920	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fGs][fAs][fU][fC][mA][fA][mC][mC][fU][mU][mC][mU][fC][mA][mA][mA][mG][mU][mCs][mGs][mG]	825
KHK-883-921	Hs-Mf commons	Low-2'-Fluoro	[MePhosphonate-4O-mUs][fAs][fGs][fA][fU][mC][fA][mA][mC][fC][mU][mU][mC]	826

		Pattern Modified Anti-sense Strand	[fU][mC][mA][mA][mG][mUs][mGs][mG]	
KHK-885-923	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fCs][fA][fG][mA][fU][mC][mA][fA][mC][mC][mU][fU][mC][mU][mC][mA][mA][mAs][mGs][mG]	827
KHK-1054-1092	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][mCs][mU][fC][mC][fG][fU][mA][fG][mC][fC][mA][fA][mA][fC][mA][mG][fC][mUs][mGs][mG]	828
KHK-1075-1113-944-786	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fCs][fU][fU][mU][fG][mC][mU][fG][mA][mC][mA][fA][mA][mC][mA][mC][mC][mAs][mGs][mG]	829
KHK-1078-1116-947-789	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fC][fA][fU][mC][fU][mU][mU][fG][mC][mU][mG][fA][mC][mA][mA][mA][mC][mAs][mGs][mG]	830
KHK-1281-1319-1150-992	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fGs][fG][fC][mA][fU][mU][mG][fA][mA][mG][mG][fU][mG][mU][mC][mU][mC][mCs][mGs][mG]	831
KHK-1288-1326	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fUs][fG][fA][mC][fG][mG][mA][fG][mG][mC][mA][fU][mU][mG][mA][mA][mG][mGs][mGs][mG]	832
KHK-1290-1328	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fGs][fA][fU][mG][fA][mC][mG][fG][mA][mG][mG][fC][mA][mU][mU][mG][mA][mAs][mGs][mG]	833
KHK-1148-1186	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fCs][fC][fU][mU][fU][mC][mC][fU][mC][mA][mC][fA][mC][mG][mA][mC][mC][mAs][mGs][mG]	834

		Strand		
KHK-1152-1190	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fAs][fG][fC][mC][fC][mU][fU][mU][mC][mC][fU][mC][mA][mC][mA][mC][mGs][mGs][mG]	835
KHK-1154-1192	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fAs][fC][fA][mG][fC][mC][fC][mU][mU][mU][fC][mC][mU][mC][mA][mC][mAs][mGs][mG]	836
KHK-1155-1193	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fGs][fCs][fA][fC][mA][fG][mC][mC][fC][mC][mU][mU][fU][mC][mC][mU][mC][mA][mCs][mGs][mG]	837
KHK-1277	Hs unique	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fUs][fU][fG][mA][fA][mG][mG][fU][mG][mU][mC][fU][mC][mC][mA][mG][mC][mUs][mGs][mG]	838
KHK-1147-1185	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fCs][fU][fU][mU][fC][mC][mU][fC][mA][mC][mA][fC][mG][mA][mC][mC][mA][mUs][mGs][mG]	839
KHK-869-934	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fAs][fA][fG][mU][fC][mU][mG][fU][mA][mG][mC][fA][mG][mA][mC][mA][mC][mAs][mGs][mG]	840
KHK-873	Hs unique	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fCs][fU][fC][mA][fA][mA][mG][fU][mC][mU][mG][fU][mA][mG][mC][mA][mG][mAs][mGs][mG]	841
KHK-879	Hs unique	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fAs][fA][fC][mC][fU][mU][mC][fU][mC][mA][mA][fA][mG][mU][mC][mU][mG][mUs][mGs][mG]	842
KHK-881	Hs unique	Low-2'-Fluoro	[MePhosphonate-4O-mUs][fAs][fUs][fC][fA][mA][fC][mC][mU][fU][mC][mU][mC]	843

		Pattern Modified Anti-sense Strand	[fA][mA][mA][mG][mU][mC][mUs][mGs][mG]	
KHK-896-934	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fUs][fU][fG][mA][fA][mC][mU][fG][mG][mU][fC][mA][mG][mA][mU][mC][mAs][mGs][mG]	844
KHK-1064-1102	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fAs][fA][fC][mA][fC][mC][mA][fC][mG][mU][mC][fU][mC][mC][mG][mU][mA][mGs][mGs][mG]	845
KHK-1077-1115-946-788	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fAs][fU][fC][mU][fU][mU][mG][fC][mU][mG][mA][fC][mA][mA][mA][mC][mA][mCs][mGs][mG]	846
KHK-1080-1118-949-791	Hs-Mf-Mm-Rn commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fCs][fA][fC][mA][fU][mC][mU][fU][mU][mG][mC][fU][mG][mA][mC][mA][mA][mAs][mGs][mG]	847
KHK-1106-1144	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fGs][fC][fU][mG][fA][mC][mU][fG][mG][mA][mA][fC][mC][mC][mC][mA][mA][mGs][mGs][mG]	848
KHK-1334-1372	Hs-Mf commons	Low-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fGs][fAs][fA][fU][mC][fU][mC][mA][fG][mU][mG][mC][fU][mU][mC][mC][mU][mG][mCs][mGs][mG]	849
KHK-516-554-385-227	Hs-Mf-Mm-Rn commons	Med-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fCs][fA][fG][mG][fA][fU][mC][fU][mG][mC][mU][fU][mC][fU][mC][mU][fU][mCs][mGs][mG]	850
KHK-804	Hs unique	Med-2'-Fluoro Pattern Modified Anti-sense	[MePhosphonate-4O-mUs][fAs][fGs][fU][fU][mG][fU][fU][mG][fA][mU][mG][mA][fU][mG][fC][mA][mG][fC][mAs][mGs][mG]	851

		Strand		
KHK-829-838	Hs-Mf commons	Med-2'- Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O- mUs][fAs][fGs][fC][fA][mC][fA][fA][mU][fG][mG][mU][mA][f C][mG][fG][mU][mU][fG][mCs][mGs][mG]	852
KHK-861- 899-730-572	Hs-Mf-Mm- Rn commons	Med-2'- Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O- mUs][fUs][fAs][fG][fC][mA][fG][fA][mC][fA][mC][mA][mU][f C][mU][fG][mG][mC][fA][mGs][mGs][mG]	853
KHK-865	Hs unique	Med-2'- Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O- mUs][fUs][fCs][fU][fG][mU][fA][fG][mC][fA][mG][mA][mC][fA][mC][fA][mU][mC][fU][mGs][mGs][mG]	854
KHK-882-920	Hs-Mf commons	Med-2'- Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O- mUs][fGs][fAs][fU][fC][mA][fA][fC][mC][fU][mU][mC][mU][f C][mA][fA][mA][mG][fU][mCs][mGs][mG]	855
KHK-883-921	Hs-Mf commons	Med-2'- Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O- mUs][fAs][fGs][fA][fU][mC][fA][fA][mC][fC][mU][mU][mC][f U][mC][fA][mA][mA][fG][mUs][mGs][mG]	856
KHK-885-923	Hs-Mf commons	Med-2'- Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O- mUs][fUs][fCs][fA][fG][mA][fU][fC][mA][fA][mC][mC][mU][f U][mC][fU][mC][mA][fA][mAs][mGs][mG]	857
KHK-1054- 1092	Hs-Mf commons	Med-2'- Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O- mUs][fUs][mCs][mU][fC][mC][fG][fU][mA][fG][mC][fC][mA][fA][mA][fC][mA][mG][fC][mUs][mGs][mG]	858
KHK-1076- 1114-945-787	Hs-Mf-Mm- Rn commons	Med-2'- Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O- mUs][fAs][fUs][fC][fU][mU][fU][fG][mC][fU][mG][mA][mC][fA][mA][fA][mC][mA][fC][mCs][mGs][mG]	859
KHK-1078- 1116-947-789	Hs-Mf-Mm- Rn	Med-2'- Fluoro	[MePhosphonate-4O- mUs][fAs][fCs][fA][fU][mC][fU][fU][mU][fG][mC][mU][mG][	860

	commons	Pattern Modified Anti-sense Strand	fA][mC][fA][mA][mA][fC][mAs][mGs][mG]	
KHK-1288-1326	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fUs][fG][fA][mC][fG][fG][mA][fG][mG][mC][mA][fU][mU][fG][mA][mA][fG][mGs][mGs][mG]	861
KHK-1290-1328	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fGs][fA][fU][mG][fA][fC][mG][fG][mA][mG][mG][fC][mA][fU][mU][mG][fA][mAs][mGs][mG]	862
KHK-1334-1372	Hs-Mf commons	Med-2'-Fluoro Pattern Modified Anti-sense Strand	[MePhosphonate-4O-mUs][fGs][fAs][fA][fU][mC][fU][fC][mA][fG][mU][mG][mC][fU][mU][fC][mC][mU][fG][mCs][mGs][mG]	863
Fam Probe	Fam Probe for NHP KHK primers	N/A	CCCTGGCCATGTTG	864
Forward-1026 Primer	Mouse KHK	N/A	TGGAGGTGGAGAAGCCA	865
Reverse - 1157 Primer	Mouse KHK	N/A	GACCATACAAGCCCCTCAAG	866
Probe-1080	Probe for Mouse KHK primers	N/A	TGGTGTGTTGTCAGCAAAGATGTGGC	867
Forward -496 Primer	5' Assay	N/A	AGGAAGCTCTGGGAGTA	868
Reverse-596 Primer	5' Assay	N/A	CCTCCTTAGGGTACTTGTC	869
Probe-518	5' Assay Probe	N/A	ATGGAAGAGAAGCAGATCCTGTGCG	870
Stem Loop	Un-modified stem loop sequence	N/A	GCAGCCGAAAGGCUGC	871
KHK-1277	Hs unique	36mer Sense Strand	AGCUGGAGACACCUUCAUAGCAGCCGAAAGGCUGC	872
KHK-1155-1193	Hs-Mf commons	36mer Sense Strand	GUGAGGAAAGGGGCUGUGCAGCAGCCGAAAGGCU GC	873
KHK-1152-1190	Hs-Mf commons	36mer Sense	CGUGUGAGGAAAGGGGCUGAGCAGCCGAAAGGCU GC	874

		Strand		
KHK-881	Hs unique	36mer Sense Strand	AGACUUUGAGAAGGUUGAUAGCAGCCGAAAGGCU GC	875
KHK-879	Hs unique	36mer Sense Strand	ACAGACUUUGAGAAGGUUGAGCAGCCGAAAGGCU GC	876
KHK-869	Hs-Mf commons	36mer Sense Strand	UGUGUCUGCUACAGACUUUAGCAGCCGAAAGGCU GC	877
KHK-873	Hs unique	36mer Sense strand	UCUGCUACAGACUUUGAGAAGCAGCCGAAAGGCU GC	878
KHK-1277	Hs unique	22mer anti-sense strand	UAUUGAAGGUGUCUCCAGCUGG	879
KHK-1155-1193	Hs-Mf commons	22mer anti-sense strand	UGCACAGCCCCUUUCCUCACGG	880
KHK-1152-1190	Hs-Mf commons	22mer anti-sense strand	UCAGCCCCUUUCCUCACACGGG	881
KHK-881	Hs unique	22mer anti-sense strand	UAUCAACCUUCUCAAGGUCUGG	882
KHK-879	Hs unique	22mer anti-sense strand	UCAACCUUCUCAAGGUCUGUGG	883
KHK-869	Hs-Mf commons	22mer anti-sense strand	UAAAGUCUGUAGCAGACACAGG	884
KHK-873	Hs unique	22mer anti-sense strand	UUCUCAAGGUCUGUAGCAGAGG	885
KHK-510-548-379-221	Hs-Mf-Mm-Rn commons	36mer Sense strand	CUCAUGGAAGAGAAGCAGAAGCAGCCGAAAGGCUG C	886
KHK-516-554-385-227	Hs-Mf-Mm-Rn commons	36mer Sense strand	GAAGAGAAGCAGAUCCUGUAGCAGCCGAAAGGCU GC	887
KHK-829-838	Hs-Mf commons	36mer Sense strand	GCAACCGUACCAUUGUGCUAGCAGCCGAAAGGCU GC	888
KHK-860-898-729-571	Hs-Mf-Mm-Rn commons	36mer Sense strand	CCUGCCAGAUGUGUCUGCUAGCAGCCGAAAGGCU GC	889
KHK-861-899-730-572	Hs-Mf-Mm-Rn commons	36mer Sense strand	CUGCCAGAUGUGUCUGCUAAGCAGCCGAAAGGCU GC	890
KHK-865	Hs unique	36mer Sense strand	CAGAUGUGUCUGCUACAGAAGCAGCCGAAAGGCU GC	891
KHK-882-920	Hs-Mf commons	36mer Sense strand	GACUUUGAGAAGGUUGAUCAGCAGCCGAAAGGCU GC	892
KHK-883-921	Hs-Mf commons	36mer Sense strand	ACUUUGAGAAGGUUGAUCUAGCAGCCGAAAGGCU GC	893

KHK-885-923	Hs-Mf commons	36mer Sense strand	UUUGAGAAGGUUGAUCUGAAGCAGCCGAAAGGCU GC	894
KHK-1054- 1092	Hs-Mf commons	36mer Sense strand	AGCUGUUUGGCUACGGAGAAGCAGCCGAAAGGCU GC	895
KHK-1075- 1113-944-786	Hs-Mf-Mm- Rn commons	36mer Sense strand	UGGUGUUUGUCAGCAAAGAAGCAGCCGAAAGGCU GC	896
KHK-1078- 1116-947-789	Hs-Mf-Mm- Rn commons	36mer Sense strand	UGUUUGUCAGCAAAGAUGUAGCAGCCGAAAGGCU GC	897
KHK-1281- 1319-1150- 992	Hs-Mf-Mm- Rn commons	36mer Sense strand	GGAGACACCUUCAUAGCCUAGCAGCCGAAAGGCU GC	898
KHK-1288- 1326	Hs-Mf commons	36mer Sense strand	CCUCAAUGCCUCCGUCAUAGCAGCCGAAAGGCU GC	899
KHK-1290- 1328	Hs-Mf commons	36mer Sense strand	UUCAUAGCCUCCGUCAUCUAGCAGCCGAAAGGCU GC	900
KHK-1148- 1186	Hs-Mf commons	36mer Sense strand	UGGUCGUGUGAGGAAAGGGAGCAGCCGAAAGGCU GC	901
KHK-1154- 1192	Hs-Mf commons	36mer Sense strand	UGUGAGGAAAGGGGCUGUGAGCAGCCGAAAGGCU GC	902
KHK-1147- 1185	Hs-Mf commons	36mer Sense strand	AUGGUCGUGUGAGGAAAGGAGCAGCCGAAAGGCU GC	903
KHK-896-934	Hs-Mf commons	36mer Sense strand	UGAUCUGACCCAGUUCAAGAGCAGCCGAAAGGCU GC	904
KHK-1064- 1102	Hs-Mf commons	36mer Sense strand	CUACGGAGACGUGGUGUUUAGCAGCCGAAAGGCU GC	905
KHK-1077- 1115-946-788	Hs-Mf-Mm- Rn commons	36mer Sense strand	GUGUUUGUCAGCAAAGAUGAGCAGCCGAAAGGCU GC	906
KHK-1080- 1118-949-791	Hs-Mf-Mm- Rn commons	36mer Sense strand	UUUGUCAGCAAAGAUGUGGAGCAGCCGAAAGGCU GC	907
KHK-1106- 1144	Hs-Mf commons	36mer Sense strand	CUUGGGGUUCCAGUCAGCAAGCAGCCGAAAGGCU GC	908
KHK-1334- 1372	Hs-Mf commons	36mer Sense strand	GCAGGAAGCACUGAGAUUCAGCAGCCGAAAGGCU GC	909
KHK-804	Hs unique	36mer Sense strand	UGCUGCAUCAUCAACAACUAGCAGCCGAAAGGCUG C	910

KHK-1076-1114-945-787	Hs-Mf-Mm-Rn commons	36mer Sense strand	GGUGUUUGUCAGCAAAGAUAGCAGCCGAAAGGCU GC	911
KHK-510-548-379-221	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UUCUGCUUCUCUCCAUGAGGG	912
KHK-516-554-385-227	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UACAGGAUCUGCUUCUCUUCGG	913
KHK-829-838	Hs-Mf commons	22mer anti-sense strand	UAGCACA AUGGUACGGUUGCGG	914
KHK-860-898-729-571	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UAGCAGACACAUCUGGCAGGGG	915
KHK-861-899-730-572	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UUAGCAGACACAUCUGGCAGGG	916
KHK-865	Hs unique	22mer anti-sense strand	UUCUGUAGCAGACACAUCUGGG	917
KHK-882-920	Hs-Mf commons	22mer anti-sense strand	UGAUCAACCUUCUCAAGUCGG	918
KHK-883-921	Hs-Mf commons	22mer anti-sense strand	UAGAUCAACCUUCUCAAGUGG	919
KHK-885-923	Hs-Mf commons	22mer anti-sense strand	UUCAGAUCAACCUUCUCAAGG	920
KHK-1054-1092	Hs-Mf commons	22mer anti-sense strand	UUCUCCGUAGCCAAACAGCUGG	921
KHK-1075-1113-944-786	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UUCUUUGCUGACAAACACCAGG	922
KHK-1078-1116-947-789	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UACAUCUUUGCUGACAAACAGG	923
KHK-1281-1319-1150-992	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UAGGCAUUGAAGGUGUCUCCGG	924
KHK-1288-1326	Hs-Mf commons	22mer anti-sense strand	UAUGACGGAGGCAUUGAAGGGG	925
KHK-1290-1328	Hs-Mf commons	22mer anti-sense strand	UAGAUGACGGAGGCAUUGAAGG	926
KHK-1148-1186	Hs-Mf commons	22mer anti-sense strand	UCCCUUCCUCACACGACCAGG	927
KHK-1154-1192	Hs-Mf commons	22mer anti-sense strand	UCACAGCCCCUUUCCUCACAGG	928
KHK-1147-1185	Hs-Mf commons	22mer anti-sense strand	UCCUUUCCUCACACGACCAUGG	929
KHK-873	Hs unique	22mer anti-sense strand	UUCUCAAGUCUGUAGCAGAGG	930
KHK-896-934	Hs-Mf commons	22mer anti-sense strand	UCUUGAACUGGGUCAGAUCAGG	931
KHK-1064-	Hs-Mf	22mer anti-	UAAACACCACGUCUCCGUAGGG	932

1102	commons	sense strand		
KHK-1077-1115-946-788	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UCAUCUUUGCUGACAAACACGG	933
KHK-1080-1118-949-791	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UCCACAUCUUUGCUGACAAAGG	934
KHK-1106-1144	Hs-Mf commons	22mer anti-sense strand	UUGCUGACUGGAACCCCAAGGG	935
KHK-1334-1372	Hs-Mf commons	22mer anti-sense strand	UGAAUCUCAGUGCUUCCUGCGG	936
KHK-804	Hs unique	22mer anti-sense strand	UAGUUGUUGAUGAUGCAGCAGG	937
KHK-1076-1114-945-787	Hs-Mf-Mm-Rn commons	22mer anti-sense strand	UAUCUUUGCUGACAAACACCGG	938
MmKHK-ALL-5-6	Forward	N/A	GCTCTTCCAGTTGTTTAGCTATGGT	939
MmKHK-ALL-5-6	Reverse	N/A	CAGGTGCTTGGCCACATCTT	940
MmKHK-ALL-5-6	Probe	N/A	AGGTGGTGTTTGTCAGC	941
KHK-516-554-385-227	Hs-Mf-Mm-Rn commons	19mer Sense strand	GAAGAGAAGCAGAUCCUGU	942
KHK-865	Hs unique	19mer Sense strand	CAGAUGUGUCUGCUACAGA	943
KHK-882-920	Hs-Mf commons	19mer Sense strand	GACUUUGAGAAGGUUGAUC	944
KHK-885-923	Hs-Mf commons	19mer Sense strand	UUUGAGAAGGUUGAUCUGA	945
KHK-1078-1116-947-789	Hs-Mf-Mm-Rn commons	19mer Sense strand	UGUUUGUCAGCAAAGAUGU	946
KHK-1334-1372	Hs-Mf commons	19mer Sense strand	GCAGGAAGCACUGAGAUUC	947
KHK-516-554-385-227	Hs-Mf-Mm-Rn commons	19mer anti-sense strand	ACAGGAUCUGCUUCUCUUC	948
KHK-865	Hs unique	19mer anti-sense strand	UCUGUAGCAGACACAUCUG	949
KHK-882-920	Hs-Mf commons	19mer anti-sense strand	GAUCAACCUUCUCAAGUC	950
KHK-885-923	Hs-Mf commons	19mer anti-sense strand	UCAGAUCAACCUUCUCAAA	951
KHK-1078-1116-947-789	Hs-Mf-Mm-Rn	19mer anti-sense strand	ACAUCUUUGCUGACAAACA	952

	commons			
KHK-1334-1372	Hs-Mf commons	19mer anti-sense strand	GAAUCUCAGUGCUUCCUGC	953

Particular aspects and embodiments of the present invention are described with reference to the following clauses:

- 5 1. A double stranded RNAi oligonucleotide for reducing ketohexokinase (*KHK*) expression, the oligonucleotide comprising an antisense strand and a sense strand, wherein the antisense strand and the sense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387 and wherein the region of complementarity is at least 15 contiguous nucleotides in length, or a pharmaceutically acceptable salt thereof.
- 10 2. The RNAi oligonucleotide of clause 1, wherein the sense strand comprises a sequence set forth in any one of SEQ ID NOs: 4-387.
3. The RNAi oligonucleotide of clause 1 or 2, wherein the antisense strand comprises a sequence set forth in any
15 one of SEQ ID NOs: 388-771.
4. A double stranded RNAi oligonucleotide for inhibiting expression of *KHK*, wherein said double stranded RNAi oligonucleotide comprises a sense strand and an antisense strand forming a duplex region, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the
20 nucleotide sequences of SEQ ID NO:4-387 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO: 388-771, or a pharmaceutically acceptable salt thereof.
5. The RNAi oligonucleotide of any one of clauses 1-4, wherein the sense strand is 15 to 50 nucleotides in length.
- 25 6. The RNAi oligonucleotide of any one of clauses 1-4, wherein the sense strand is 18 to 36 nucleotides in length.
7. The RNAi oligonucleotide of any one of clauses 1-4, wherein the sense strand is 15 to 30 nucleotides in length.
- 30 8. The RNAi oligonucleotide of any one of clauses 1-7, wherein the antisense strand is 15-30 nucleotides in length.
9. The RNAi oligonucleotide of any one of clauses 1-8, wherein the antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length, optionally at least 20 nucleotides in length.

10. The RNAi oligonucleotide of any one of clauses 1-3 and 5-9, wherein the region of complementarity is at least 19 contiguous nucleotides in length, optionally at least 20 nucleotides in length.

11. A double stranded RNAi oligonucleotide for reducing *KHK* expression, the oligonucleotide comprising:

(i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is selected from SEQ ID NOs: 948-953, and

(ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

12. The RNAi oligonucleotide of any one of clauses 1-11, wherein the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

13. The RNAi oligonucleotide of clause 12, wherein L is a triloop or a tetraloop.

14. The RNAi oligonucleotide of clause 13, wherein L is a tetraloop.

15. The RNAi oligonucleotide of clause 14, wherein the tetraloop comprises the sequence 5'-GAAA- 3'.

16. The RNAi oligonucleotide of any one of clauses 12-15, wherein the S1 and S2 are 1-10 nucleotides in length and have the same length.

17. The RNAi oligonucleotide of clause 16, wherein S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length.

18. The RNAi oligonucleotide of clause 17, wherein S1 and S2 are 6 nucleotides in length.

19. The RNAi oligonucleotide of any one of clauses 12-18, wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 871).

20. The RNAi oligonucleotide of any one of clauses 1-19, comprising a nicked tetraloop structure.

21. The RNAi oligonucleotide of any one of clauses 1-19, comprising a nick between the 3' terminus of the sense strand and the 5' terminus of the antisense strand.

22. The RNAi oligonucleotide of any one of clauses 1-21, wherein the antisense and sense strands are not covalently linked.

23. The RNAi oligonucleotide of any one of clauses 1-10 and 12-22, wherein the antisense strand comprises an
5 overhang of one or more nucleotides in length at the 3' terminus.

24. The RNAi oligonucleotide of any one of clauses 11-23, wherein the overhang comprises purine nucleotides.

25. The RNAi oligonucleotide of any one of clauses 11-24, wherein the overhang is 2 nucleotides in length.

26. The RNAi oligonucleotide of clause 25, wherein the 3' overhang is selected from AA, GG, AG, and GA.

27. The RNAi oligonucleotide of clause 26, wherein the overhang is GG or AA.

28. The RNAi oligonucleotide of clause 26, wherein the overhang is GG.

29. The RNAi oligonucleotide of any one of the preceding clauses, wherein the oligonucleotide comprises at least one modified nucleotide.

30. The RNAi oligonucleotide of clause 29, wherein the modified nucleotide comprises a 2'-modification.

31. The RNAi oligonucleotide of clause 30, wherein the 2'-modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid.

32. The RNAi oligonucleotide of any one of clauses 29-31, wherein about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise a 2'-fluoro modification.

33. The RNAi oligonucleotide of any one of clauses 29-32, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprise a 2'-fluoro modification.

34. The RNAi oligonucleotide of any one of clauses 29-33, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the oligonucleotide comprise a 2'-fluoro modification.

35. The RNAi oligonucleotide of any one of clauses 29-34, wherein all the nucleotides of the oligonucleotide are modified.

36. The RNAi oligonucleotide of any one of clauses 29-34, wherein the sense strand comprises 36 nucleotides with positions 1-36 numbered from 5' to 3', wherein positions 8, 9, 10 and 11 of the sense strand are modified.

37. The RNAi oligonucleotide of any one of clauses 29-34, wherein the sense strand comprises 36 nucleotides with positions 1-36 numbered from 5' to 3', wherein positions 3, 8, 9, 10, 12, 13 and 17 of the sense strand are modified.

38. The RNAi oligonucleotide of any one of clauses 29-34, wherein the antisense strand comprises 22 nucleotides with positions 1-22 numbered from 5' to 3', and wherein positions 2, 3, 4, 5, 7, 10 and 14 of the antisense strand are modified.

39. The RNAi oligonucleotide of any one of clauses 29-34, wherein the antisense strand comprises 22 nucleotides with positions 1-22 numbered from 5' to 3', and wherein positions 2-5, 7, 8, 10, 14, 16 and 19 of the antisense strand are modified.

40. The RNAi oligonucleotide of any one of clauses 36-39, where the modification is 2'-fluoro.

41. The RNAi oligonucleotide of any one of clauses 32-34 and 36-40, wherein the remaining nucleotides comprise a 2'-O-methyl modification.

42. The RNAi oligonucleotide of any one of the preceding clauses, wherein the oligonucleotide comprises at least one modified internucleotide linkage.

43. The RNAi oligonucleotide of clause 42, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

44. The RNAi oligonucleotide of clause 43, wherein the antisense strand comprises a phosphorothioate linkage (i) between positions 1 and 2, and between positions 2 and 3; or (ii) between positions 1 and 2, between positions 2 and 3, and between positions 3 and 4, wherein positions are numbered 1-4 from 5' to 3'.

45. The RNAi oligonucleotide of clause 43 or 44, wherein the antisense strand is 22 nucleotides in length, and wherein the antisense strand comprises a phosphorothioate linkage between positions 20 and 21 and between positions 21 and 22, wherein positions are numbered 1-22 from 5' to 3'.

46. The RNAi oligonucleotide of any one of clauses 1-45, wherein the antisense strand comprises a phosphorylated nucleotide at the 5' terminus, wherein the phosphorylated nucleotide is selected from uridine and adenosine.

47. The RNAi oligonucleotide of clause 46, wherein the phosphorylated nucleotide is uridine.

48. The RNAi oligonucleotide of any one of the preceding clauses, wherein the 4'-carbon of the sugar of the 5'-terminal nucleotide of the antisense strand comprises a phosphate analog.

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49. The RNAi oligonucleotide of clause 48, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonyl phosphonate, optionally wherein the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.

10 50. The RNAi oligonucleotide of any one of the preceding clauses, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.

51. The RNAi oligonucleotide of clause 50, wherein each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid.

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52. The RNAi oligonucleotide of any one of clauses 11-51, wherein the stem loop comprises one or more targeting ligands conjugated to one or more nucleotides of the stem loop.

20 53. The RNAi oligonucleotide of clause 52, wherein the one or more targeting ligands is conjugated to one or more nucleotides of the loop.

54. The RNAi oligonucleotide of clause 53, wherein the loop comprises 4 nucleotides numbered 1-4 from 5' to 3', wherein nucleotides at positions 2, 3, and 4 each comprise one or more targeting ligands, wherein the targeting ligands are the same or different.

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55. The RNAi oligonucleotide of any one of clauses 50-54, wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety.

30 56. The RNAi oligonucleotide of clause 55, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety.

57. The RNAi oligonucleotide of any one of clauses 11-56, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

35 58. The RNAi oligonucleotide of any one of clauses 1-57, wherein the region of complementarity comprised by the antisense strand is fully complementary to the *KHK* mRNA target sequence at nucleotide positions 2-8 of the antisense strand, wherein nucleotide positions are numbered 5' to 3'.

59. The RNAi oligonucleotide of any one of clauses 1-57, wherein the region of complementarity comprised by the antisense strand is fully complementary to the *KHK* mRNA target sequence at nucleotide positions 2-11 of the antisense strand, wherein nucleotide positions are numbered 5' to 3'.

5

60. The RNAi oligonucleotide of any one of clauses 1-59, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 872-878 and 886-911.

61. The RNAi oligonucleotide of any one of clauses 1-60, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 879-884 and 912-938.

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62. The RNAi oligonucleotide of any one of clauses 1-61, wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 886 and 912, respectively;

15

(b) SEQ ID NOs: 887 and 913, respectively;

(c) SEQ ID NOs: 910 and 937, respectively;

(d) SEQ ID NOs: 888 and 914, respectively;

(e) SEQ ID NOs: 889 and 915, respectively;

(f) SEQ ID NOs: 890 and 916, respectively;

20

(g) SEQ ID NOs: 891 and 917, respectively;

(h) SEQ ID NOs: 877 and 884, respectively;

(i) SEQ ID NOs: 878 and 930, respectively;

(j) SEQ ID NOs: 876 and 883, respectively;

(k) SEQ ID NOs: 875 and 882, respectively;

25

(l) SEQ ID NOs: 892 and 918, respectively;

(m) SEQ ID NOs: 893 and 919, respectively;

(n) SEQ ID NOs: 894 and 920, respectively;

(o) SEQ ID NOs: 904 and 931, respectively;

(p) SEQ ID NOs: 895 and 921, respectively;

30

(q) SEQ ID NOs: 905 and 932, respectively;

(r) SEQ ID NOs: 896 and 922, respectively;

(s) SEQ ID NOs: 911 and 938, respectively;

(t) SEQ ID NOs: 906 and 933, respectively;

(u) SEQ ID NOs: 897 and 923, respectively;

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(v) SEQ ID NOs: 907 and 934, respectively;

(w) SEQ ID NOs: 908 and 935, respectively;

(x) SEQ ID NOs: 903 and 929, respectively;

- (y) SEQ ID NOs: 901 and 927, respectively;
- (z) SEQ ID NOs: 874 and 881, respectively;
- (aa) SEQ ID NOs: 902 and 928, respectively;
- (bb) SEQ ID NOs: 873 and 880, respectively;
- 5 (cc) SEQ ID NOs: 872 and 879, respectively;
- (dd) SEQ ID NOs: 898 and 924, respectively;
- (ee) SEQ ID NOs: 899 and 925, respectively;
- (ff) SEQ ID NOs: 900 and 926, respectively; and
- (gg) SEQ ID NOs: 909 and 936, respectively.

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63. The RNAi oligonucleotide of any one of clauses 1-62, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 909 and 936, respectively.

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64. The RNAi oligonucleotide of any one of clauses 1-62, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 894 and 920, respectively.

65. The RNAi oligonucleotide of any one of clauses 1-62, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 897 and 923, respectively.

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66. The RNAi oligonucleotide of any one of clauses 1-62, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 892 and 918, respectively.

67. The RNAi oligonucleotide of any one of clauses 1-62, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 891 and 917, respectively.

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68. The RNAi oligonucleotide of any one of clauses 1-62, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 887 and 913, respectively.

69. The RNAi oligonucleotide of any one of clauses 1-59, wherein the antisense strand is 22 nucleotides in length.

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70. The RNAi oligonucleotide of clause 69, wherein the antisense strand comprises a nucleotide sequence selected from SEQ ID NOs: 913, 917, 918, 920, 923 and 936.

71. The RNAi oligonucleotide of any one of clauses 1-59 and 69-70, wherein the sense strand comprises a nucleotide sequence selected from SEQ ID NOs: 942-947.

35

72. The RNAi oligonucleotide of any one of clauses 1-59 and 69-71, wherein the sense strand is 36 nucleotides in length.

73. The RNAi oligonucleotide of clause 72, wherein the sense strand comprises a nucleotide sequence selected from
5 SEQ ID NOs: 887, 891, 892, 894, 897 and 909.

74. The RNAi oligonucleotide of any one of clauses 60-73, wherein the sense strand and the antisense strand are modified, wherein the antisense strand and the sense strand comprise one or more 2'-fluoro and 2'-O-methyl modified nucleotides and at least one phosphorothioate linkage, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the
10 antisense strand comprises a phosphate analog.

75. The RNAi oligonucleotide of any one of clauses 1-59, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 774-804.

15 76. The RNAi oligonucleotide of any one of clauses 1-59 and 75, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 819-849.

77. The RNAi oligonucleotide of any one of clauses 1-59 and 75-76, wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- 20 (a) SEQ ID NOs: 774 and 819, respectively;
- (b) SEQ ID NOs: 775 and 820, respectively;
- (c) SEQ ID NOs: 776 and 821, respectively;
- (d) SEQ ID NOs: 777 and 822, respectively;
- (e) SEQ ID NOs: 778 and 823, respectively;
- 25 (f) SEQ ID NOs: 779 and 824, respectively;
- (g) SEQ ID NOs: 780 and 825, respectively;
- (h) SEQ ID NOs: 781 and 826, respectively;
- (i) SEQ ID NOs: 782 and 827, respectively;
- (j) SEQ ID NOs: 783 and 828, respectively;
- 30 (k) SEQ ID NOs: 784 and 829, respectively;
- (l) SEQ ID NOs: 785 and 830, respectively;
- (m) SEQ ID NOs: 786 and 831, respectively;
- (n) SEQ ID NOs: 787 and 832, respectively;
- (o) SEQ ID NOs: 788 and 833, respectively;
- 35 (p) SEQ ID NOs: 789 and 834, respectively;
- (q) SEQ ID NOs: 790 and 835, respectively;
- (r) SEQ ID NOs: 791 and 836, respectively;

- (s) SEQ ID NOs: 792 and 837, respectively;
- (t) SEQ ID NOs: 793 and 838, respectively;
- (u) SEQ ID NOs: 794 and 839, respectively;
- (v) SEQ ID NOs: 795 and 840, respectively;
- 5 (w) SEQ ID NOs: 796 and 841, respectively;
- (x) SEQ ID NOs: 797 and 842, respectively;
- (y) SEQ ID NOs: 798 and 843, respectively;
- (z) SEQ ID NOs: 799 and 844, respectively;
- (aa) SEQ ID NOs: 800 and 845, respectively;
- 10 (bb) SEQ ID NOs: 801 and 846, respectively;
- (cc) SEQ ID NOs: 802 and 847, respectively;
- (dd) SEQ ID NOs: 803 and 848, respectively; and
- (ee) SEQ ID NOs: 804 and 849, respectively.
- 15 78. The RNAi oligonucleotide of any one of clauses 1-59 and 75-76, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 804 and 849, respectively.
79. The RNAi oligonucleotide of any one of clauses 1-59 and 75-76, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 782 and 827, respectively.
- 20 80. The RNAi oligonucleotide of any one of clauses 1-59 and 75-76, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 775 and 820, respectively.
81. The RNAi oligonucleotide of any one of clauses 1-59 and 75-76, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 779 and 824, respectively.
- 25 82. The RNAi oligonucleotide of any one of clauses 1-59 and 75-76, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 780 and 825, respectively.
- 30 83. The RNAi oligonucleotide of any one of clauses 1-59 and 75-76, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 785 and 830, respectively.
84. The RNAi oligonucleotide of any one of clauses 1-59, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 805-818.
- 35 85. The RNAi oligonucleotide of any one of clauses 1-59 and 84, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 850-863

86. The RNAi oligonucleotide of any one of clauses 1-59 and 84-85, wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 805 and 850, respectively;
- 5 (b) SEQ ID NOs: 806 and 851, respectively;
- (c) SEQ ID NOs: 807 and 852, respectively;
- (d) SEQ ID NOs: 808 and 853, respectively;
- (e) SEQ ID NOs: 809 and 854, respectively;
- (f) SEQ ID NOs: 810 and 855, respectively;
- 10 (g) SEQ ID NOs: 811 and 856, respectively;
- (h) SEQ ID NOs: 812 and 857, respectively;
- (i) SEQ ID NOs: 813 and 858, respectively;
- (j) SEQ ID NOs: 814 and 859, respectively;
- (k) SEQ ID NOs: 815 and 860, respectively;
- 15 (l) SEQ ID NOs: 816 and 861, respectively;
- (m) SEQ ID NOs: 817 and 862, respectively and;
- (n) SEQ ID NOs: 818 and 863, respectively.

87. The RNAi oligonucleotide of any one of clauses 1-59 and 84-86, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 805 and 850, respectively.

88. The RNAi oligonucleotide of any one of clauses 1-59 and 84-86, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 809 and 854, respectively.

25 89. The RNAi oligonucleotide of any one of clauses 1-59 and 84-86, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 810 and 855, respectively.

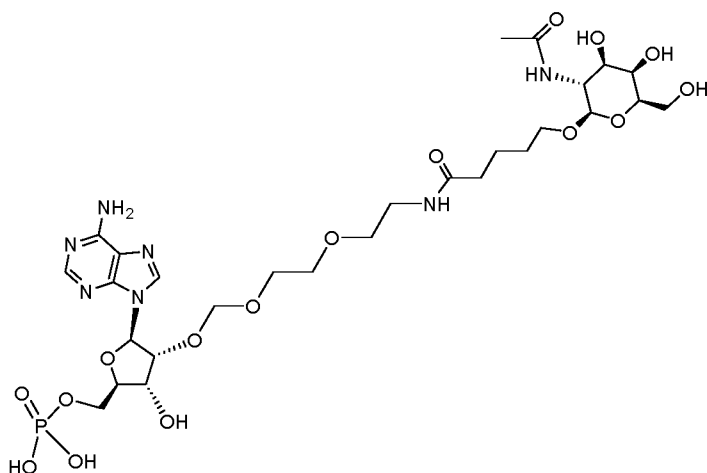
90. The RNAi oligonucleotide of any one of clauses 1-59 and 84-86, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 812 and 857, respectively.

30 91. The RNAi oligonucleotide of any one of clauses 1-59 and 84-86, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 815 and 860, respectively.

92. The RNAi oligonucleotide of any one of clauses 1-59 and 84-86, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 818 and 863, respectively.

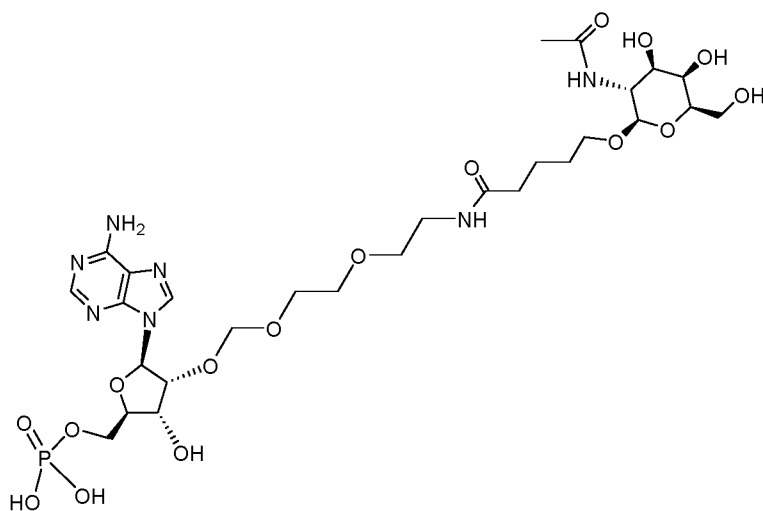
35

93. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of KHK, wherein said dsRNAi comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mG-S-mC-mA-mG-mG-mA-mA-fG-fC-fA-fC-mU-mG-mA-mG-mA-mU-mU-mC-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 804), and
 5 mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 804), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fG-S-fA-S-fA-fU-mC-fU-mC-mA-fG-mU-mG-mC-fU-mU-mC-mC-mU-mG-mC-S-mG-S-mG-3' (SEQ ID NO: 849), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



10 , or a pharmaceutically acceptable salt thereof.

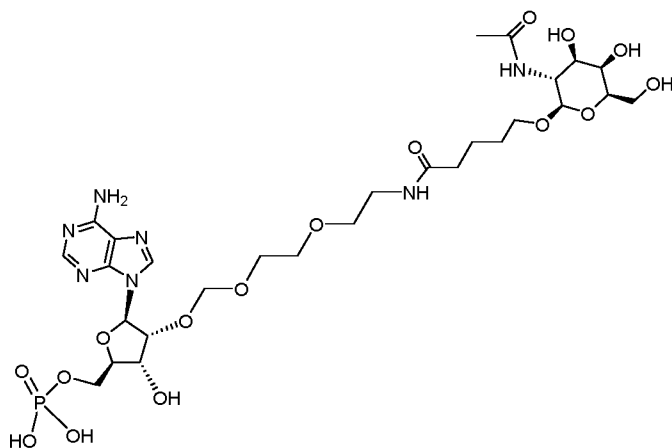
94. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of KHK, wherein said dsRNAi comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mU-S-mU-mU-mG-mA-mG-mA-fA-fG-fG-fU-mU-mG-mA-mU-mC-mU-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 782), and
 15 mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 782), and wherein the antisense strand comprises the sequence and all of the modifications of 5' [MePhosphonate-4O-mU]-S-fU-S-fC-S-fA-fG-mA-fU-mC-mA-fA-mC-mC-mU-fU-mC-mU-mC-mA-mA-mA-S-mG-S-mG-3' (SEQ ID NO: 827),
 20 wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



, or a pharmaceutically acceptable salt

thereof.

95. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of KHK, wherein said dsRNAi
 5 comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mG-S-mA-mA-mG-mA-mG-mA-fA-fG-fC-fA-mG-mA-mU-mC-mC-mU-mG-mU-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 775), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fA-S-fC-fA-fG-mG-fA-mU-mC-fU-mG-mC-mU-fU-mC-mU-mC-mU-mU-mC-S-mG-S-mG-3' (SEQ ID NO: 820),
 10 wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



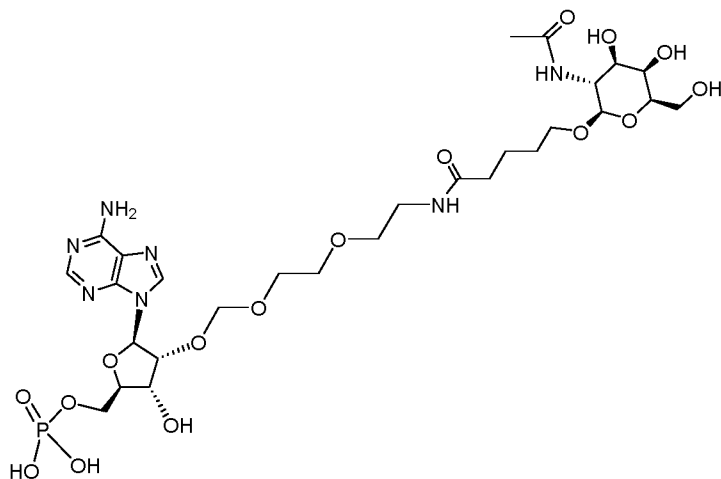
, or a pharmaceutically acceptable salt thereof.

96. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of KHK, wherein said dsRNAi
 15 comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mC-S-mA-mG-mA-mU-mG-mU-fG-fU-fC-fU-mG-mC-mU-mA-mC-mA-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 779), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-

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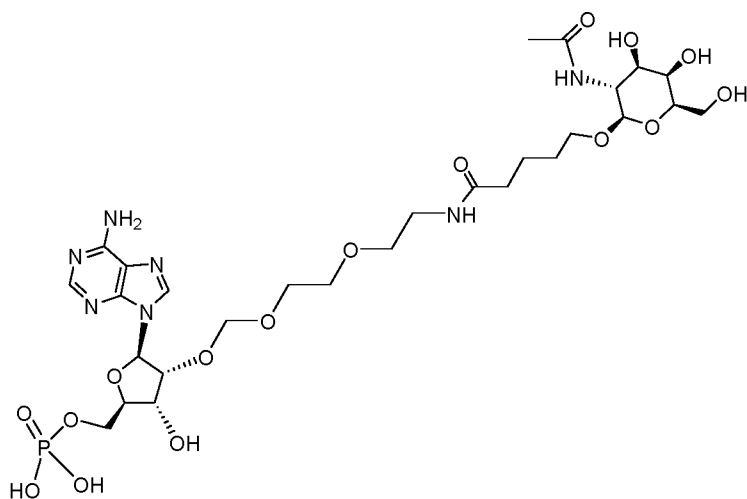
fU-S-fC-S-fU-fG-mU-fA-mG-mC-fA-mG-mA-mC-fA-mC-mA-mU-mC-mU-mG-S-mG-S-mG-3' (SEQ ID NO: 824), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



, or a pharmaceutically acceptable salt

5 thereof.

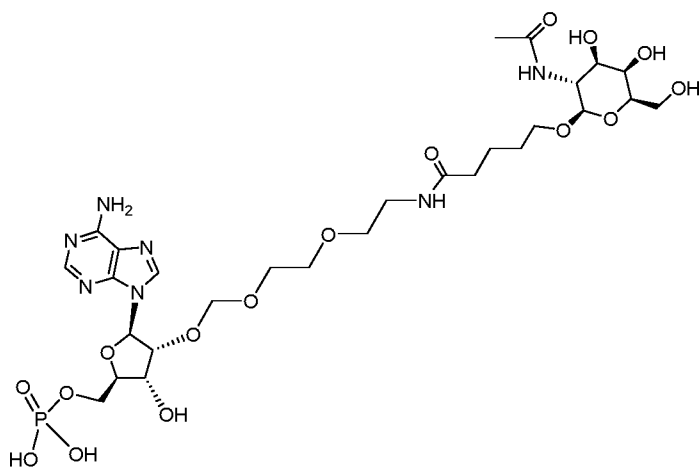
97. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of KHK, wherein said dsRNAi comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mG-S-mA-mC-mU-mU-mG-fA-fG-fA-fA-mG-mU-mU-mG-mA-mU-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 780), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fG-S-fA-S-fU-fC-mA-fA-mC-mC-fU-mU-mC-mU-fC-mA-mA-mA-mG-mU-mC-S-mG-S-mG-3' (SEQ ID NO: 825), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



, or a pharmaceutically acceptable salt

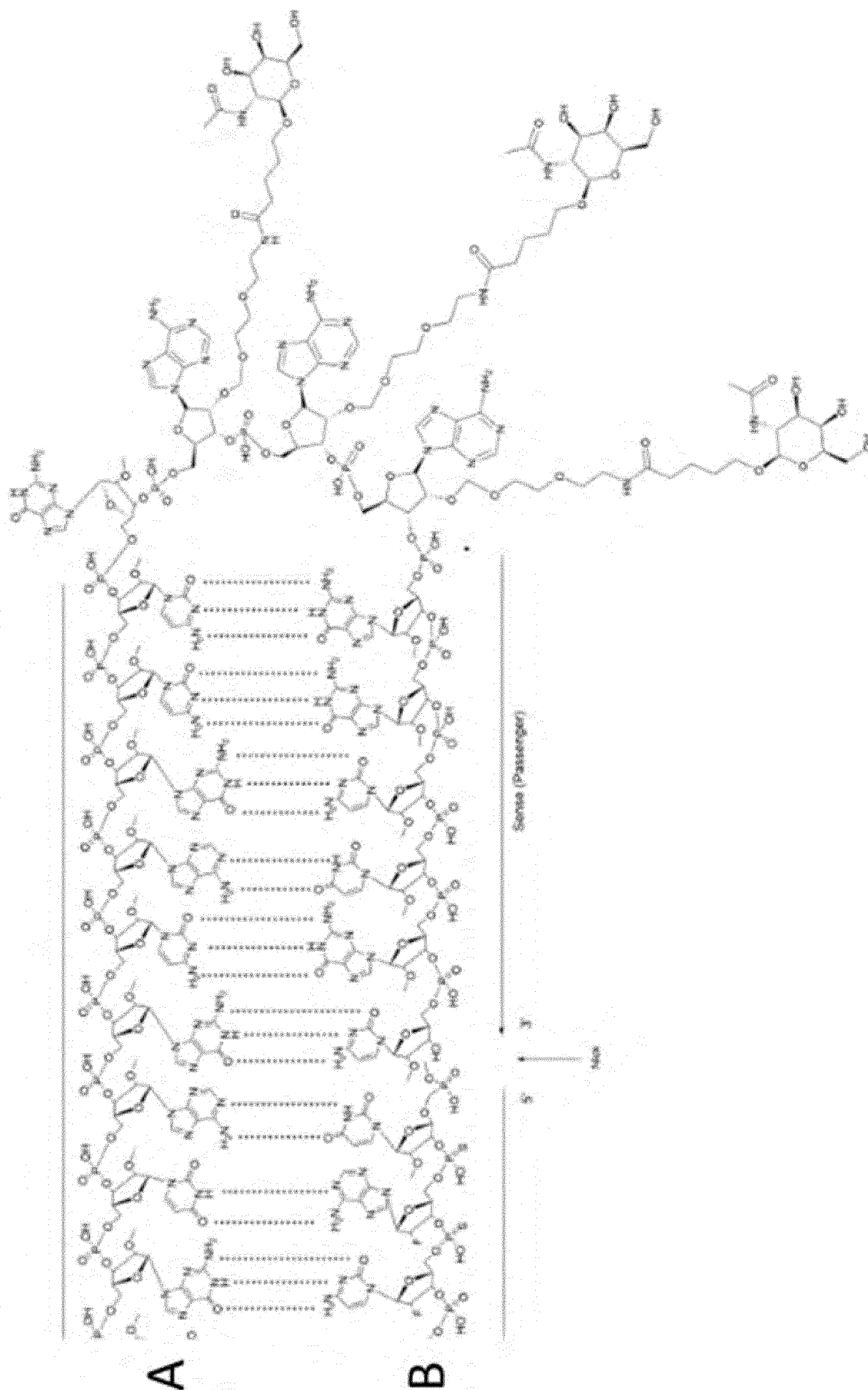
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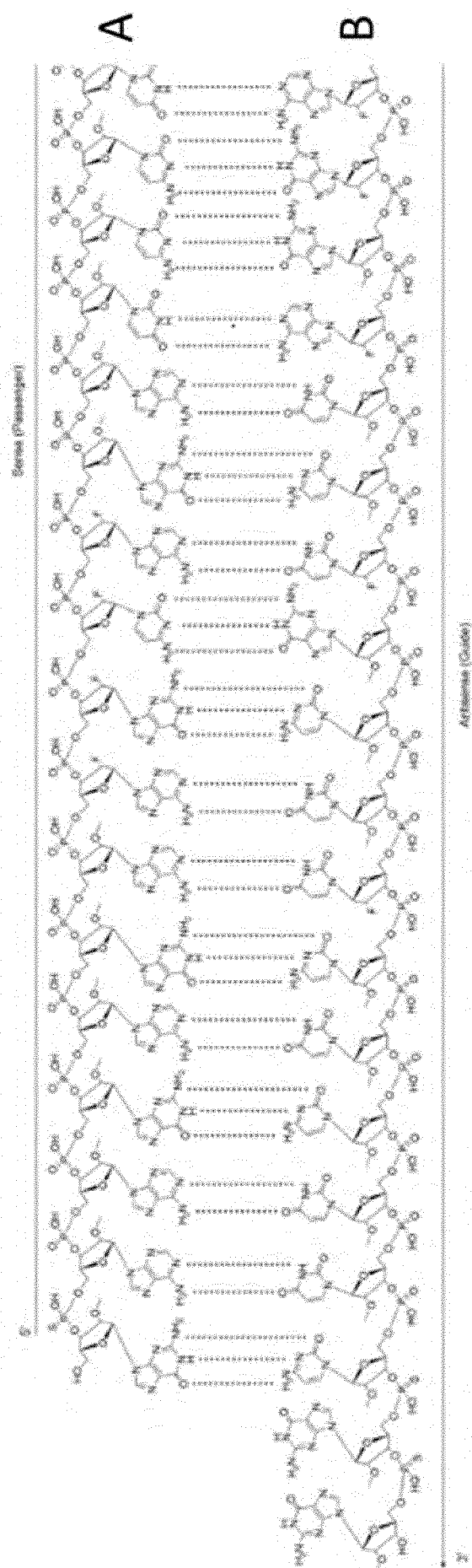
98. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of KHK, wherein said dsRNAi comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein the sense strand comprises the sequence and all of the modifications of 5'-mU-S-mG-mU-mU-mU-mG-mU-fC-fA-fG-fC-mA-mA-mA-mG-mA-mU-mG-mU-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 785), and
 5 wherein the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fA-S-fC-fA-fU-mC-fU-mU-mU-fG-mC-mU-mG-fA-mC-mA-mA-mA-mC-mA-S-mG-S-mG-3' (SEQ ID NO: 830), wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



, or a pharmaceutically acceptable salt thereof.

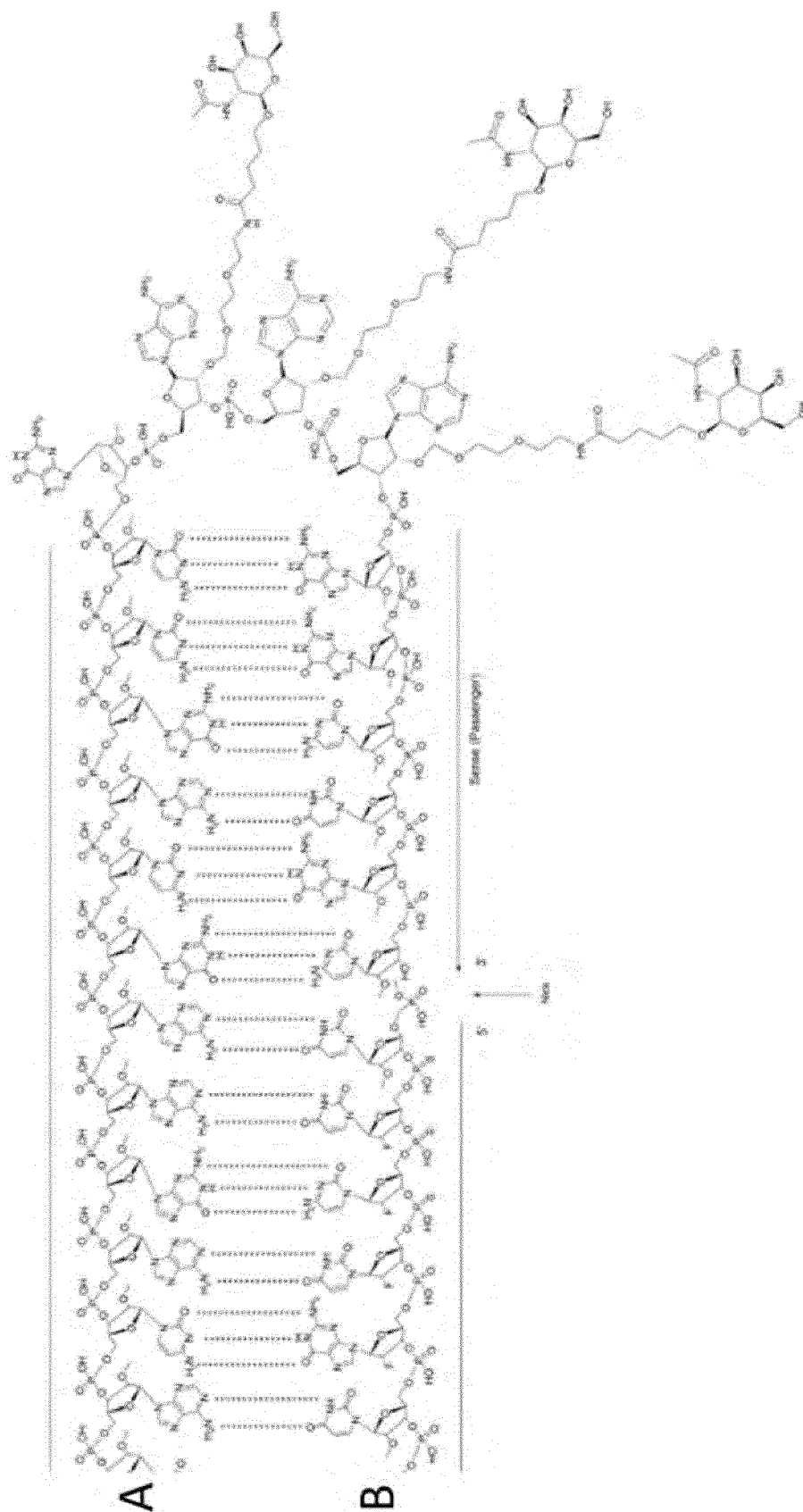
99. A dsRNAi oligonucleotide for inhibiting expression of KHK, wherein said dsRNAi comprises a sense strand comprising SEQ ID NO: 775 and an antisense strand comprising SEQ ID NO: 820, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein said dsRNAi is in the form of a
 15 conjugate having the structure of:

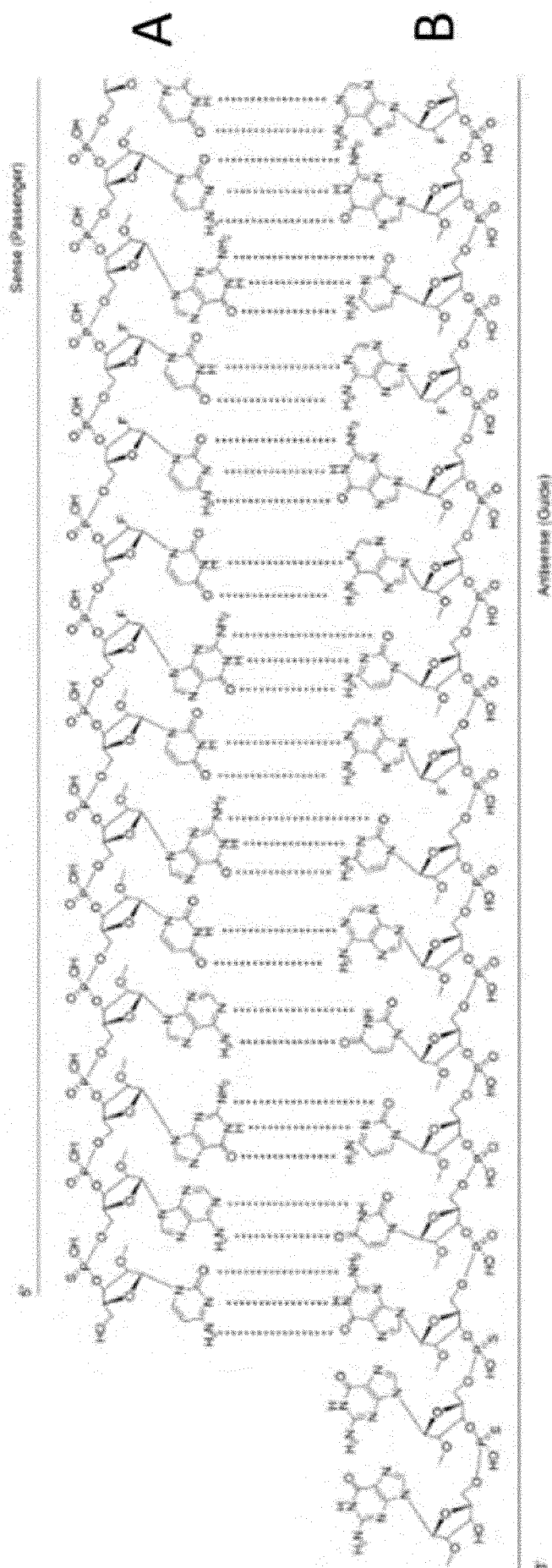




, or a pharmaceutically acceptable salt thereof.

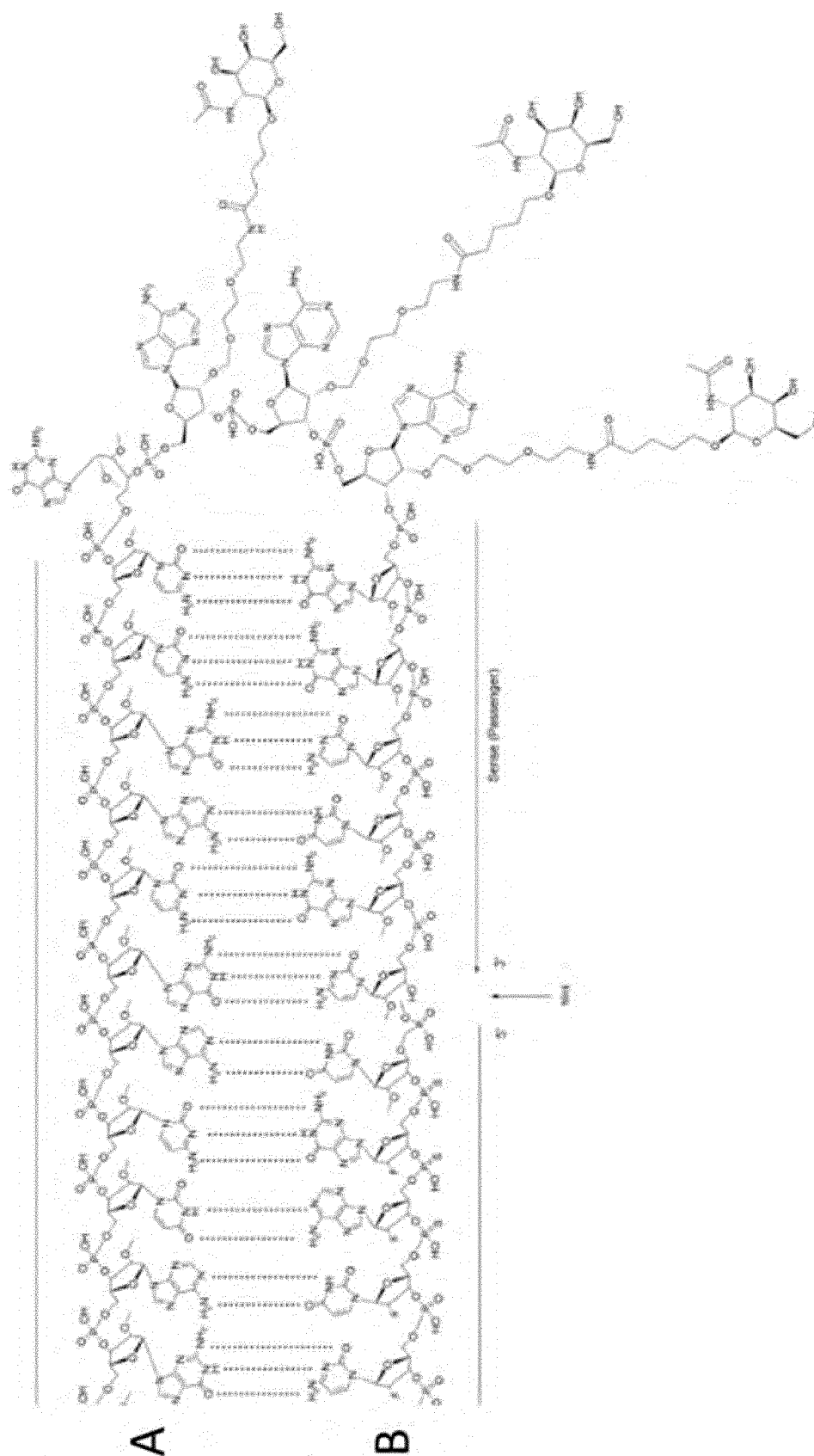
100. A dsRNAi oligonucleotide for inhibiting expression of KHK, wherein said dsRNAi comprises a sense strand comprising SEQ ID NO: 779 and an antisense strand comprising SEQ ID NO: 824, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein said dsRNAi is in the form of a conjugate having the structure of:





, or a pharmaceutically acceptable salt thereof.

101. A dsRNAi oligonucleotide for inhibiting expression of KHK, wherein said dsRNAi comprises a sense strand comprising SEQ ID NO: 780 and an antisense strand comprising SEQ ID NO: 825, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein said dsRNAi is in the form of a conjugate having the structure of:



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LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 233

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 233

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

1. A double stranded RNAi oligonucleotide for reducing ketohexokinase (*KHK*) expression, the oligonucleotide comprising an antisense strand and a sense strand, wherein the antisense strand and the sense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *KHK* mRNA target sequence of any one of SEQ ID NOs: 4-387 and wherein the region of complementarity is at least 15 contiguous nucleotides in length, or a pharmaceutically acceptable salt thereof, wherein preferably the sense strand comprises a sequence set forth in any one of SEQ ID NOs: 4-387 and/or the antisense strand comprises a sequence set forth in any one of SEQ ID NOs: 388-771.
2. A double stranded RNAi oligonucleotide for inhibiting expression of *KHK*, wherein said double stranded RNAi oligonucleotide comprises a sense strand and an antisense strand forming a duplex region, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO:4-387 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO: 388-771, or a pharmaceutically acceptable salt thereof, wherein preferably the sense strand is 18 to 36 nucleotides in length and/or the antisense strand is 15-30 nucleotides in length.
3. A double stranded RNAi (dsRNAi) oligonucleotide for reducing or inhibiting ketohexokinase (*KHK*) expression, the oligonucleotide comprising:
 - (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *KHK* mRNA target sequence, wherein the region of complementarity is selected from SEQ ID NOs: 948-953; and
 - (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.
4. The RNAi oligonucleotide of any one of claims 1 or 3, wherein the region of complementarity comprised by the antisense strand is at least 19 contiguous nucleotides in length, preferably 19 nucleotides.
5. The RNAi oligonucleotide of any one of claims 1-4, wherein the duplex region is at least 20 nucleotides in length, preferably 20 nucleotides.
6. The RNAi oligonucleotide of any one of claims 1-5, wherein the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and

wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length,
preferably the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 871).

7. The RNAi oligonucleotide of any one of claims 1-6,

5 wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands,
wherein preferably each targeting ligand comprises an N-acetylgalactosamine (GalNAc) moiety,
wherein more preferably the one or more targeting ligands is conjugated to one or more nucleotides of the loop
according to claim 6.

10 8. The RNAi oligonucleotide of any one of claims 1-7,

wherein the overhang is 2 nucleotides in length,
preferably selected from AA, GG, AG, and GA,
more preferably the overhang is GG.

15 9. The RNAi oligonucleotide of any one of claims 1-8,

wherein all the nucleotides of the oligonucleotide are modified,
preferably 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise a 2'-fluoro
modification
and/or about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the
20 antisense strand comprise a 2'-fluoro modification.

10. The RNAi oligonucleotide of any one of claims 1-9,

wherein the oligonucleotide comprises at least one phosphorothioate linkage,
preferably between positions 1 and 2, between positions 2 and 3, and between positions 3 and 4,
25 wherein positions are numbered 1-4 from 5' to 3'.

11. The RNAi oligonucleotide of any one of claims 1-10,

wherein the 4'-carbon of the sugar of the 5'-terminal nucleotide of the antisense strand comprises a phosphate
analog,
30 preferably a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.

12. The RNAi oligonucleotide of any one of claims 1-11,

wherein the antisense strand is 22 nucleotides in length and/or
wherein the sense strand is 36 nucleotides in length.

35 13. The RNAi oligonucleotide of any one of claims 1-12,

wherein the sense and antisense strands comprise the nucleotide sequences set forth in

- (a) SEQ ID NOs: 887 and 913, respectively, or
- (b) SEQ ID NOs: 891 and 917, respectively, or
- (c) SEQ ID NOs: 892 and 918, respectively, or
- 5 (d) SEQ ID NOs: 894 and 920, respectively, or
- (e) SEQ ID NOs: 897 and 923, respectively, or
- (f) SEQ ID NOs: 909 and 936, respectively.

14. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of KHK, wherein said dsRNAi

- 10 comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein

(a) the sense strand comprises the sequence and all of the modifications of 5'-mG-S-mA-mA-mG-mA-mG-mA-fA-fG-fC-fA-mG-mA-mU-mC-mC-mU-mG-mU-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-

- 15 GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 775), and

the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fA-S-fC-fA-fG-mG-fA-mU-mC-fU-mG-mC-mU-fU-mC-mU-mC-mU-mC-S-mG-S-mG-3' (SEQ ID NO: 820); or

(b) the sense strand comprises the sequence and all of the modifications of 5'-mC-S-mA-mG-mA-mU-mG-mU-fG-fU-fC-fU-mG-mC-mU-mA-mC-mA-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 779), and

- 20 the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fU-S-fC-S-fU-fG-mU-fA-mG-mC-fA-mG-mA-mC-fA-mC-mA-mU-mC-mU-mG-S-mG-S-mG-3' (SEQ ID NO: 824); or

(c) the sense strand comprises the sequence and all of the modifications of 5'-mG-S-mA-mC-mU-mU-mU-mG-fA-fG-fA-fA-mG-mG-mU-mU-mG-mA-mU-mC-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 780), and

- 25 the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fG-S-fA-S-fU-fC-mA-fA-mC-mC-fU-mU-mC-mU-fC-mA-mA-mA-mG-mU-mC-S-mG-S-mG-3' (SEQ ID NO: 825); or

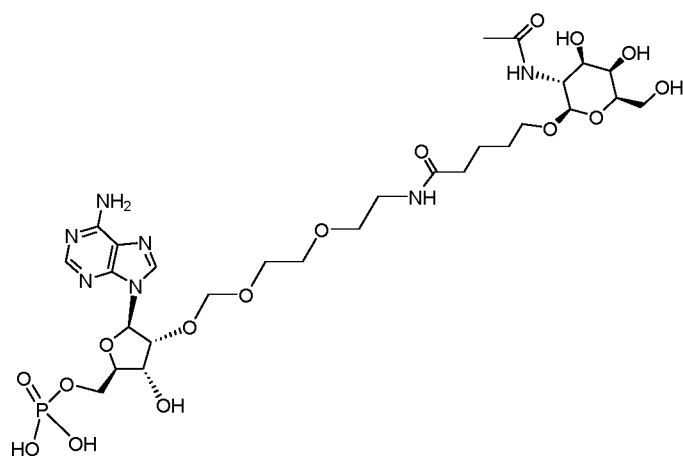
(d) the sense strand comprises the sequence and all of the modifications of 5'-mU-S-mU-mU-mG-mA-mG-mA-fA-fG-fG-fU-mU-mG-mA-mU-mC-mU-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 782), and

- 30 the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fU-S-fC-S-fA-fG-mA-fU-mC-mA-fA-mC-mC-mU-fU-mC-mU-mC-mA-mA-mA-S-mG-S-mG-3' (SEQ ID NO: 827); or

the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fA-S-fC-fA-fU-mC-fU-mU-mU-fG-mC-mU-mG-fA-mC-mA-mA-mA-mC-mA-S-mG-S-mG-3' (SEQ ID NO: 830); or

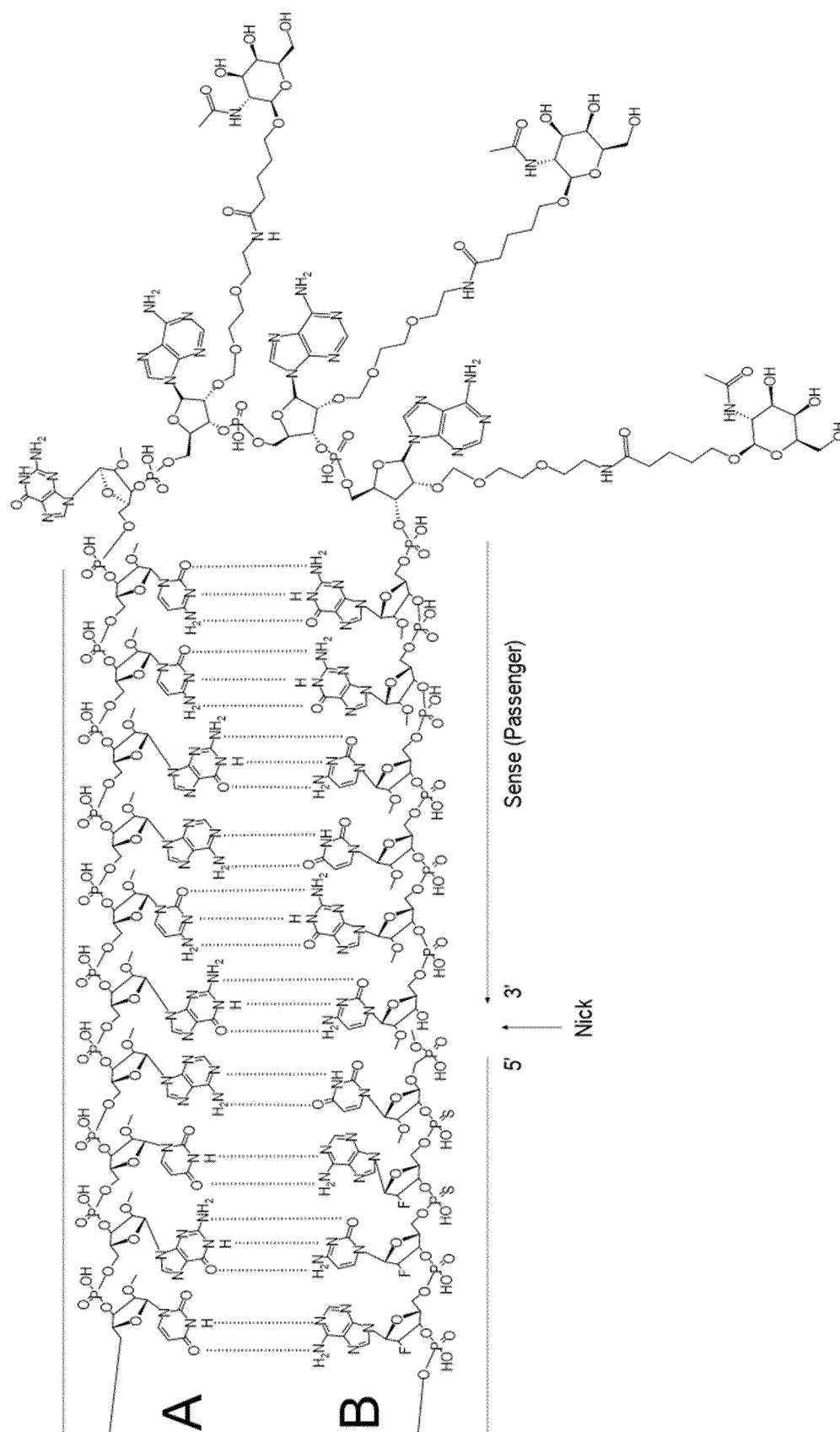
the antisense strand comprises the sequence and all of the modifications of 5'-[MePhosphonate-4O-mU]-S-fG-S-fA-S-fA-fU-mC-fU-mC-mA-fG-mU-mG-mC-fU-mU-mC-mC-mU-mG-mC-S-mG-S-mG-3' (SEQ ID NO: 849);

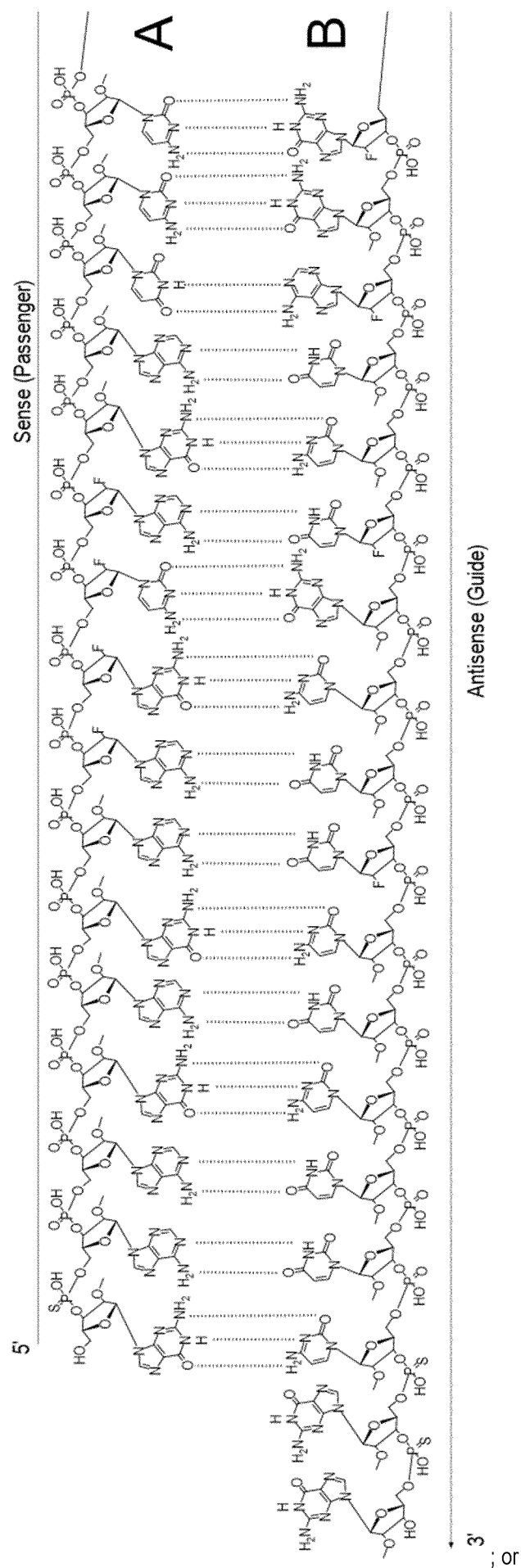
wherein mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'F ribonucleosides; "-"=phosphodiester linkage, "-S-"=phosphorothioate linkage, and wherein ademA-GalNAc =



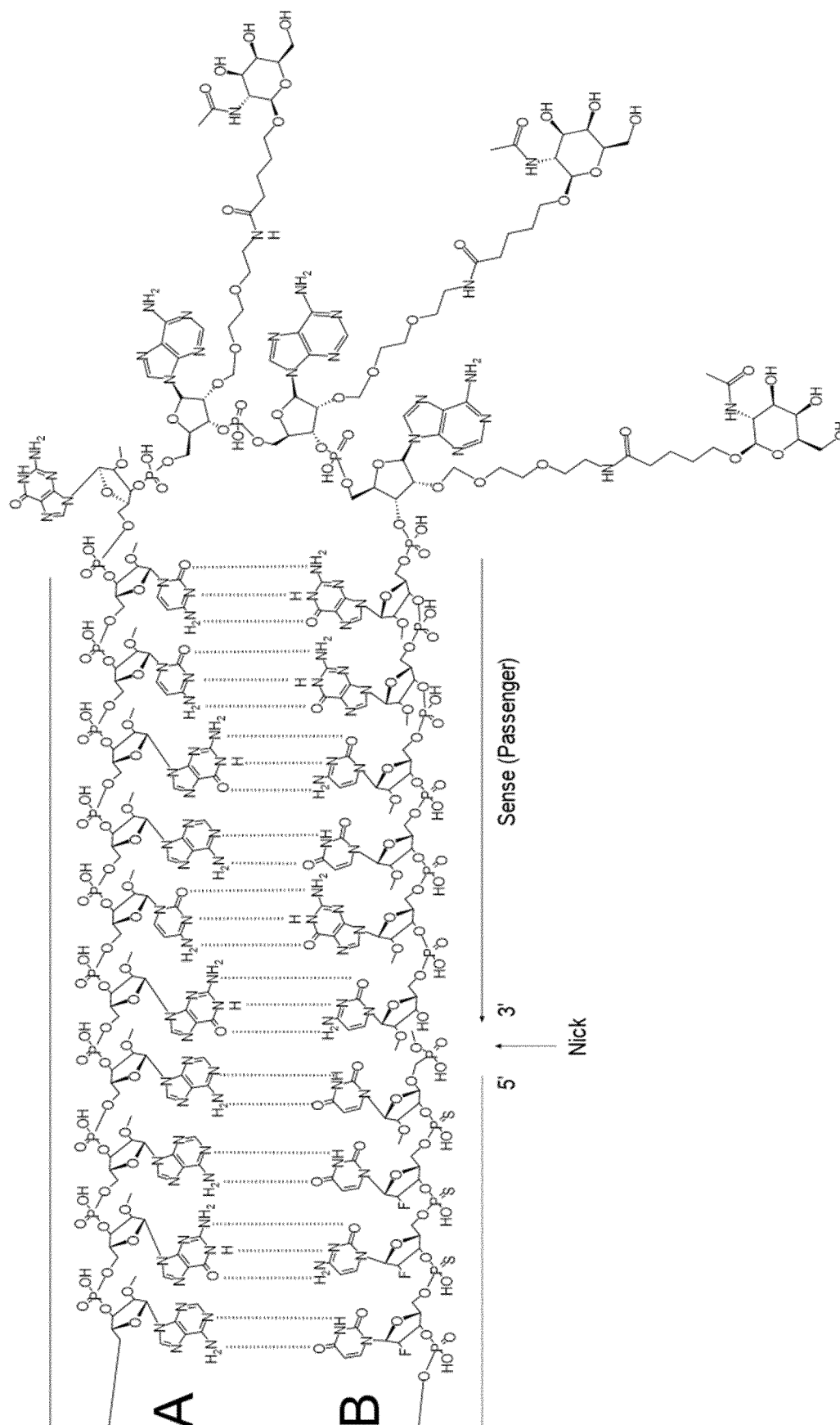
or a pharmaceutically acceptable salt thereof.

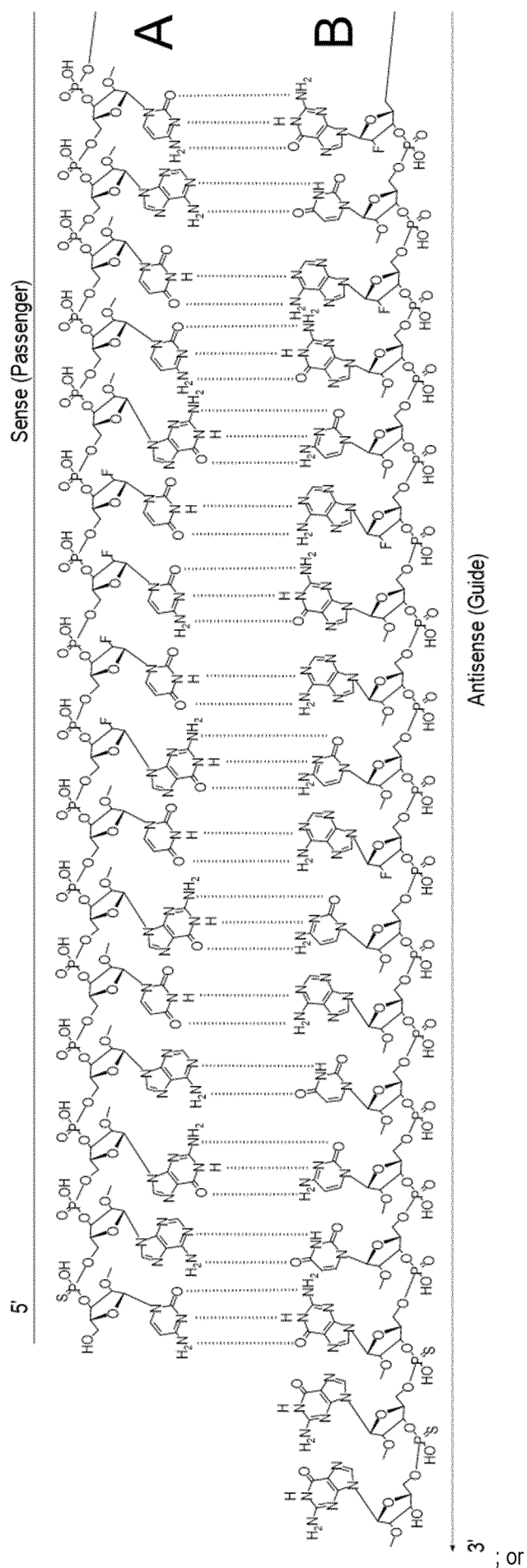
15. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of KHK, wherein said dsRNAi comprises (a) a sense strand comprising SEQ ID NO: 775 and an antisense strand comprising SEQ ID NO: 820, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein said dsRNAi is in the form of a conjugate having the structure of:



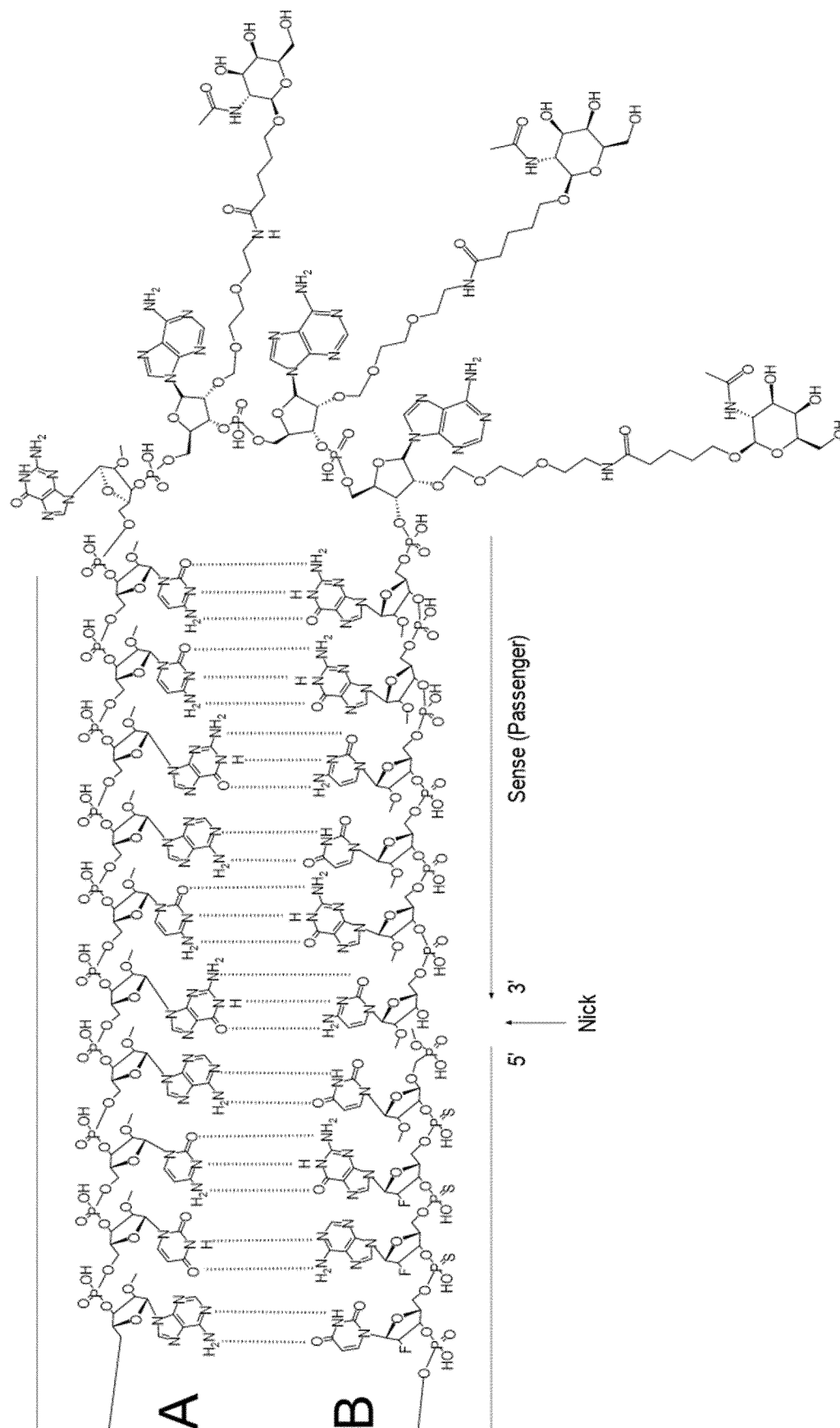


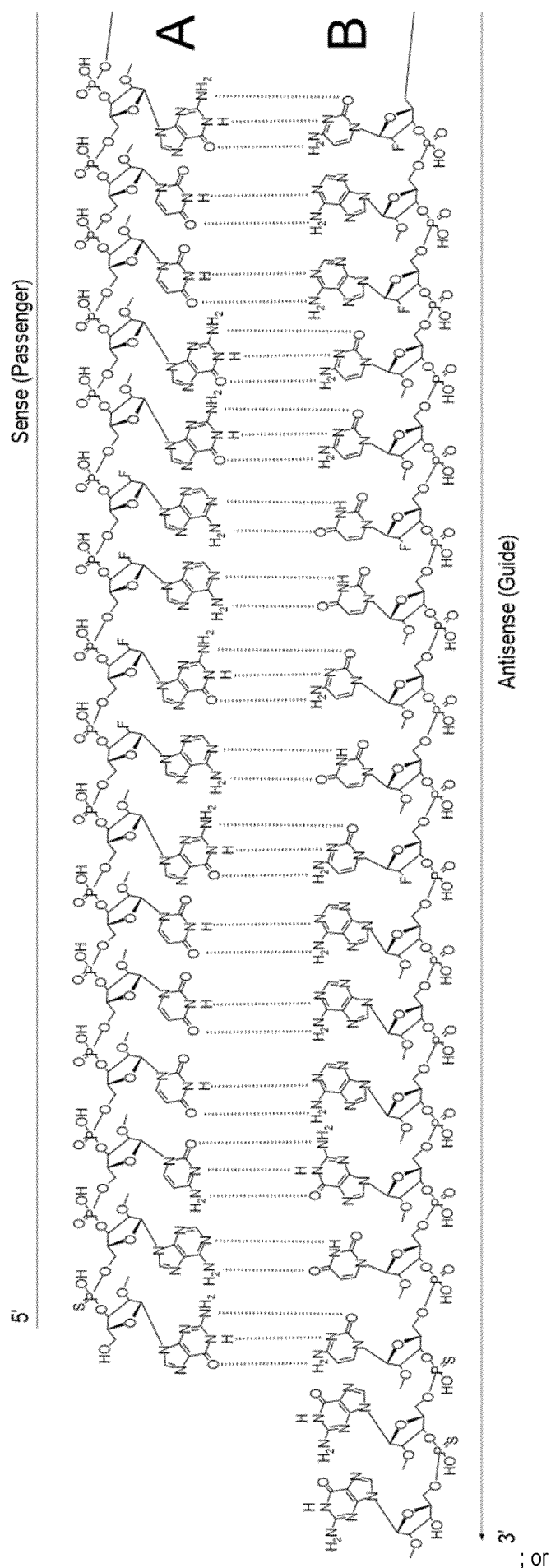
(b) a sense strand comprising SEQ ID NO: 779 and an antisense strand comprising SEQ ID NO: 824, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein said dsRNAi is in the form of a conjugate having the structure of:





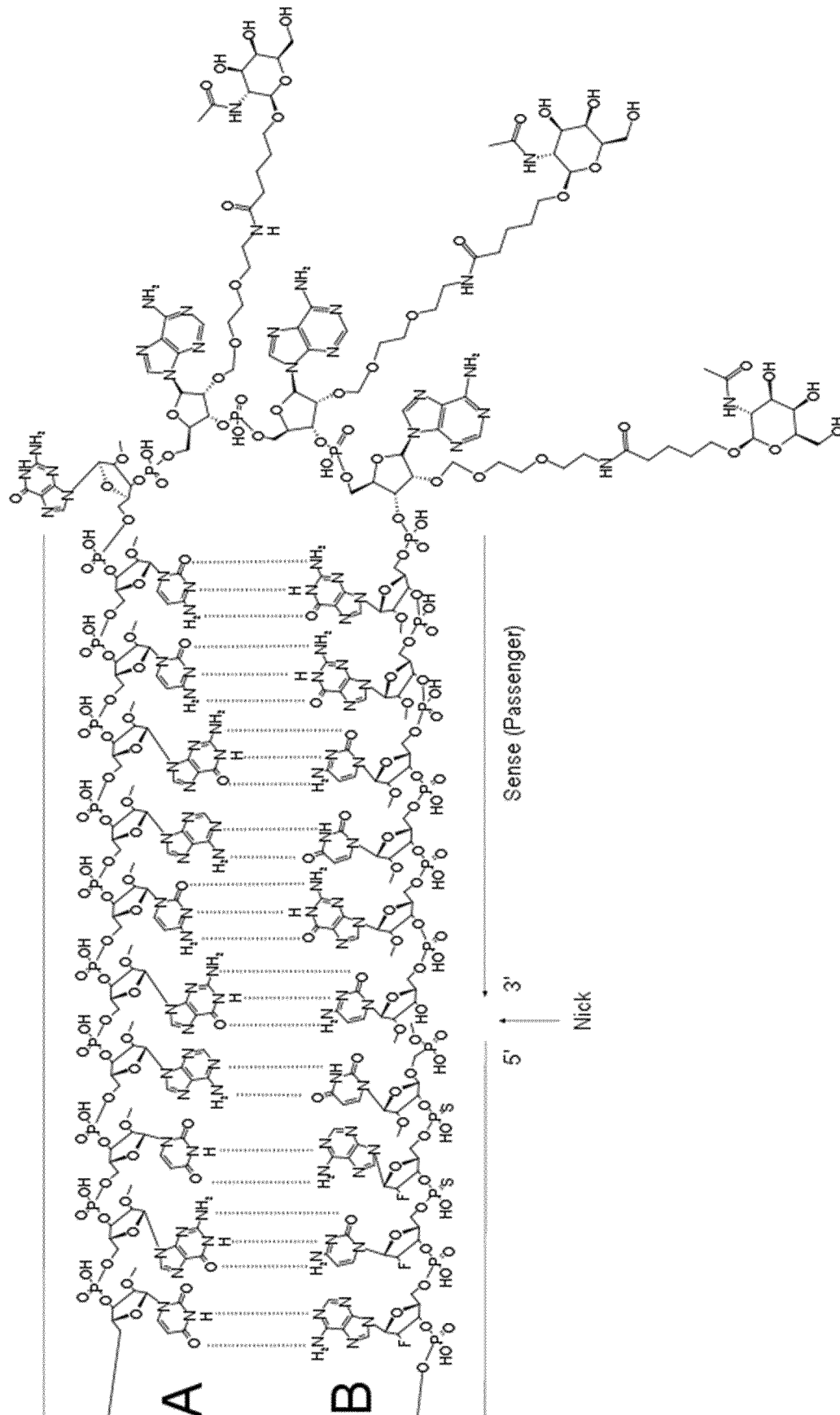
(c) a sense strand comprising SEQ ID NO: 780 and an antisense strand comprising SEQ ID NO: 825, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein said dsRNAi is in the form of a conjugate having the structure of:

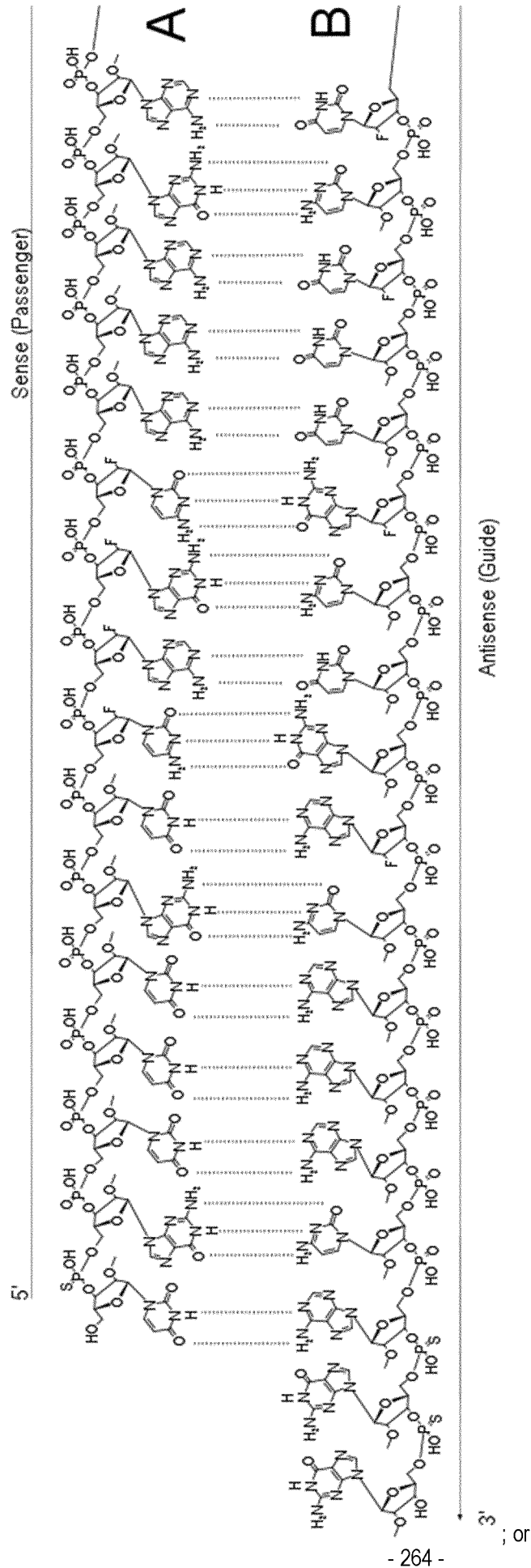




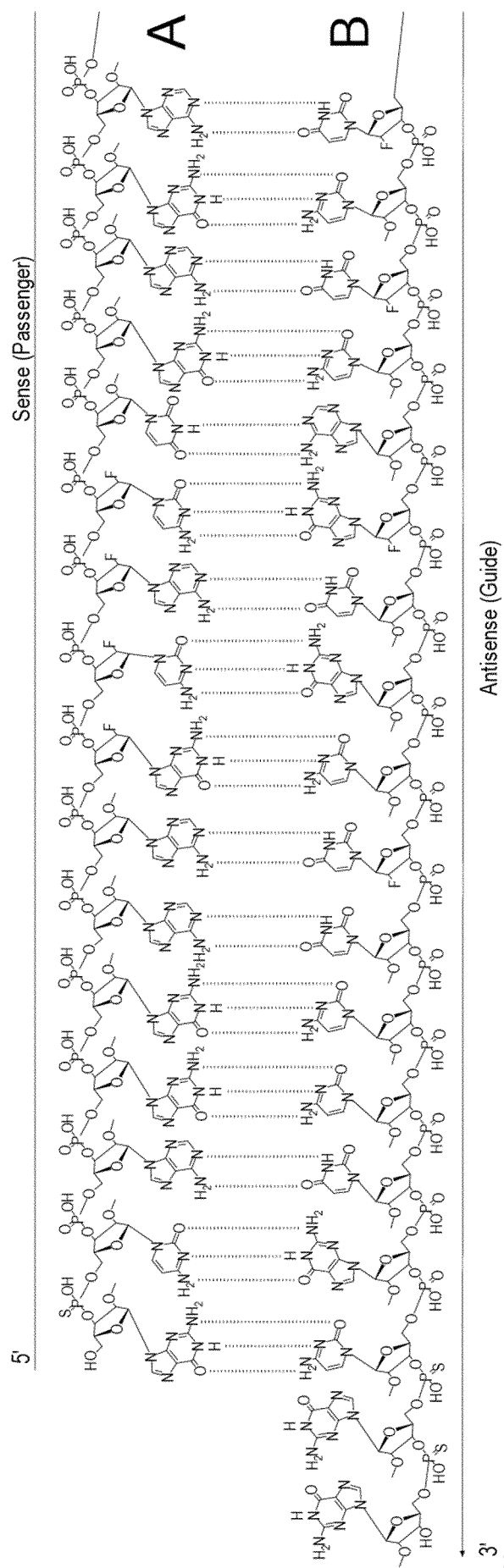
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(e) a sense strand comprising SEQ ID NO: 785 and an antisense strand comprising SEQ ID NO: 830, the antisense strand comprising a region of complementarity to a KHK RNA transcript, e.g. KHK mRNA, wherein said dsRNAi is in the form of a conjugate having the structure of:





[illegible]



or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising the dsRNAi oligonucleotide of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, delivery agent or excipient.

5

17. The RNAi oligonucleotide of any one of claims 1-15, or the pharmaceutical composition of claim 16, for use as a medicament.

18. The RNAi oligonucleotide of any one of claims 1-15, or the pharmaceutical composition of claim 16, for use in the treatment of a disease, disorder or condition associated with *KHK* expression, optionally for the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

10

19. The RNAi oligonucleotide of any one of claims 1-15, or the pharmaceutical composition of claim 16, for use according to claim 18, wherein the RNAi oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.

15

20. A method for reducing *KHK* expression in a cell, a population of cells or a subject, the method comprising the step of:

- i. contacting the cell or the population of cells with the RNAi oligonucleotide, or a pharmaceutically acceptable salt thereof, of any one of claims 1-16, or the pharmaceutical composition of claim 17; or
- ii. administering to the subject the RNAi oligonucleotide, or a pharmaceutically acceptable salt thereof of any one of claims 1-16, or the pharmaceutical composition of claim 17.

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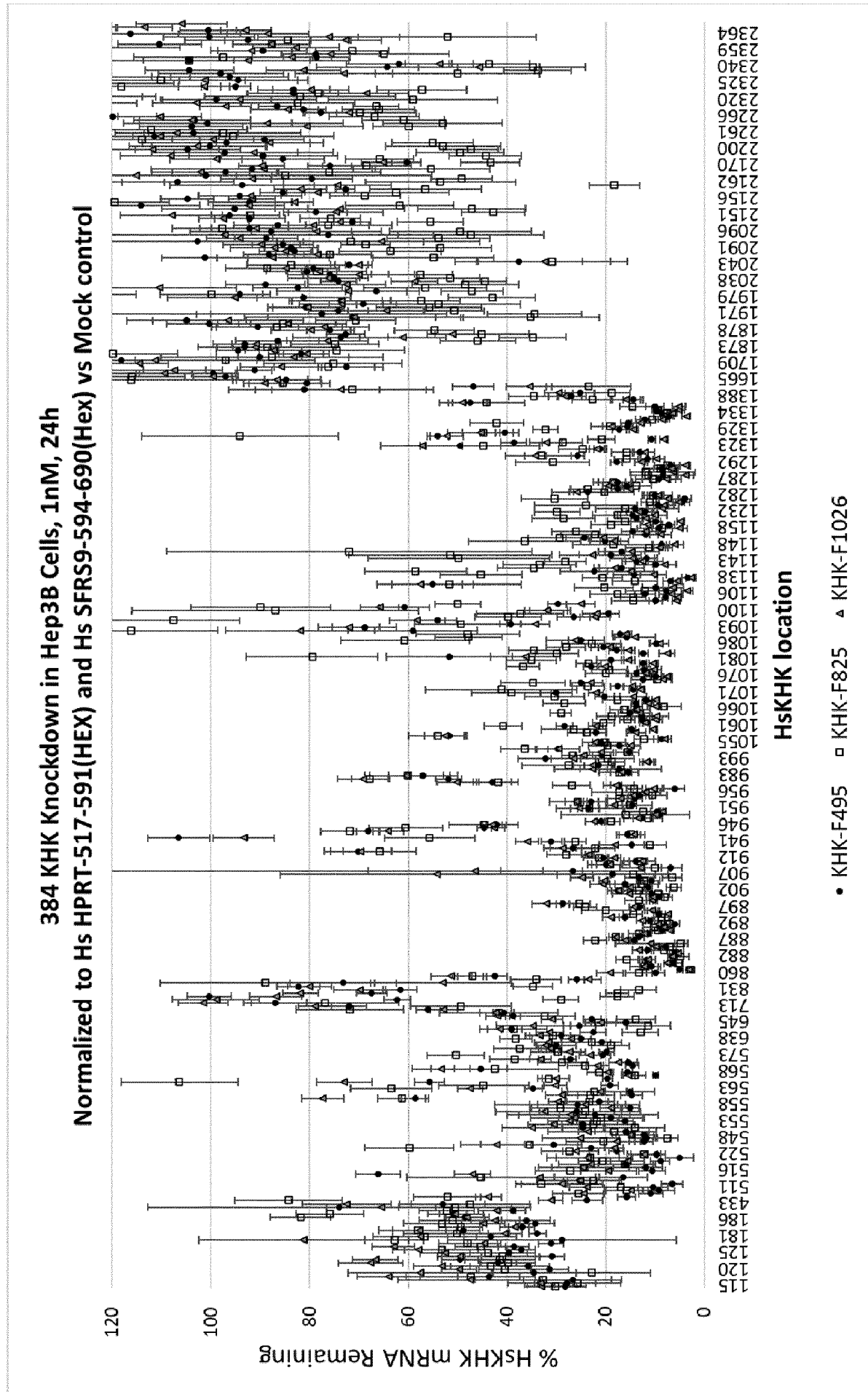
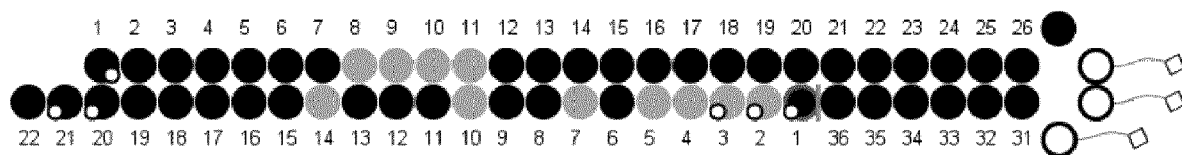
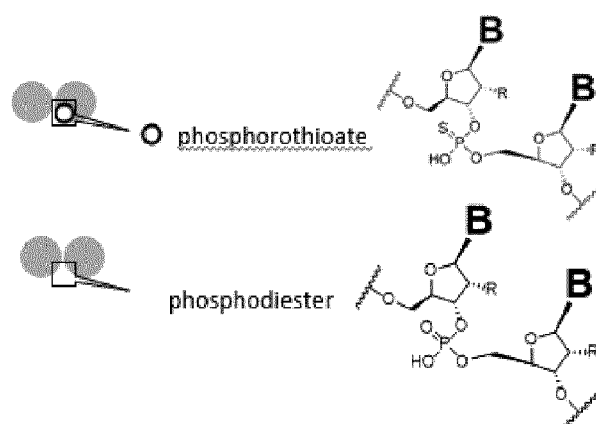


FIG. 1



Low-2'-Fluoro (3PS)

- 2'-OMe
 ● 2'-F
 ○ GalNAc conjugated nucleotide
 1 2 Numeric labels: nucleotide positions from 5'-end to 3'-end for each strand
 | tetraloop nick
 ○ phosphorothioate linkage
 ● MePhosphonate-4O-mX



B = any nucleobase

FIG. 2A

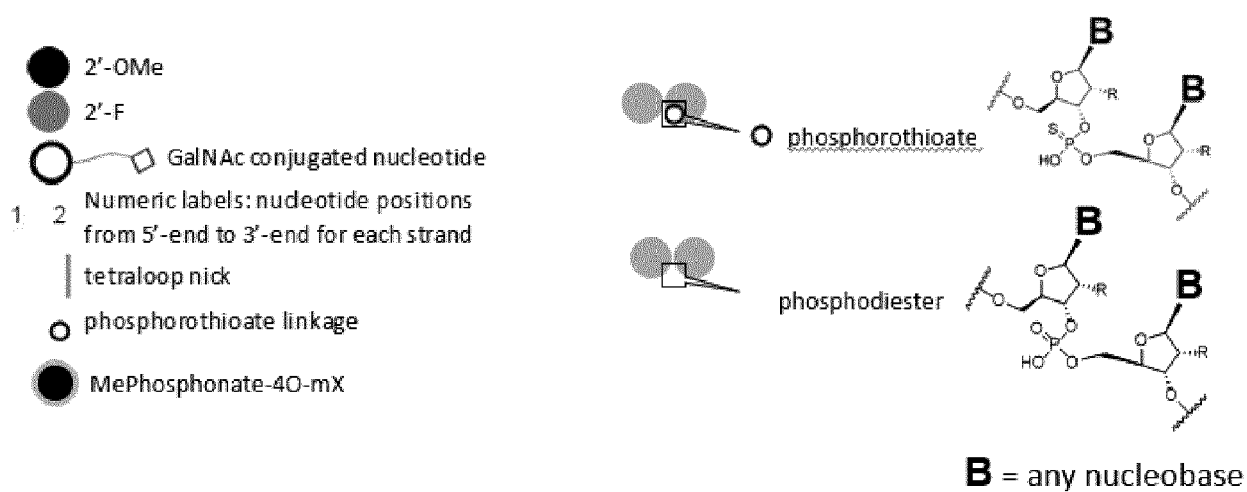
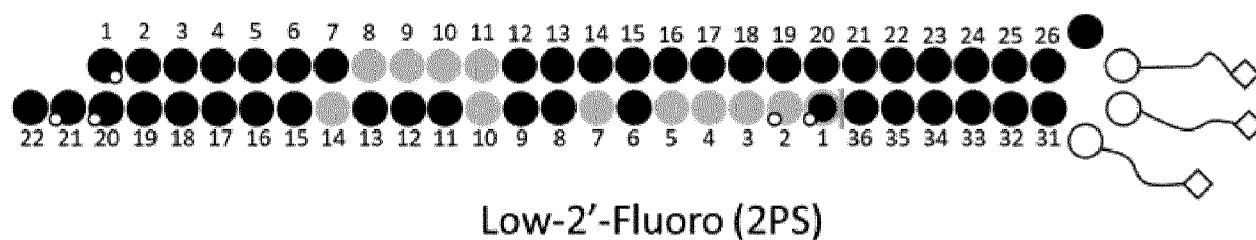


FIG. 2B

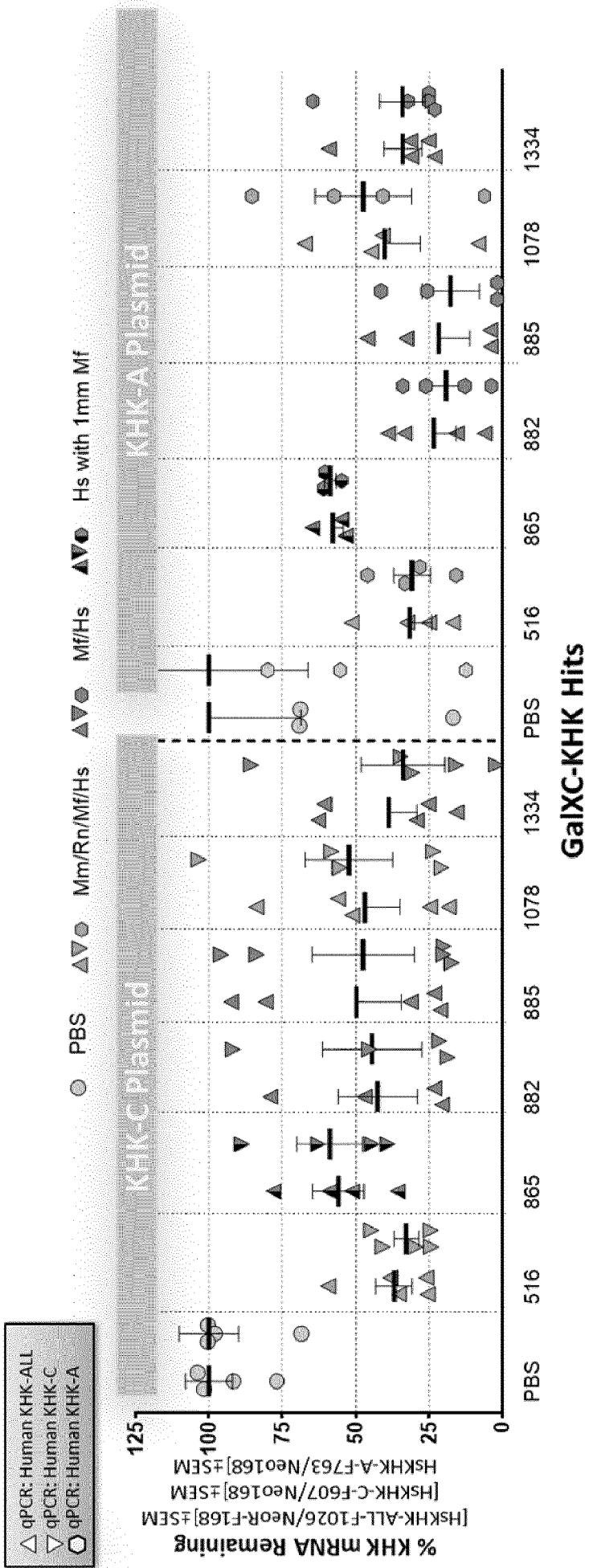


FIG. 3

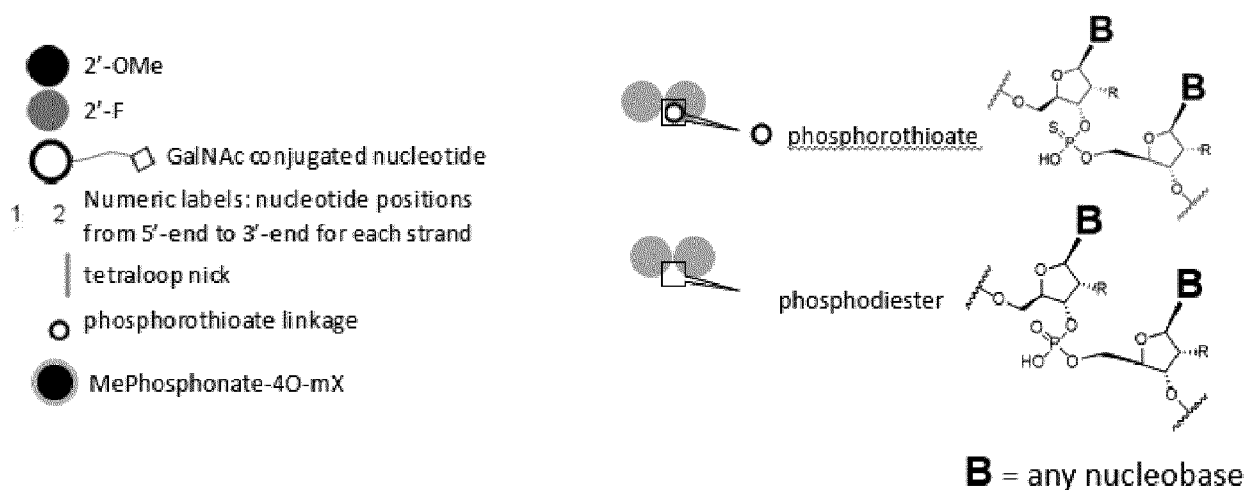
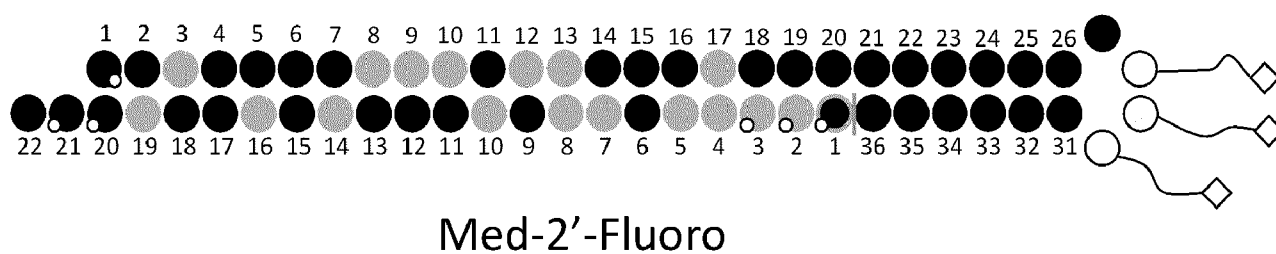
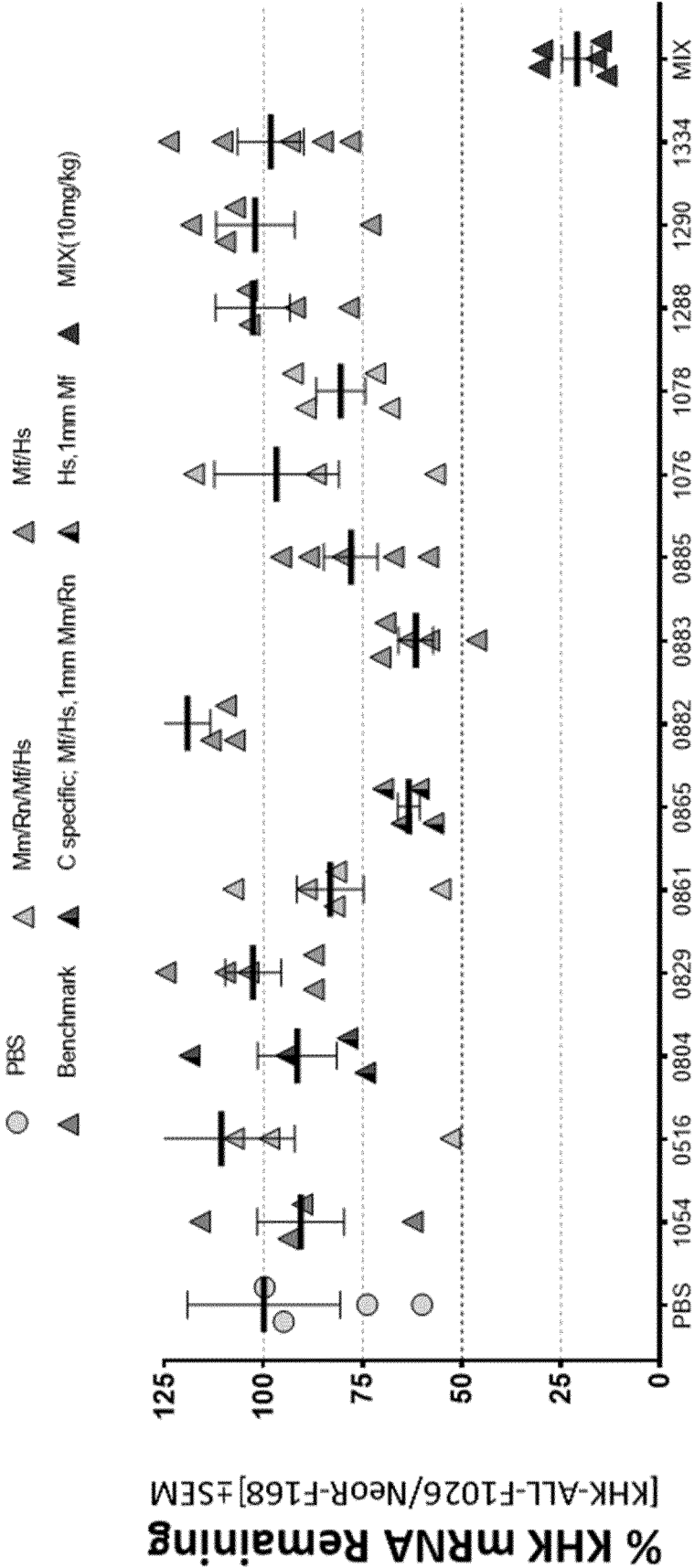


FIG. 4A

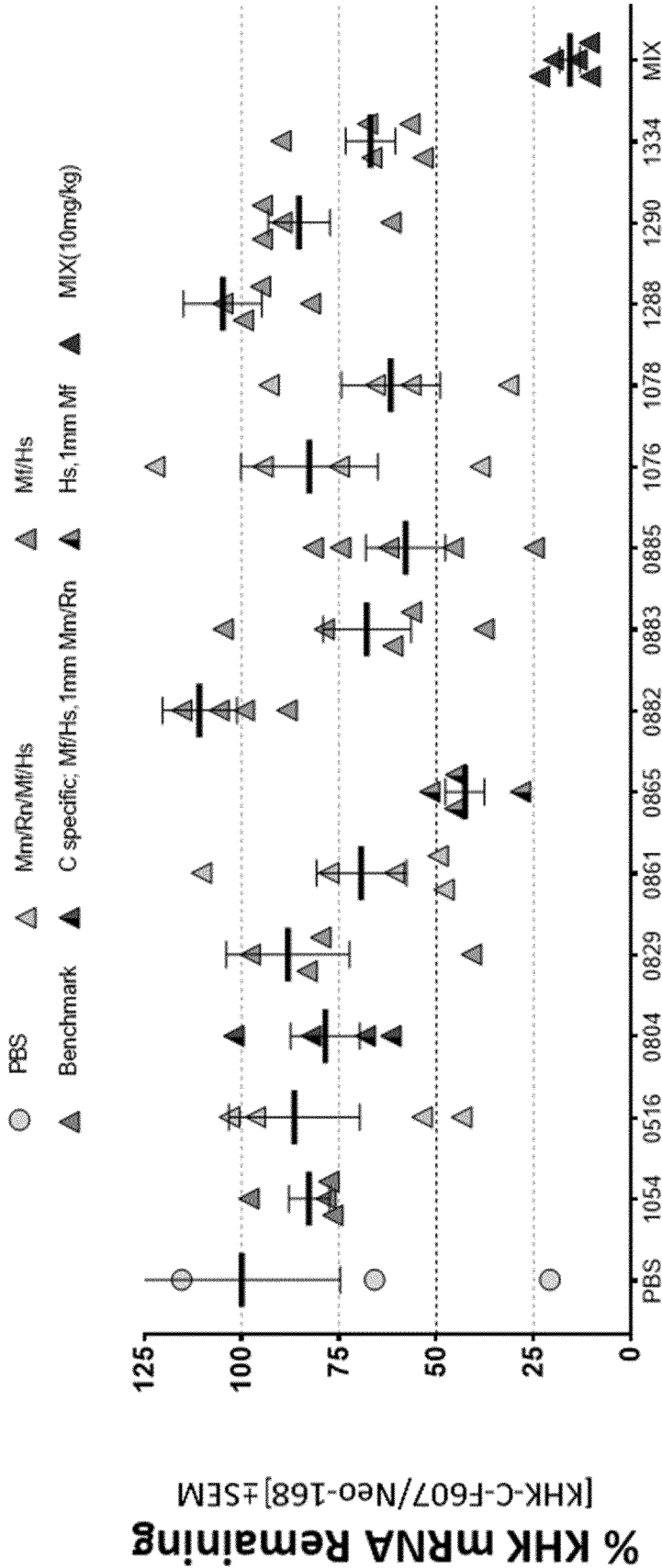
Human KHK-All



GalXC-KHK Hits

FIG. 4B

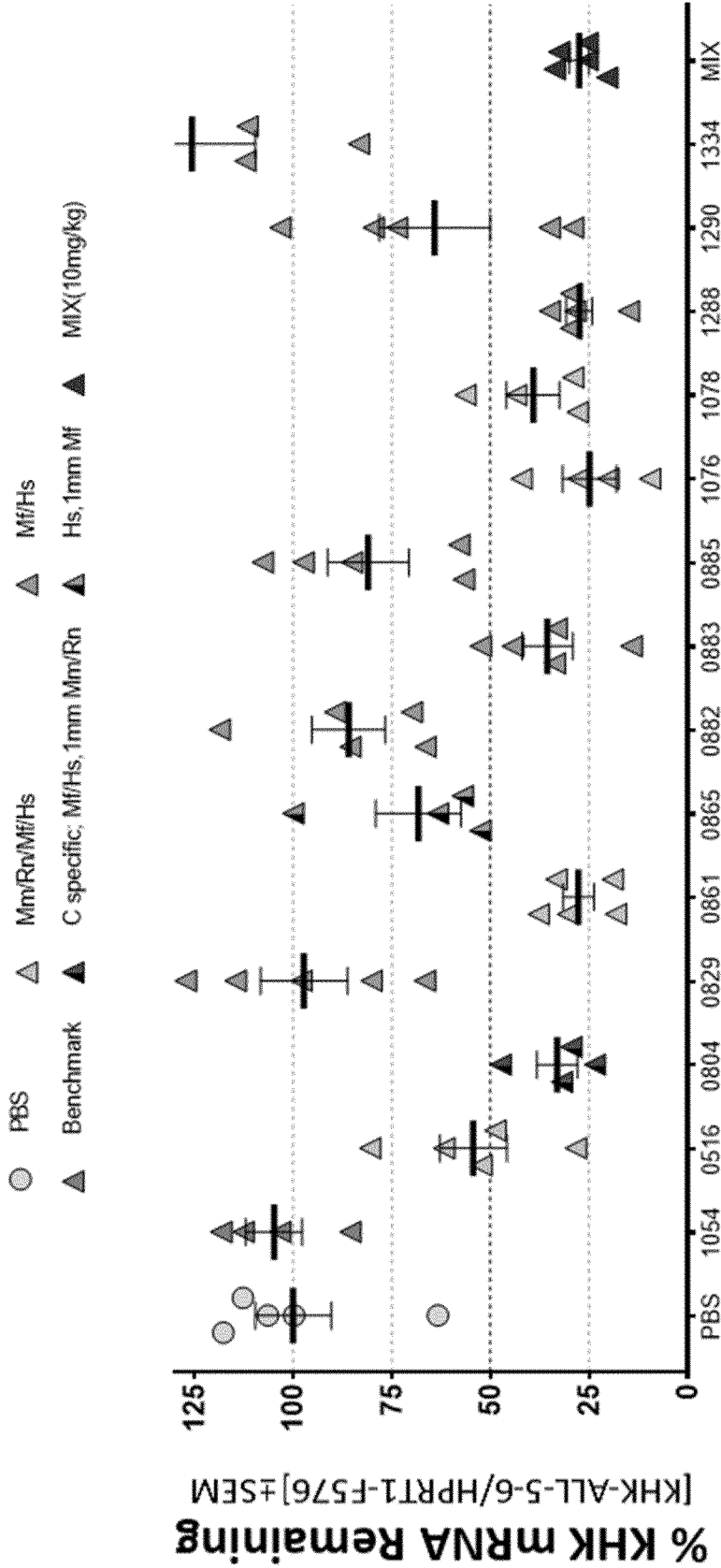
Human KHK-C



GalXC-KHK Hits

FIG. 4C

Mouse KHK



GalXC-KHK Hits

FIG. 4D

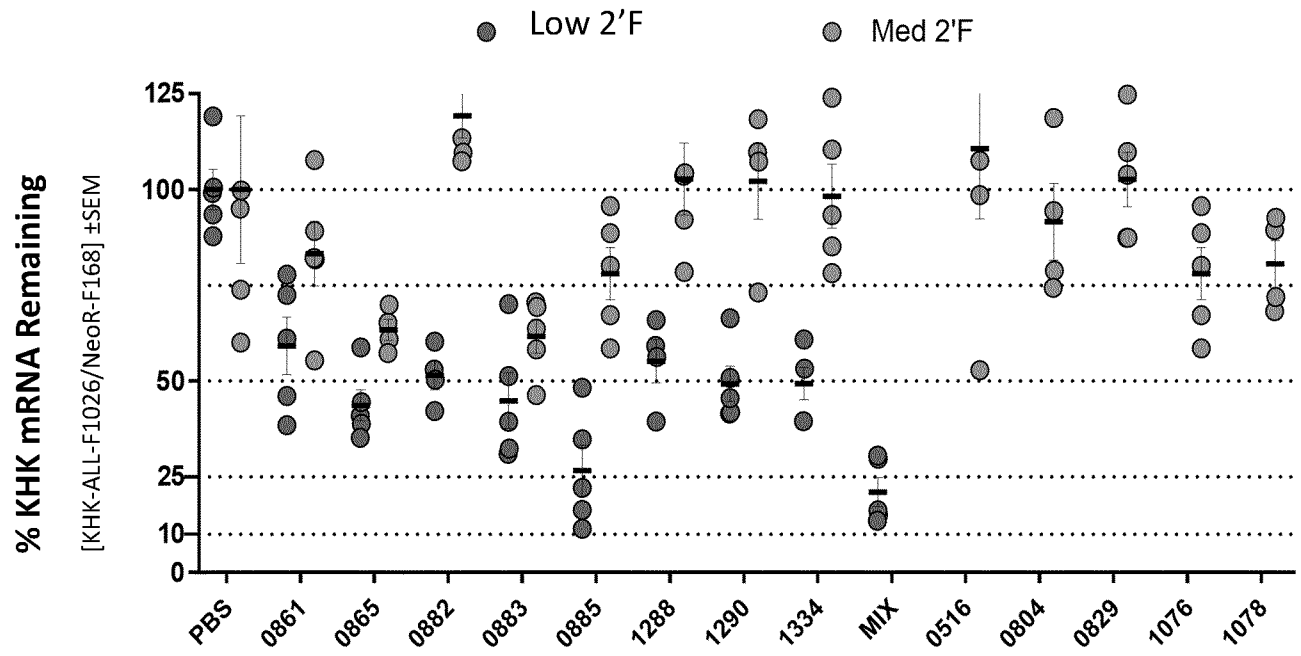
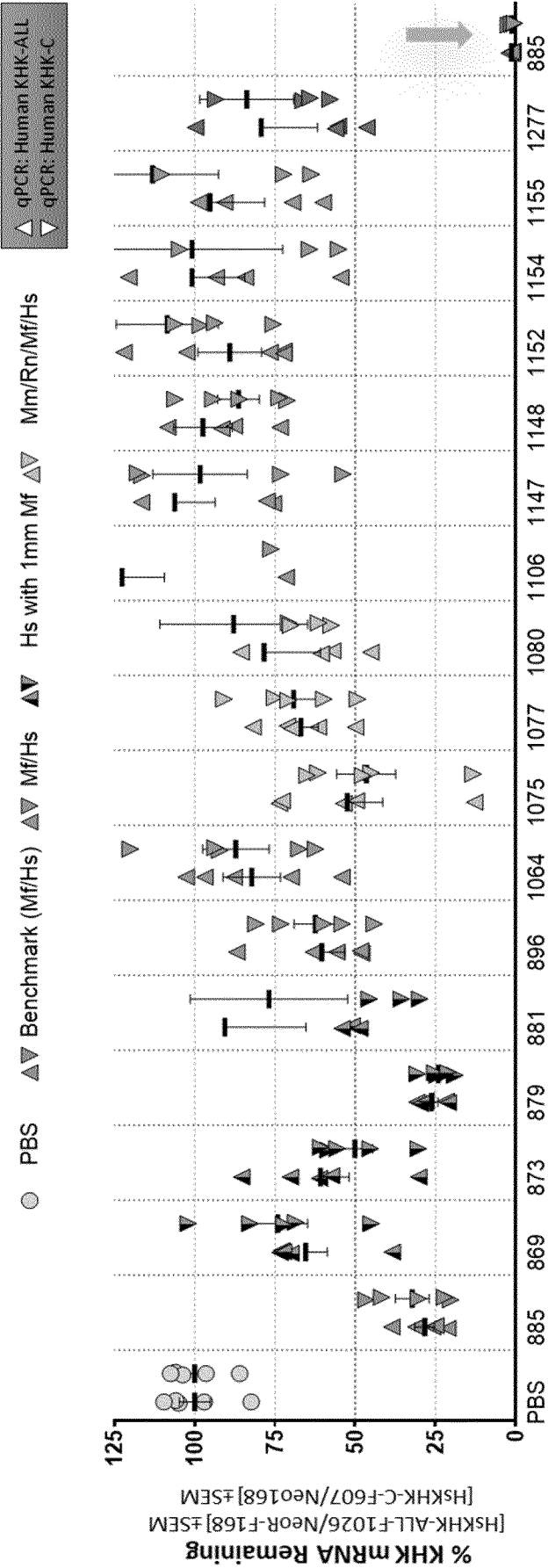
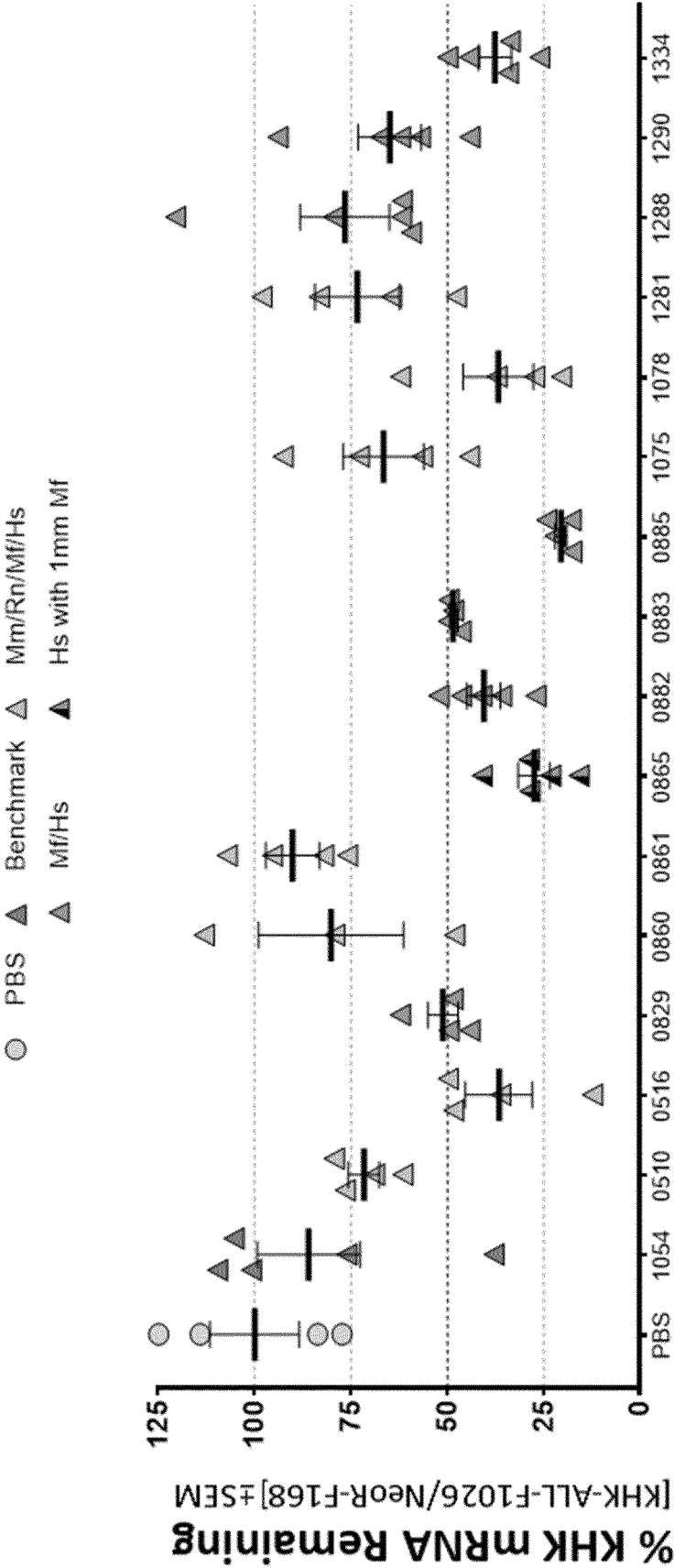


FIG. 4E



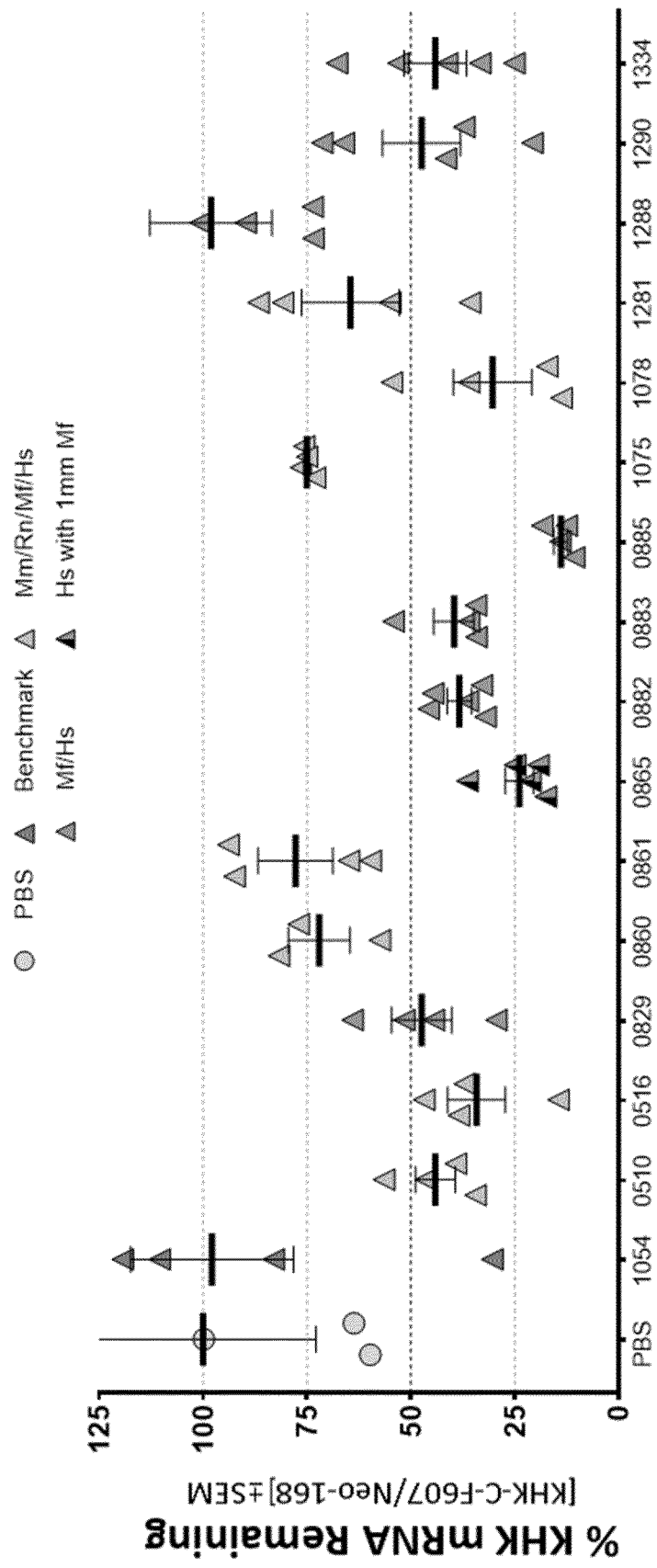
GalXC-KHK Hits

FIG. 5



GalXC-KHK Hits

FIG. 6A



GalXC-KHK Hits

FIG. 6B

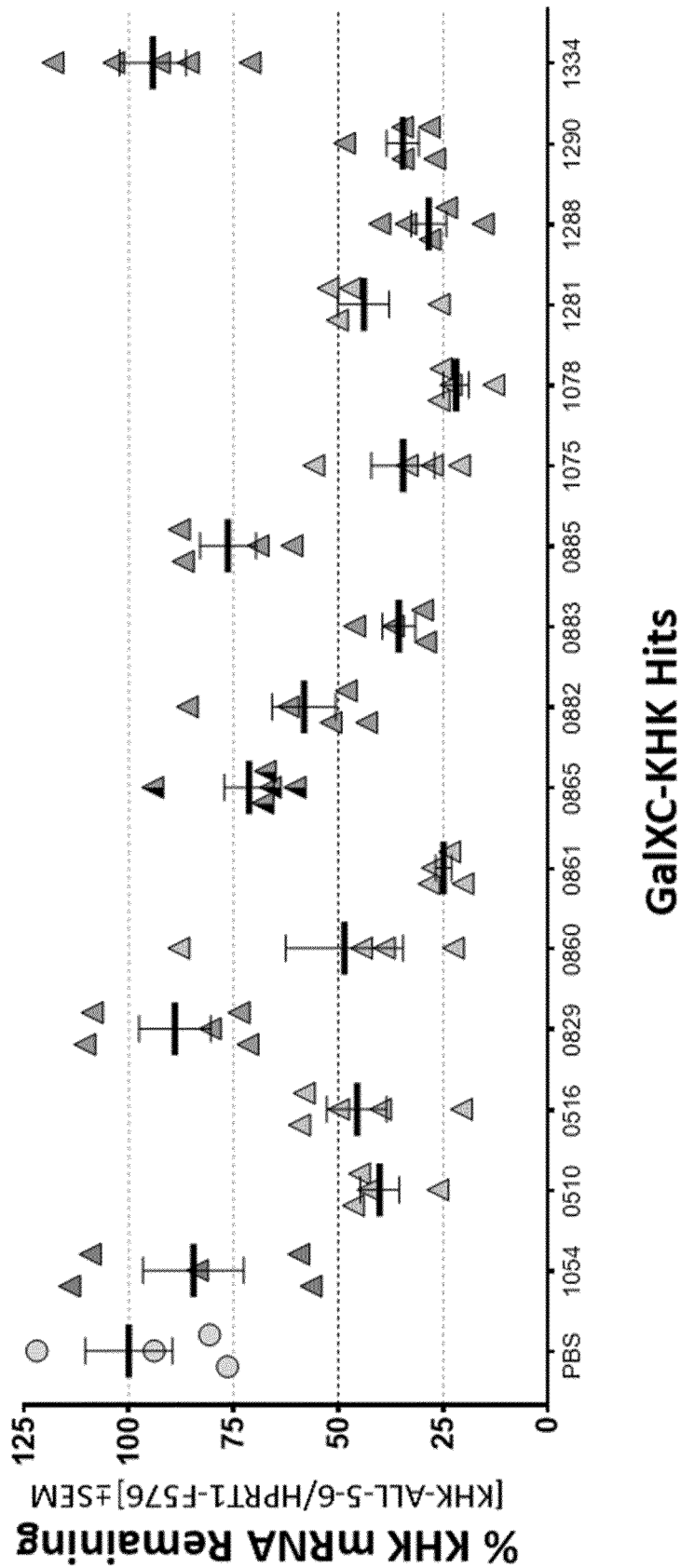


FIG. 6C

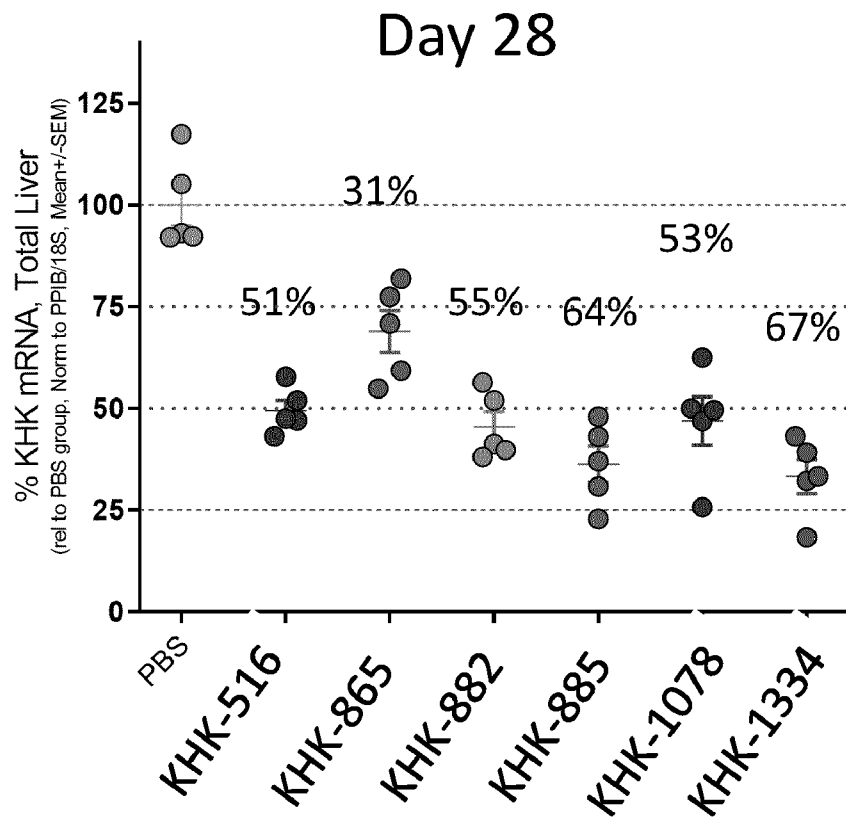


FIG. 7A

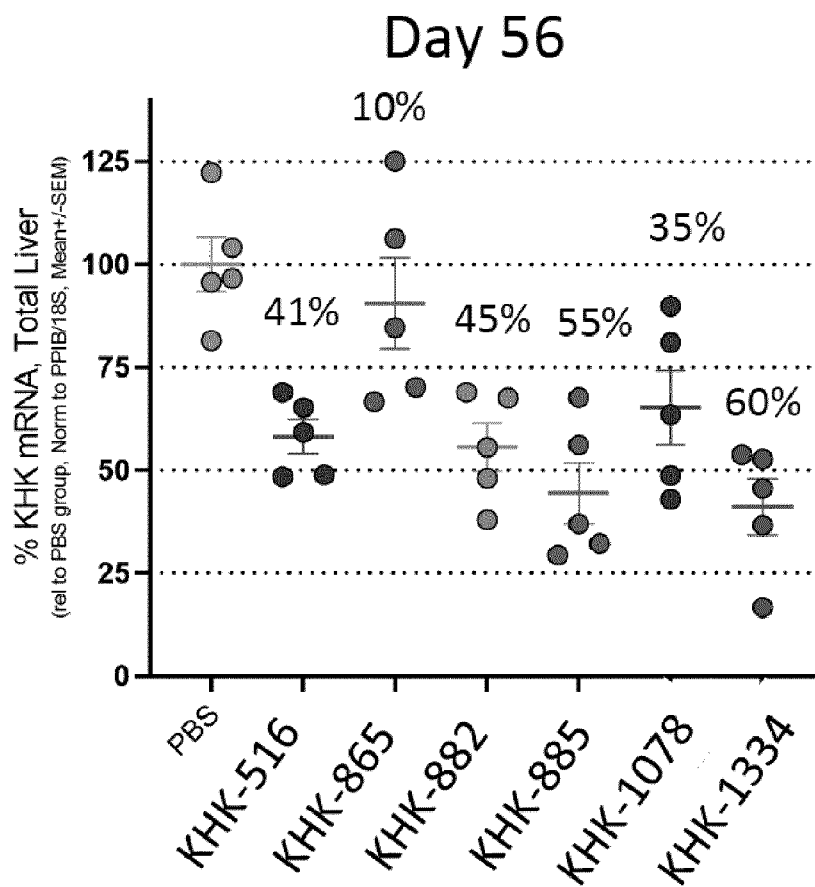


FIG. 7B

Day 84

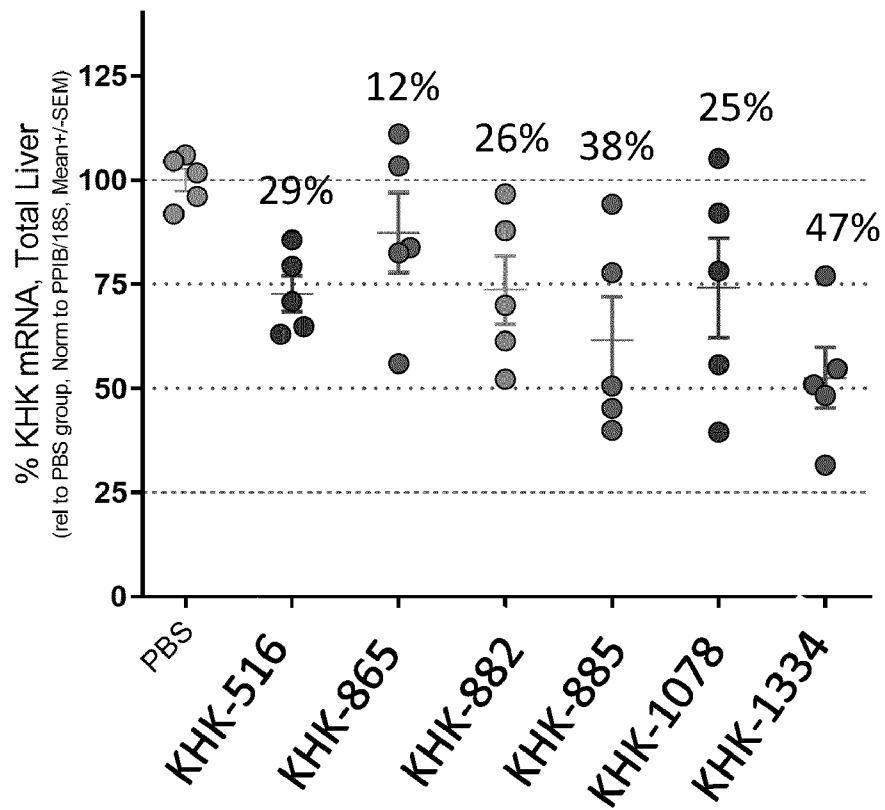


FIG. 7C

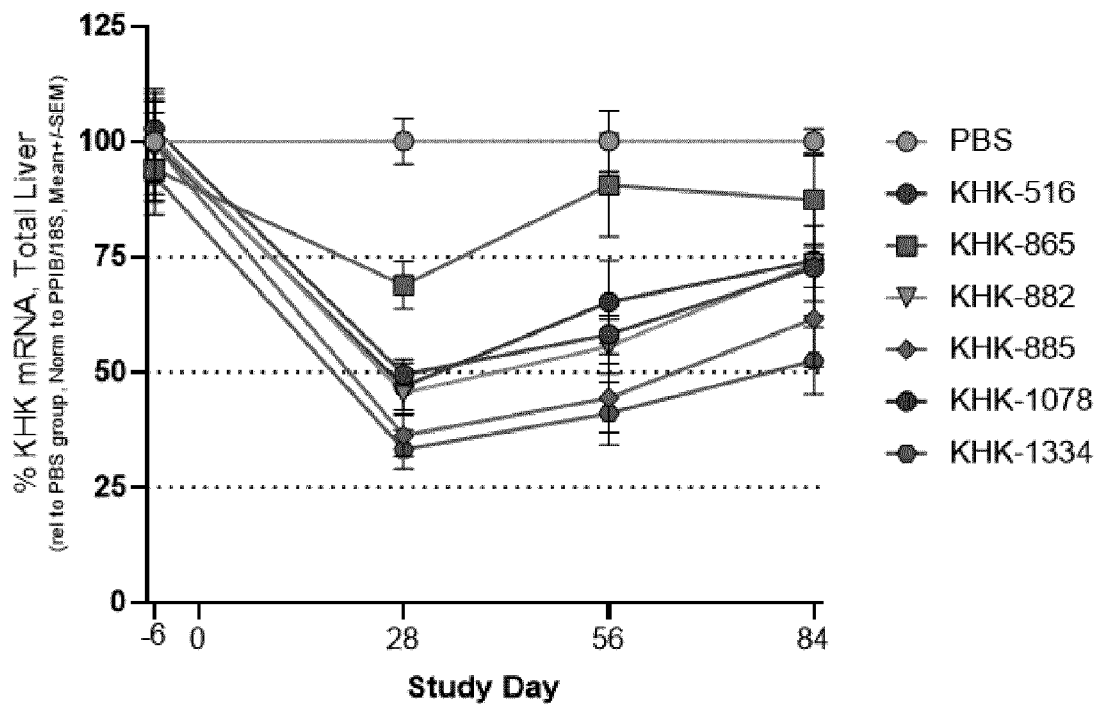


FIG. 7D

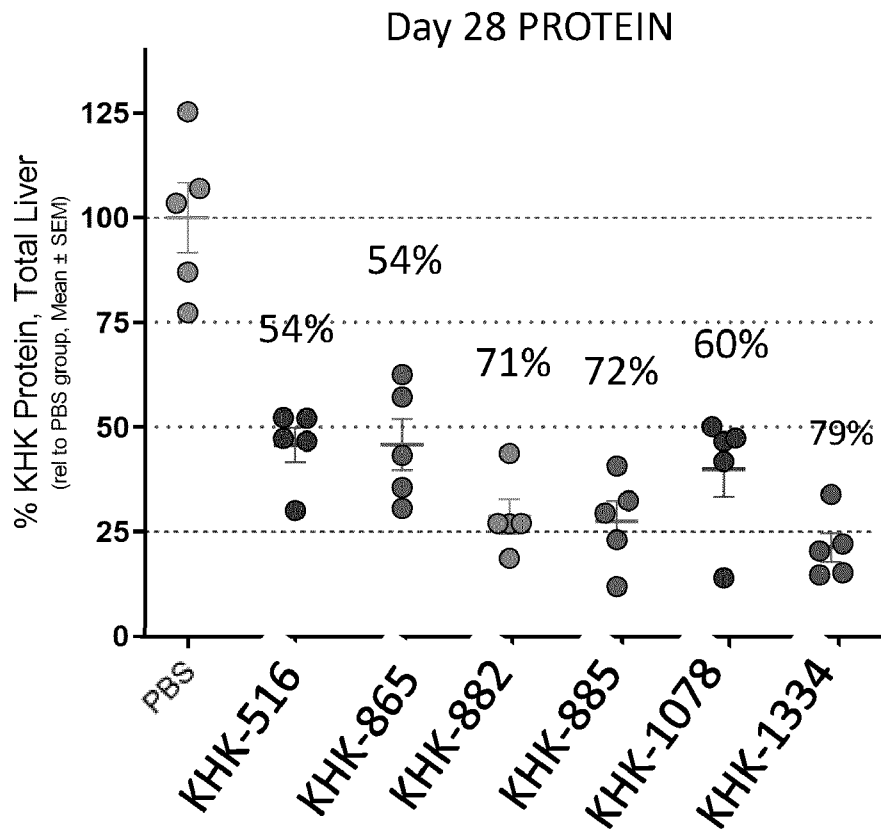


FIG. 8A

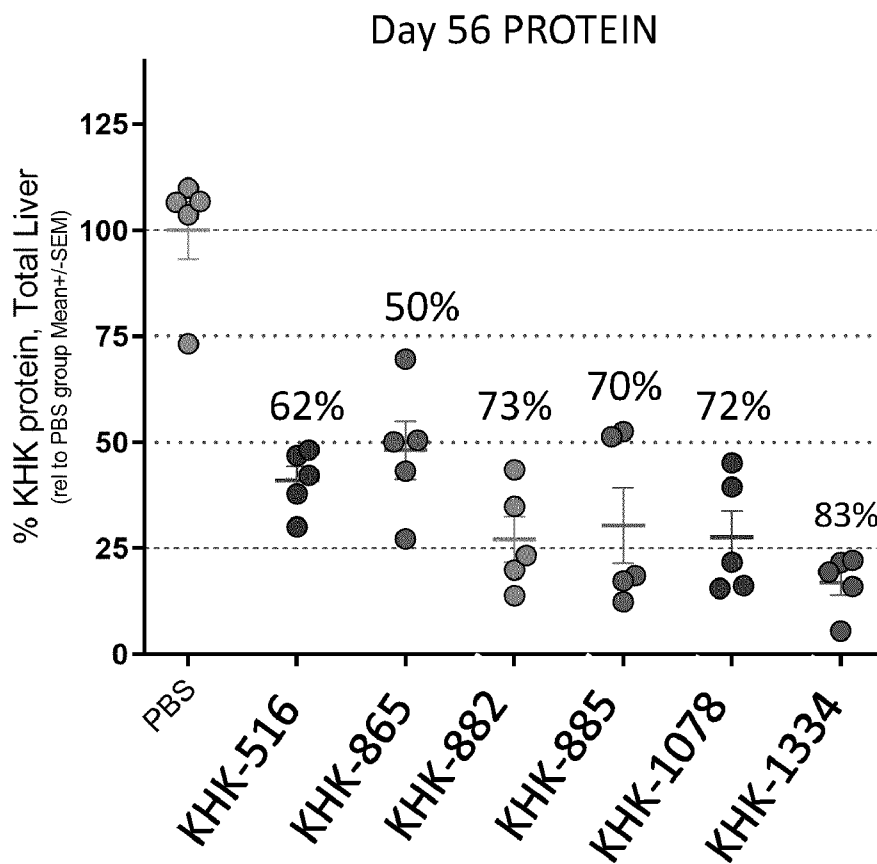


FIG. 8B

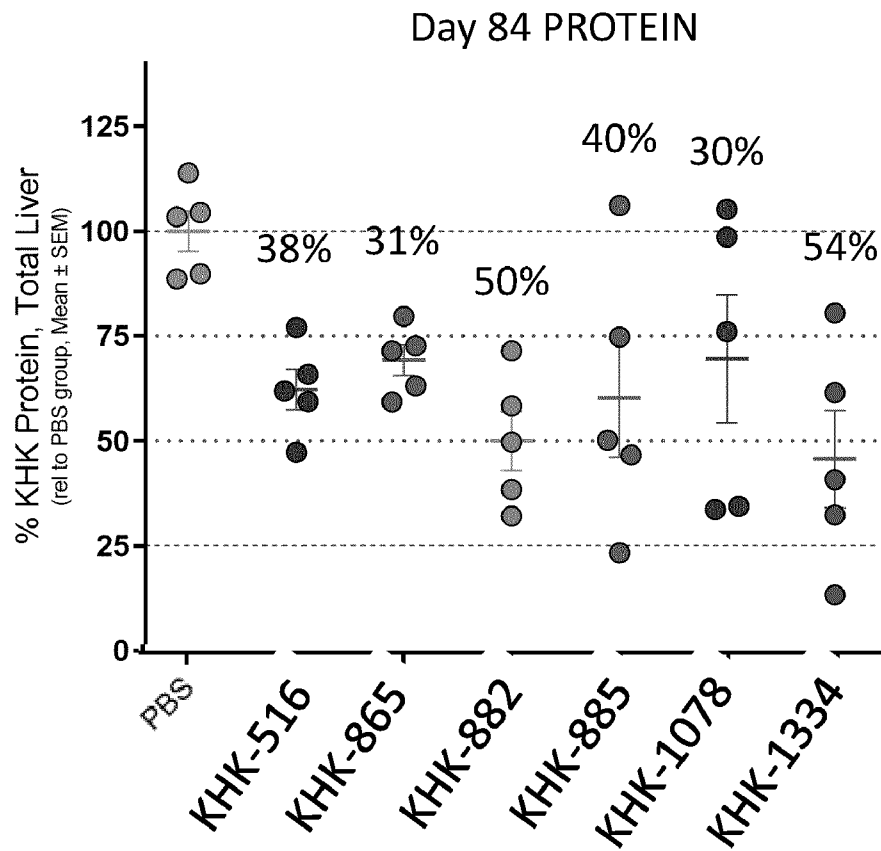


FIG. 8C

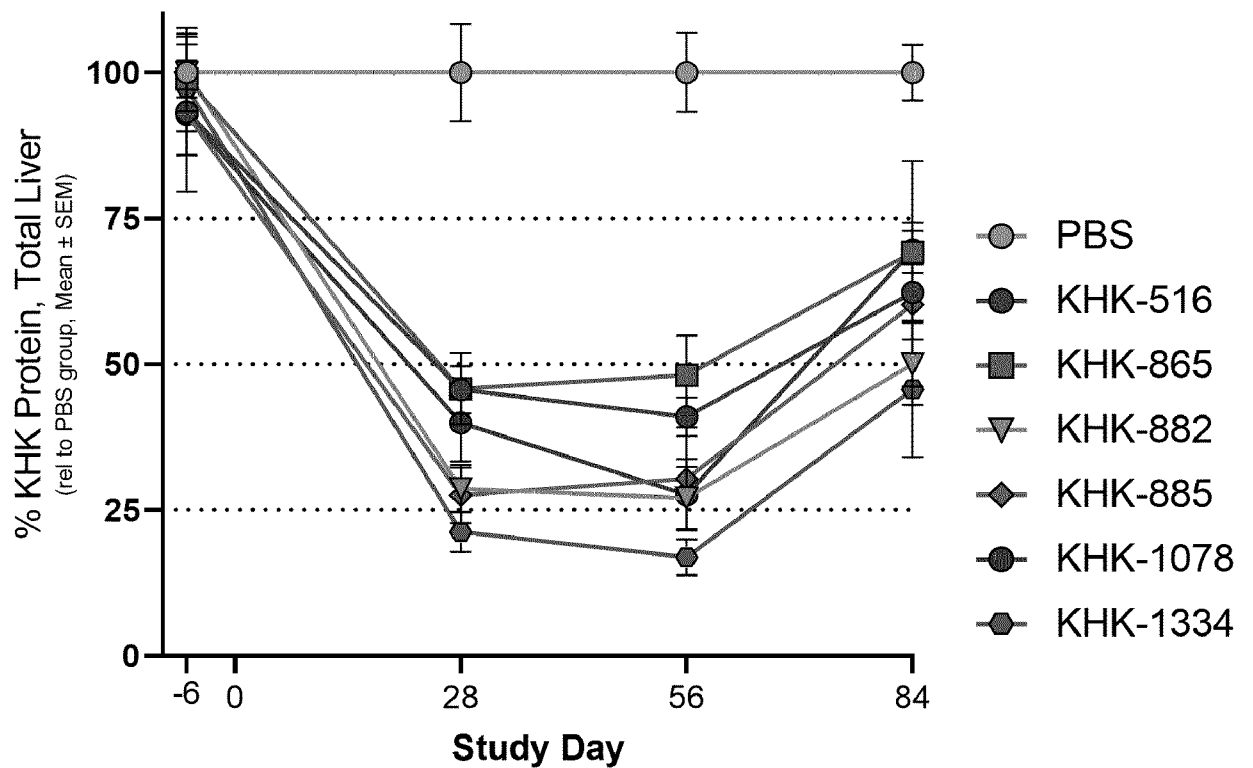


FIG. 8D

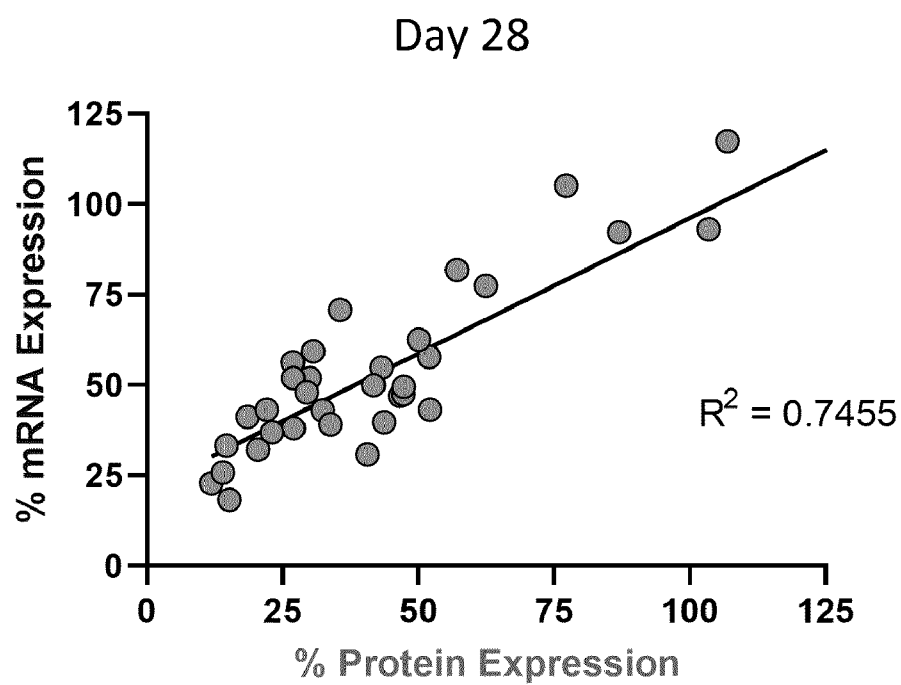


FIG. 9A

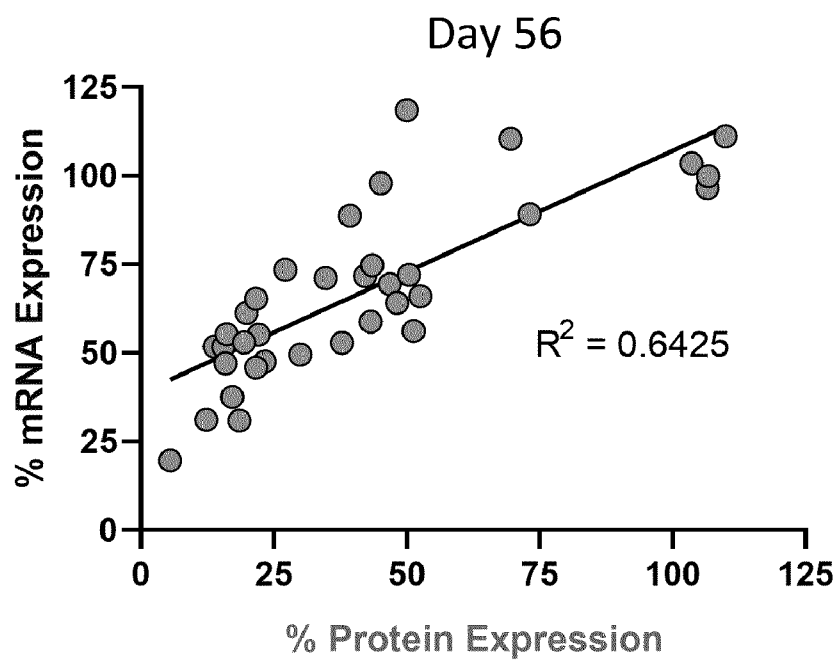


FIG. 9B

Day 84

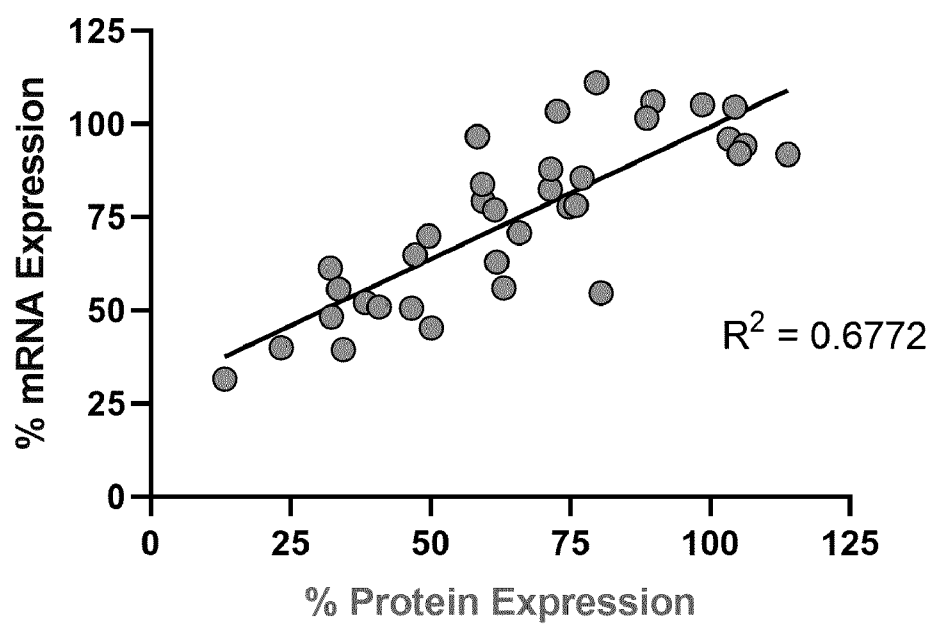


FIG. 9C