

OLIGONUCLEOTIDES TARGETING SAMHD1**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. Provisional Application No. 63/609,644, filed December 13, 2023, the content of which is herein incorporated by reference in its entirety.

BACKGROUND

[0002] dNTPs are essential in order to replicate the mitochondrial DNA (mtDNA) to maintain the mitochondrial genome. The mitochondrial genome encodes the various subunits of the electron transport chain (see, *e.g.*, Shokolenko, I.N., et al., *Annu. Rev. Biochem.*, 85, 133-160, 2016). Specifically, transcription of the mitochondrial genome is necessary for the expression of 13 subunits of the oxidative phosphorylation (OXPHOS) system, as well as two rRNAs and 22 tRNAs (see, *e.g.*, Shokolenko, I.N., et al., *Frontiers in Bioscience, Landmark*, 22, 835-853, 2017). Thus, having sufficient pools of dNTPs available in a cell is essential for biogenesis of the OXPHOS system, resulting in ATP production. This, in turn, is vital for energy homeostasis in the cell.

[0003] The sterile alpha motif (SAM) domain and histidine-aspartate (HD) domain-containing protein 1, ("SAMHD1") is a negative regulator of dNTP pools. When active, dNTP triphosphohydrolase activity of SAMHD1 degrades dNTPs into their 2'-deoxynucleoside (dN) and triphosphate subparts, steadily depleting intracellular dNTP pools.

[0004] Dysregulation of dNTP pools and the mitochondrial genome has been implicated in various mitochondrial diseases, including mitochondrial (mt) DNA depletion syndromes (MDS) and mitochondrial DNA maintenance defects (MDMDs). Accordingly, there exists a need to develop therapeutics that stabilize and increase dNTP pools and promote energy homeostasis.

SUMMARY

[0005] The present disclosure is based, at least in part, on the insight that dysregulation of dNTP pools has been implicated in various disease states including metabolic disease, such as mitochondrial (mt) DNA depletion syndromes (MDS) and/or mitochondrial DNA maintenance defects (MDMDs), and the protein SAMHD1 is a regulator of dNTP pools in mammalian cells. The present disclosure provides, among other things, the recognition that oligonucleotides that

inhibit SAMHD1 expression and/or activity are particularly beneficial to increase dNTP pools and downstream mtDNA levels in a subject, a cell, and/or a biological sample obtained from a subject.

[0006] The present disclosure provides, in one aspect, an oligonucleotide comprising a sequence that is substantially complementary to 8 to 30 contiguous nucleotides of a SAMHD1 RNA transcript. In some embodiments, the oligonucleotide comprises a sequence that is at least 85%, at least 90%, or at least 95% complementary to 8 to 30 contiguous nucleotides of a SAMHD1 RNA transcript. In some embodiments, the oligonucleotide comprises a sequence that is perfectly complementary to 8 to 30 contiguous nucleotides of a SAMHD1 RNA transcript. In some embodiments, the 8 to 30 contiguous nucleotides is 15 to 25 contiguous nucleotides. In some embodiments, the oligonucleotide is 8 to 30 nucleotides in length. In some embodiments, the oligonucleotide is 18 to 22 nucleotides in length. In some embodiments, the oligonucleotide is 14 to 18 nucleotides in length. In some embodiments, the oligonucleotide is 20 nucleotides in length. In some embodiments, the oligonucleotide is 16 nucleotides in length.

[0007] In some embodiments, the SAMHD1 RNA transcript is a human SAMHD1 RNA transcript. In some embodiments, the human SAMHD1 RNA transcript comprises SEQ ID NO: 131.

[0008] In some embodiments, the 8 to 30 contiguous nucleotides of the SAMHD1 RNA transcript is within or includes an exon region of the SAMHD1 RNA transcript. In some embodiments, the 8 to 30 contiguous nucleotides comprises a sequence that corresponds to nucleotides 21722-21741, 21744-21763, 21749-21768, 21750-21769, 21780-21799, 21786-21805, 29605-29624, 44308-44327, 44309-44328, 44310-44329, 44311-44330, 44555-44574, 44584-44603, 44714-44733, 44715-44734, 44936-44955, 44937-44956, 44938-44957, 45297-45316, 45298-45317, 45299-45318, 45300-45319, 45301-45320, 45302-45321, 45303-45322, 45306-45325, 45307-45326, 45308-45327, 45309-45328, 45310-45329, 45311-45330, 58885-58904, 58933-58952, 58934-58953, 58935-58954, 58936-58955, 58983-59002, 58984-59003, 59011-59022 and 63778-63785, 59012-59022 and 63778-63786, 59013-59022 and 63778-63787, 63816-63835, 64243-64262, 64244-64263, 64245-64264, 64247-64266, 64248-64267, 64249-64268, 64616-64635, 64617-64636, 64618-64637, 64885-64904, 65149-65168, 65337-

65356, 65338-65357, 65343-65362, 65443-65462, 65445-65464, 65446-65465, 65451-65470, 65453-65472, 65454-65473, 65455-65474, 65742-65761, 44298-44317, 40026-40045, 44297-44316, 44305-44324, 44312-44331, 44295-44314, 40025-40044, 44296-44315, 44307-44326, 44299-44318, 44306-44325, 44300-44319, 44302-44321, 44304-44323, 44301-44320, 44303-44322, or 40024-40043 of SEQ ID NO: 1. In some embodiments, the 8 to 30 contiguous nucleotides corresponds to nucleotides 44295-44314, 44296-44315, 44297-44316, 44298-44317, 44299-44318, 44300-44319, 44301-44320, 44302-44321, 44303-44322, 44304-44323, 44305-44324, 44306-44325, 44307-44326, 44308-44327, 44309-44328, 44310-44329, 44311-44330, 44312-44331, 44302-44317, 40030-40045, 44301-44316, 44309-44324, 44316-44331, 44299-44314, 40029-40044, 40026-40041, 26048-26063, 44295-44310, 44300-44315, 333-348, 44311-44326, 44303-44318, 63796-63811, 44310-44325, 26049-26064, 44312-44327, 44304-44319, 44297-44312, 44306-44321, 44308-44323, 44315-44330, 40027-40042, 44296-44311, 44313-44328, 44305-44320, 44298-44313, 44307-44322, 40028-40043, 44314-44329, 64386-64401, 40024-40039, 64387-64402, or 40025-40040 of SEQ ID NO: 1. In some embodiments, the oligonucleotide is substantially complementary to 8 to 30 contiguous nucleotides of a sequence that corresponds to nucleotides 44295-44331 of SEQ ID NO: 1. In some embodiments, the oligonucleotide is perfectly complementary to 8 to 30 contiguous nucleotides of a sequence that corresponds to nucleotides 44295-44331 of SEQ ID NO: 1.

[0009] In another aspect, the present disclosure provides an oligonucleotide comprising a sequence having at least 80% identity to a sequence selected from a group consisting of SEQ ID NOs: 9-12, 135, 137-140, 142-150, and 169-203. In some embodiments, the oligonucleotide comprises a sequence having at least 90% identity to a sequence selected from a group consisting of SEQ ID NOs: 9-12, 135, 137-140, 142-150, and 169-203. In some embodiments, the oligonucleotide comprises a sequence selected from a group consisting of SEQ ID NOs: 9-12, 135, 137-140, 142-150, and 169-203.

[0010] In another aspect, the present disclosure provides an oligonucleotide comprising a sequence that is substantially complementary to a sequence selected from a group consisting of SEQ ID NOs: 73-76, 152, 154-157, 159-167, and 204-238. In some embodiments, the oligonucleotide is at least 85%, at least 90%, or at least 95% complementary to a sequence selected from a group consisting of SEQ ID NOs: 73-76, 152, 154-157, 159-167, and 204-238.

In some embodiments, the oligonucleotide is perfectly complementary to a sequence selected from a group consisting of SEQ ID NOs: 73-76, 152, 154-157, 159-167, and 204-238.

[0011] In some embodiments, the oligonucleotide is perfectly complementary to SEQ ID NO: 167. In some embodiments, the oligonucleotide is perfectly complementary to SEQ ID NO: 166. In some embodiments, the oligonucleotide is perfectly complementary to SEQ ID NO: 73. In some embodiments, the oligonucleotide is perfectly complementary to SEQ ID NO: 74. In some embodiments, the oligonucleotide is perfectly complementary to SEQ ID NO: 75. In some embodiments, the oligonucleotide is perfectly complementary to SEQ ID NO: 76.

[0012] In some embodiments, an oligonucleotide described herein is a chirally pure oligonucleotide.

[0013] In some embodiments, the oligonucleotide described herein comprises at least one modified nucleotide. In some embodiments, the modified nucleotide comprises a base modification, a sugar modification, a sugar phosphate modification, an internucleotidic linkage modification, or a combination thereof. In some embodiments, the internucleotidic linkage modification comprises a phosphorothioate or phosphodithioate linkage modification. In some embodiments, the sugar modification comprises a 2'-O-methoxyethyl (2'-MOE) modification, a 2'-Fluoro (2'-F) modification, a 2'-O-methyl (2'-O-Me) modification, an unlocked nucleic acid (UNA), or a locked nucleic acid (LNA). In some embodiments, the sugar phosphate modification comprises a phosphorodiamidate morpholino (PMO) modification and/or a peptide nucleic acid (PNA) modification. In some embodiments, the base modification comprises a 5'-methylcytosine modification or a G-clamp modification.

[0014] In some embodiments, each nucleotide comprises a phosphorothioate (PS) internucleotide linkage. In some embodiments, the oligonucleotide comprises five nucleotides at the 5'-end and five nucleotides at the 3'-end of the oligonucleotide sequence which contain a 2'-MOE modification. In some embodiments, each nucleotide contains a 2'-MOE modification.

[0015] In some embodiments, the oligonucleotide further comprises at least one ligand attached to the 5' end and/or the 3' end. In some embodiments, the ligand comprises at least one

lipid, peptide, and/or sugar. In some embodiments, the sugar comprises N-acetylgalactosamine (GalNAc) moiety.

DEFINITIONS

[0016] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in “Organic Chemistry”, Thomas Sorrell, University Science Books, Sausalito: 1999, and “March’s Advanced Organic Chemistry”, 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0017] *Acyl*: As used herein, the term “acyl” means $-C(O)R$, wherein R is C₁₋₂₀ aliphatic.

[0018] *Aliphatic*: The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “carbocycle” “cycloaliphatic” or “cycloalkyl”), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, “cycloaliphatic” (or “carbocycle” or “cycloalkyl”) refers to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0019] **Alkyl:** As used herein, the term “alkyl” means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated and that has a single point of attachment to the rest of the molecule.

[0020] **Alkenyl:** As used herein, the term “alkenyl” means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that comprises at least one carbon-carbon double bond and that has a single point of attachment to the rest of the molecule.

[0021] **Alkynyl:** As used herein, the term “alkynyl” means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that comprises at least one carbon-carbon triple bond and that has a single point of attachment to the rest of the molecule.

[0022] **Alkylene:** As used herein, the term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms in the chain are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0023] **Alkenylene:** As used herein, the term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one carbon-carbon double bond in which one or more hydrogen atoms in the chain are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0024] **Alkynylene:** As used herein, the term “alkynylene” refers to a bivalent alkynyl group. A substituted alkynylene chain is a polymethylene group containing at least one carbon-carbon triple bond in which one or more hydrogen atoms in the chain are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0025] **Approximately:** As used herein, the terms “approximately” or “about” in reference to a number are generally taken to include numbers that fall within a range of 5%, 10%, 15%, or 20% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value).

[0026] **Aryl:** As used herein, the term “aryl” used alone or as part of a larger moiety as in “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, refers to monocyclic and bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term “aryl” may be used interchangeably with the term “aryl ring”. In certain embodiments of the present invention, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl”, as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like. In certain preferred embodiments, the term aryl refers to phenyl.

[0027] **Carbocyclic:** As used herein, the terms “cycloaliphatic”, “carbocycle” or “cycloalkyl” refer to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule.

[0028] **Complementary:** As used herein, in accordance with its art-accepted meaning, “complementary” refers to the capacity for pairing between particular bases, nucleosides, nucleotides or nucleic acids. For example, adenine (A) and uracil (U) are complementary; adenine (A) and thymine (T) are complementary; and guanine (G) and cytosine (C) are complementary and are referred to in the art as Watson-Crick base pairings. If an oligonucleotide, *i.e.*, a sequence of nucleic acids, at a certain position (at a certain nucleic acid) within its sequence is complementary to a nucleic acid in a second oligonucleotide when the oligonucleotides are aligned in anti-parallel orientation, the nucleic acids of each oligonucleotide form a complementary base pairing and the oligonucleotides are said to be complementary at that certain position. Thus, two oligonucleotides can be characterized by their percent of complementary base pairing of their nucleic acids. For example, the percent complementarity of a first oligonucleotide having a first nucleic acid sequence to a second oligonucleotide having a longer nucleic acid sequence may be evaluated by aligning them in antiparallel orientation and maximizing their complementary base pairing. When an oligonucleotide is engineered to a target gene, the oligonucleotide may be evaluated for its complementarity to the pre-RNA or mRNA

sequence of the target gene, and the alignment is said to be done over a window of evaluation along the RNA sequence. In this example, the percent complementarity of the base pairs in the oligonucleotide to the RNA sequence window is determined by the total number of nucleotides in the oligonucleotide and RNA sequence window that form Watson-Crick base pairings, dividing by the total number of nucleotides within the RNA sequence window, and multiplying by 100. For example, if the RNA sequence is AATTTGTTATAA, the window of evaluation ("RNA sequence window") may be from nucleic acid at position #3, i.e., T (counting from left to right) to the nucleotide in position number #10, which is also a T. The RNA sequence window of this exemplary RNA sequence is 8 contiguous nucleotides in length. Aligning an oligonucleotide of AAAAAAAAAA along the aforementioned RNA sequence window would have an optimized alignment resulting in a maximum 75% complementary base pairings since there are 6 nucleotides in Watson-Crick base pairings out of a total of 8 nucleotide in the RNA sequence window. A position occupied by two, non-complementary nucleotides constitutes a mismatch, *i.e.*, the position is occupied by a non-complementary base pair. In the above example, 2 of the 8 nucleotides within the RNA sequence window are mismatched. When each nucleotide of an oligonucleotide is in Watson-Crick base pairing with each nucleotide of a second sequence of equal length (be it another oligonucleotide or RNA sequence window), such sequences can be referred to as "perfectly complementary" (100% complementarity) with respect to each other. Two nucleic acid sequences that are at least 80% complementary over a window of evaluation are considered "substantially complementary" over that window. In certain embodiments, two nucleic acid sequences are at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% complementary over a window of evaluation. Where a first nucleic acid sequence is referred to as "substantially complementary" with respect to a second nucleic acid sequence herein, they may comprise one or more unmatched bases upon hybridization, *e.g.*, up to about 5%, 10%, 15%, or 20% unmatched bases upon hybridization, *e.g.*, 1, 2, 3, 4, 5, or 6 mismatched base pairs upon hybridization for a duplex up to 30 base pairs. It should be understood that where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs are not regarded as mismatches or unpaired nucleotides with regard to the determination of percent complementarity. "Complementary" sequences, as used herein may include one or more non-Watson-Crick base pairs and/or base pairs formed from non-natural nucleobases, in so far as the requirements with respect to their

ability to hybridize are fulfilled. Such non-Watson-Crick base pairs include, but are not limited to, G:U Wobble or Hoogsteen base pairing. Those of ordinary skill in the art are aware that guanine, cytosine, adenine, thymine, and uracil can be replaced by other bases without substantially altering the base pairing properties of a polynucleotide comprising a nucleotide bearing such bases, according to the so-called “wobble” rules (see, e.g., Murphy, FV IV & V Ramakrishnan, V., Nature Structural and Molecular Biology 11: 1251 - 1252 (2004)). For example, a nucleotide comprising inosine as its base can base pair with nucleotides containing adenine, cytosine, thymine, or uracil. Thus, nucleotides containing uracil, guanine, thymine, or adenine can be replaced in the nucleic acid sequence of an oligonucleotide described herein by a nucleotide containing, for example, inosine, without decreasing the % complementarity. If a pair of bases is able to base pair (e.g., through Watson-Crick or Wobble base pairing), then such base pairs are considered to be complementary for purposes of determining % complementarity.

[0029] *Corresponding to:* As used herein, the term “corresponding to” may be used to designate the position/identity of a structural element in a compound or composition through comparison with an appropriate reference compound or composition. For example, in some embodiments, a monomeric residue in a polymer (e.g., an amino acid residue in a polypeptide or a nucleic acid residue in an oligonucleotide) may be identified as “corresponding to” a residue in an appropriate reference polymer. For example, those of ordinary skill will appreciate that, for purposes of simplicity, residues in a polypeptide are often designated using a canonical numbering system based on a reference related polypeptide, so that an amino acid “corresponding to” a residue at position 190, for example, need not actually be the 190th amino acid in a particular amino acid chain but rather corresponds to the residue found at 190 in the reference polypeptide; those of ordinary skill in the art readily appreciate how to identify “corresponding” amino acids and “corresponding” oligonucleotides. For example, those skilled in the art will be aware of various sequence alignment strategies, including software programs such as, for example, BLAST, CS-BLAST, CUSASW++, DIAMOND, FASTA, GGSEARCH/GLSEARCH, Genoogle, HMMER, HHpred/HHsearch, IDF, Infernal, KLAST, USEARCH, parasail, PSI-BLAST, PSI-Search, ScalaBLAST, Sequilab, SAM, SSEARCH, SWAPHI, SWAPHI-LS, SWIMM, or SWIPE that can be utilized, for example, to identify “corresponding” residues in polypeptides, oligonucleotides and/or nucleic acid sequences in accordance with the present disclosure.

[0030] **Halogen:** As used herein, the term “halogen” means F, Cl, Br, or I.

[0031] **Heteroaryl:** As used herein, the terms “heteroaryl” and “heteroar-”, used alone or as part of a larger moiety, e.g., “heteroaralkyl”, or “heteroaralkoxy”, refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term “heteroatom” refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-”, as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnoliny, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring”, “heteroaryl group”, or “heteroaromatic”, any of which terms include rings that are optionally substituted. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0032] **Heteroatom:** As used herein, the term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

[0033] **Heterocycle:** As used herein, the terms “heterocycle”, “heterocyclyl”, “heterocyclic radical”, and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or

partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0034] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms “heterocycle”, “heterocyclyl”, “heterocyclyl ring”, “heterocyclic group”, “heterocyclic moiety”, and “heterocyclic radical”, are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group may be mono- or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0035] *Host cell:* As used herein, the term “host cell” refers to a cell into which exogenous DNA (recombinant or otherwise) has been introduced. Persons of skill upon reading this disclosure will understand that such terms refer not only to the particular subject cell, but also to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term “*host cell*” as used herein. In some embodiments, host cells include prokaryotic and eukaryotic cells selected from any of the Kingdoms of life that are suitable for expressing an exogenous DNA (e.g., a recombinant nucleic acid sequence). Exemplary cells include those of prokaryotes and eukaryotes (single-cell or multiple-cell), bacterial cells (e.g., strains of *E. coli*, *Bacillus spp.*, *Streptomyces spp.*, etc.), mycobacteria cells, fungal cells, yeast cells (e.g., *S. cerevisiae*, *S. pombe*, *P. pastoris*, *P.*

methanolica, etc.), plant cells, insect cells (e.g., SF-9, SF-21, baculovirus-infected insect cells, *Trichoplusia ni*, etc.), non-human animal cells, human cells, or cell fusions such as, for example, hybridomas or quadromas. In some embodiments, the cell is a human, monkey, ape, hamster, rat, or mouse cell. In some embodiments, the cell is eukaryotic and is selected from the following cells: CHO (e.g., CHO Kl, DXB-1 1 CHO, Veggie-CHO), COS (e.g., COS-7), retinal cell, Vero, CV1, kidney (e.g., HEK293, 293 EBNA, MSR 293, MDCK, HaK, BHK), HeLa, HepG2, WI38, MRC 5, Colo205, HB 8065, HL-60, (e.g., BHK21), Jurkat, Daudi, A431 (epidermal), CV-1, U937, 3T3, L cell, C127 cell, SP2/0, NS-0, MMT 060562, Sertoli cell, BRL 3 A cell, HT1080 cell, myeloma cell, tumor cell, and a cell line derived from an aforementioned cell. In some embodiments, the cell comprises one or more viral genes.

[0036] *Identity*: As used herein, the term “identity” refers to the overall relatedness between polymeric molecules, *e.g.*, between nucleic acid molecules (*e.g.*, DNA molecules and/or RNA molecules, such as oligonucleotides) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be “substantially identical” to one another if their sequences are at least 80%, 85%, 90%, 95%, or 99% identical. Calculation of the percent identity of two nucleic acid or polypeptide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or substantially 100% of the length of a reference sequence. The nucleotides at corresponding positions are then compared. When a position in the first sequence is occupied by the same residue (*e.g.*, nucleotide or amino acid) as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4: 11-17), which has been incorporated into the ALIGN program (version 2.0). In some exemplary

embodiments, nucleic acid sequence comparisons made with the ALIGN program use a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can alternatively be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix.

[0037] *Linked:* As used herein, the term “linked”, when used with respect to two or more moieties, means that the moieties are physically associated or connected with one another to form a molecular structure that is sufficiently stable so that the moieties remain associated under the conditions in which the linkage is formed and, preferably, under the conditions in which the new molecular structure is used, *e.g.*, physiological conditions. In certain preferred embodiments of the invention the linkage is a covalent linkage. In other embodiments the linkage is noncovalent. Moieties may be linked either directly or indirectly. When two moieties are directly linked, they are either covalently bonded to one another or are in sufficiently close proximity such that intermolecular forces between the two moieties maintain their association. When two moieties are indirectly linked, they are each linked either covalently or noncovalently to a third moiety, which maintains the association between the two moieties. In general, when two moieties are referred to as being linked by a “linker” or “linking moiety” or “linking portion”, the linkage between the two linked moieties is indirect, and typically each of the linked moieties is covalently bonded to the linker. The linker can be any suitable moiety that reacts with the two moieties to be linked within a reasonable period of time, under conditions consistent with stability of the moieties (which may be protected as appropriate, depending upon the conditions), and in sufficient amount, to produce a reasonable yield.

[0038] *Operably linked:* As used herein, the term “operably linked” refers to a juxtaposition wherein the components described are in a relationship permitting them to function in their intended manner. A control element “operably linked” to a functional element is associated in such a way that expression and/or activity of the functional element is achieved under conditions compatible with the control element. In some embodiments, “operably linked” control elements are contiguous (*e.g.*, covalently linked) with the coding elements of interest; in some embodiments, control elements act in trans to or otherwise at a distance from the functional element of interest.

[0039] *Optionally substituted or substituted:* As described herein, compounds of the invention may contain “optionally substituted” moieties. In general, the term “substituted”, whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable”, as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0040] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}$ -pyridyl which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $(CH_2)_{0-4}OC(O)NR^\circ_2$; $C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $(CH_2)_{0-4}S(O)R^\circ$; $N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $P(O)R^\circ_2$; $OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3 ; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$ -(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition

above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3–12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0041] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene) $C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=O$ and $=S$.

[0042] Suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group include the following: $=O$, $=S$, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0043] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, $(haloR^\bullet)$, OH , $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6-membered

saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0044] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0045] Suitable substituents on the aliphatic group of $R^{\bullet}$ are independently halogen, $-R^{\bullet}$, $(haloR^{\bullet})$, $-OH$, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or NO_2 , wherein each $R^{\bullet}$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0046] *Partially unsaturated:* As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0047] *Recombinant:* As used herein, the term “recombinant” is intended to refer to polypeptides, polynucleotides, or oligonucleotides that are designed, engineered, prepared, expressed, created, manufactured, and/or isolated by recombinant means, such as polypeptides expressed using a recombinant expression vector transfected into a host cell; polypeptides isolated from a recombinant, combinatorial human polypeptide library; polypeptides isolated from an animal (e.g., a mouse, rabbit, sheep, fish, etc.) that is transgenic for or otherwise has been manipulated to express a gene or genes, or gene components that encode and/or direct expression of the polypeptide or one or more component(s), portion(s), element(s), or domain(s)

thereof; and/or polypeptides prepared, expressed, created or isolated by any other means that involves splicing or ligating selected nucleic acid sequence elements to one another, chemically synthesizing selected sequence elements, and/or otherwise generating a nucleic acid that encodes and/or directs expression of the polypeptide or one or more component(s), portion(s), element(s), or domain(s) thereof. In some embodiments, one or more of such selected sequence elements is found in nature. In some embodiments, one or more of such selected sequence elements is designed *in silico*. In some embodiments, one or more such selected sequence elements results from mutagenesis (e.g., *in vivo* or *in vitro*) of a known sequence element, e.g., from a natural or synthetic source such as, for example, in the germline of a source organism of interest (e.g., of a human, a mouse, etc.).

[0048] *Subject:* As used herein, the term “subject” or “test subject” refers to any organism to which a provided compound or composition is administered in accordance with the present invention *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans; insects; worms; *etc.*) and plants. In some embodiments, a subject may be suffering from, and/or susceptible to a disease, disorder, and/or condition.

[0049] *Substantially:* As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and/or chemical phenomena.

[0050] *Suffering from:* An individual who is “suffering from” a disease, disorder, and/or condition has been diagnosed with and/or displays one or more symptoms of a disease, disorder, and/or condition.

[0051] *Target gene:* A “target gene”, as used herein, refers to a gene whose expression is to be modulated, *e.g.*, inhibited.

[0052] Target region: As used herein, the term “target region” refers to a region within the RNA transcript of the target gene, where the RNA is to be degraded or translationally repressed or otherwise inhibited using one or more oligonucleotides. In some embodiments, an oligonucleotide described herein is complementary to a target region (*e.g.*, substantially or perfectly complementary), such that the oligonucleotide is capable of hybridizing to the target region. A target region, as described herein, may be described by its position (*i.e.*, the coordinates of the nucleotides of the target region) within a target RNA sequence or the corresponding region within a target gene sequence. The RNA may be a primary RNA transcript transcribed from the target gene (*e.g.*, a pre-mRNA) or a processed transcript, *e.g.*, mRNA encoding a polypeptide. In some embodiments, a target region of an mRNA is at least long enough to serve as a substrate for RNAase-mediated degradation within that portion in the presence of a suitable oligonucleotide. A target region may be from about 8-36 nucleotides in length, *e.g.*, about 8-30, 10-20, or about 15-30 nucleotides in length. A target region length may have specific value or subrange within the afore-mentioned ranges.

[0053] Therapeutic agent: As used herein, the phrase “therapeutic agent” refers to any agent that, when administered to a subject, has a therapeutic effect and/or elicits a desired biological and/or pharmacological effect. In some embodiments, a therapeutic agent is any substance that can be used to alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. In some embodiments, a therapeutic agent is an oligonucleotide designed to target a certain region of target gene.

[0054] Therapeutically effective amount: As used herein, the term “therapeutically effective amount” means an amount of a substance (*e.g.*, a therapeutic agent, composition, and/or formulation) that elicits a desired biological response when administered as part of a therapeutic regimen. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, *etc.* For example, the effective

amount of compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or signs of the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is administered in a single dose; in some embodiments, multiple unit doses are required to deliver a therapeutically effective amount.

[0055] *Nucleic acid:* The term “nucleic acid” includes any nucleotides, analogs thereof, and polymers thereof. The term “polynucleotide” or “oligonucleotide” as used herein refer to a polymeric form of nucleotides of any length, either ribonucleotides (RNA) or deoxyribonucleotides (DNA). These terms refer to the primary structure of the molecules and, thus, include double- and single-stranded DNA, and double- and single-stranded RNA. These terms include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs and modified polynucleotides such as, though not limited to, methylated, protected and/or capped nucleotides or polynucleotides. The terms encompass poly- or oligo-ribonucleotides (RNA) and poly- or oligo-deoxyribonucleotides (DNA); RNA or DNA derived from N-glycosides or C-glycosides of nucleobases and/or modified nucleobases; nucleic acids derived from sugars and/or modified sugars; and nucleic acids derived from phosphate bridges and/or modified phosphorus-atom bridges (also referred to herein as “internucleotide linkages”). The terms further encompass nucleic acids containing any combinations of nucleobases, modified nucleobases, sugars, modified sugars, phosphate bridges or modified phosphorus atom bridges. Examples include, and are not limited to, nucleic acids containing ribose moieties, nucleic acids containing deoxy-ribose moieties, nucleic acids containing both ribose and deoxyribose moieties, and nucleic acids containing ribose and modified ribose moieties. In some embodiments, the prefix poly- refers to a nucleic acid containing 2 to about 10,000, 2 to about 50,000, or 2 to about 100,000 nucleotide monomer units. In some embodiments, the prefix oligo- refers to a nucleic acid containing 2 to about 200 nucleotide monomer units.

[0056] *Unsaturated:* The term “unsaturated”, as used herein, means that a moiety has one or more units of unsaturation.

BRIEF DESCRIPTION OF THE DRAWING

[0057] **Figure 1** shows relative SAMHD1 mRNA expression in 143B cells transfected with exemplary oligonucleotides.

[0058] **Figure 2** shows a dose response curve of relative SAMHD1 mRNA expression in mouse cells (wildtype MEFs) transfected with exemplary oligonucleotides at varying concentrations. Exemplary oligonucleotides include the oligonucleotide represented in SEQ ID NO: 9 (panel A), the oligonucleotide represented in SEQ ID NO: 10 (panel B), the oligonucleotide represented in SEQ ID NO: 11 (panel C), the oligonucleotide represented in SEQ ID NO: 12 (panel D), and the scrambled control (panel E).

[0059] **Figure 3** shows a dose response curve of relative SAMHD1 mRNA expression in human 143B cells transfected with exemplary oligonucleotides at varying concentrations. Exemplary oligonucleotides include oligonucleotides represented in SEQ ID NO: 9 (panel A), the oligonucleotide represented in SEQ ID NO: 10 (panel B), the oligonucleotide represented in SEQ ID NO: 11 (panel C), the oligonucleotide represented in SEQ ID NO: 12 (panel D), and scrambled control (panel E).

[0060] **Figure 4** shows a graph of relative SAMHD1 expression of exemplary oligonucleotides described herein in human 143B cells (x-axis) and mouse WT MEFs (y-axis), including oligonucleotides represented in SEQ ID NOs: 9-12 as exemplary oligonucleotides that show effective knockdown in SAMHD1 expression in both the human and mouse cells.

[0061] **Figure 5** shows relative SAMHD1 mRNA expression levels in human 143B cells transfected with exemplary oligonucleotides (panel A) and their viability (panel B) relative to a vehicle control.

[0062] **Figure 6** shows a schematic of target regions within the SAMHD1 transcript that are acted upon by various oligonucleotides targeting those regions.

[0063] **Figure 7** shows relative SAMHD1 mRNA expression levels (expressed as a % change in expression compared to control) in human 143B cells transfected with each of the oligonucleotides in Table 9.

[0064] **Figure 8** shows relative SAMHD1 mRNA expression levels (expressed as a % change in expression compared to control) in mouse WT NIH3T3 cells transfected with each of the oligonucleotides in Table 9.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

SAMHD1

[0065] The protein sequence of active, wildtype human SAMHD1 is as follows (626 amino acids):

MQRADSEQPSKRPRCDDSPRTPSNTPSAEADWSPGLELHPDYKTWGPEQVCSFLRRGGF
EEPVLLKNIRENEITGALLPCLDESRFENLGVSSLGERKKLLSYIQLRVQIHVDTMKVIND
PIHGHIELHPLLVRIIDTPQFQRLRYIKQLGGGYVFPGASHNRFEHSLGVGYLAGCLVH
ALGEKQPELQISERDVLVCVQIAGLCHDLGHGPFSHMFDGRFIPLARPEVKWTHEQGSVM
MFEHLINSNGIKPVMEQYGLIPEEDICFIKEQIVGPLESPVEDSLWPYKGRPENKSFLYEIV
SNKRNGIDVDKWDYFARDCHHLGIQNNFDYKRFIKFARVCEVDNELRICARDKEVGNL
YDMFHTRNSLHRRAYQHKVGNIIDTMITDAFLKADDYIEITGAGGKKYRISTAIDDMEA
YTKLTDNIFLEILYSTDPKLKDAREILKQIEYRNLFKYVGETQPTGQIKIKREDYESLPKEV
ASAKPKVLLDVKLKAEDFIVDVINMDYGMQEKNPIDHVSFYCKTAPNRAIRITKNQVSQ
LLPEKF AEQLIRVYCKKVDRKSLYAARQYFVQWCADRNFTKPQDGDVIAPLTPQKKE
WNDSTSVQNPTRLREASKSRVQLFKDDPM (SEQ ID NO: 130; UniProt Q9Y3Z3-1)

[0066] The SAMHD1 protein sequence includes a SAM domain (residues 45-110) and a HD domain (residues 164-316). Unlike in mice, the SAM domain in human SAMHD1 is not required for deoxynucleoside triphosphate (dNTPase) activity.

[0067] The SAMHD1 gene is found at human chromosome 20. The complete gene sequence is shown in SEQ ID NO: 1 (NG_017059.1). The SAMHD1 gene has 30 different transcripts (splice variants), found in ENSEMBL database entry ENSG00000101347 (https://useast.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000101347;r=20:36890574-36951843;t=ENST00000646673, which is herein incorporated by reference in its entirety). An exemplary transcript of SAMHD1 is shown in **FIG. 6** and SEQ ID NO: 131 (ENST00000646673.2 SAMHD1-221) and comprises 16 exons. This transcript encodes SAMHD1 protein shown in SEQ ID NO: 130.

[0068] The present disclosure provides, among other things, compositions and methods for inhibiting expression of SAMHD1 and/or increasing dNTP pools in a subject.

SAMHD1 Oligonucleotides

[0069] In some embodiments, the present disclosure provides oligonucleotides that bind to and inhibit expression of messenger RNA (mRNA) produced by a target gene (*e.g.*, SAMHD1). As used herein, the terms “oligonucleotides” and “antisense oligonucleotides” (ASOs) are used interchangeably.

[0070] In some embodiments, administration of an oligonucleotide can decrease or inhibit expression of SAMHD1 in a subject or in a biological sample compared to a level before administration. In some embodiments, administration of an oligonucleotide can decrease level of SAMHD1 protein in a subject, or in a cell or biological sample compared to a level before administration. In some embodiments, administration of an oligonucleotide can decrease SAMHD1 activity (thereby decreasing mitochondrial transcription) in a subject or in a cell or biological sample compared to a level before administration.

[0071] As described herein, SAMHD1 is a master regulator of dNTP pools in mammalian cells through its triphosphohydrolase activity that cleaves deoxynucleoside triphosphates (dNTPs) into deoxyribonucleosides and inorganic triphosphate. Indications of decreased SAMHD1 activity in a cell includes an increase in dNTP pools in a cell.

[0072] As dNTPs are required for DNA replication and transcription, restoring and increasing dNTP pools, as a result of decreased SAMHD1 activity, may also lead to increased level of mitochondrial transcription. In some embodiments, increased level of mitochondrial transcription can be measured by total mtDNA, mtDNA expression, or mtDNA copy number. Indication of decreased SAMHD1 activity also includes increased level ATP production.

[0073] In some embodiments, the level of SAMHD1 mRNA expression, SAMHD1 protein, and/or SAMHD1 activity is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to a level before the administration. In some embodiments, administration of

an oligonucleotide can lead to complete or substantially complete inhibition of SAMHD1 mRNA expression.

[0074] In some embodiments, an oligonucleotide described herein is an RNase H-dependent oligonucleotide, wherein the oligonucleotide induces the degradation of mRNA by RNase H. In some embodiments, an oligonucleotide inhibits expression of a target gene through steric-blocking, wherein the oligonucleotide physically prevents or inhibits the progression of splicing or translational machinery. Oligonucleotides, as described herein, are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity. In some embodiments, antisense activity comprises degradation of a target nucleic acid by RNase H. In some embodiments, antisense activity comprises an oligonucleotide physically preventing or inhibiting the progression of splicing or translational machinery.

[0075] In some embodiments, oligonucleotides described herein specifically hybridize to one or more target regions on an RNA transcript of a target gene (*e.g.*, SAMHD1). In some embodiments, a target region comprises a region of an mRNA. In some embodiments, a target region comprises a region of a pre-mRNA. In some embodiments, a target region comprises a region of pre-mRNA that spans an exon/intron junction. In some embodiments, a target region comprises a region of pre-mRNA spanning or including an intron region. In some embodiments, a target region corresponds to a region of a DNA sequence, *i.e.*, a target gene sequence. In some embodiments, a target region comprises a region near to, that includes, or is within a 5'-UTR region. In some embodiments, a target region comprises a region near to, that includes, or is within a 3'-UTR region. In some embodiments, a target region comprises a region near to, that includes, or is within an exon region (*e.g.*, as shown in the transcript of **FIG. 6**).

[0076] Exemplary target regions as described herein are shown in the SAMHD1 transcript of **FIG. 6**. The amino acid and nucleotide sequences of human SAMHD1 are known in the art and can be found in publicly available databases. For example, SAMHD1 transcript sequences are identified in Transcript ID Numbers ENST00000646673.2, ENST00000262878.5, ENST00000643918.1, ENST00000646066.1, ENST00000643825.1, ENST00000465985.2, ENST00000645033.1, ENST00000646904.1, ENST00000642246.1, ENST00000645444.2, ENST00000682773.1, ENST00000644250.2, ENST00000647163.1, ENST00000642186.1,

ENST00000646869.1, ENST00000683766.1, ENST00000683720.1, ENST00000644114.2, ENST00000642616.1, ENST00000643078.1, ENST00000646866.1, ENST00000646121.1, ENST00000643161.1, ENST00000644370.1, ENST00000647095.1, ENST00000647459.1, ENST00000644688.2, ENST00000643243.1, ENST00000643003.1, ENST00000643907.1. Additionally, the full human SAMHD1 gene sequence is represented in Reference No. NG_017059.1 (SEQ ID NO: 1).

[0077] A SAMHD1 RNA transcript sequence is presented herein in SEQ ID NO: 131 (ENSEMBL ID: ENST00000646673.2 SAMHD1-221), where U residues are represented by T residues in the provided sequence. One of ordinary skill in the art will appreciate that where one refers to a sequence as “RNA” or “mRNA” or “pre-mRNA” or “transcript” the actual sequence contains U rather than T, but may be presented either way in the present disclosure.

[0078] Strategies for targeting particular regions of a particular SAMHD1 transcript (*e.g.*, within SEQ ID NO: 131) may be utilized in targeting other SAMHD1 transcripts. **FIG. 6** provides an exemplary SAMHD1 transcript sequence that may be targeted by oligonucleotides described herein. One of skill in the art understands that an oligonucleotide targeting a target region within SEQ ID NO: 131 may also target the corresponding region in other SAMHD1 transcripts, although they may vary slightly in the exact coordinates within the nucleic acid sequence. For example, in some embodiments, an oligonucleotide described herein may target a specific region of the SAMHD1 mRNA transcript shown in SEQ ID NO: 131 and also target the corresponding target region in the transcript represented in Reference Number ENST00000262878.5. Such a region may be present in both sequences and correspond to the same target region. Additionally, one of skill in the art will understand that a target region within a SAMHD1 transcript (*e.g.*, SEQ ID NO: 131) may be characterized by the corresponding coordinates within the full SAMHD1 gene sequence (SEQ ID NO: 1, corresponding to NCBI Reference No. NG_017059.1).

[0079] In some embodiments, an oligonucleotide has a nucleotide sequence comprising a region having sufficient complementarity to a target nucleic acid sequence to allow hybridization and result in antisense activity and insufficient complementarity to any non-target sequences so as to avoid non-specific hybridization to any non-target nucleic acid sequences under conditions

in which specific hybridization is desired (*e.g.*, under physiological conditions for *in vivo* or therapeutic uses, and under conditions in which assays are performed in the case of *in vitro* assays).

[0080] In some embodiments, the present disclosure provides oligonucleotides that are perfectly complementary to a SAMHD1 nucleic acid sequence over the entire length of the oligonucleotide. In some embodiments, an oligonucleotide is at least 95% complementary to a SAMHD1 nucleic acid sequence over the entire length of the oligonucleotide. In some embodiments, an oligonucleotide is at least 90% complementary to a SAMHD1 nucleic acid over the entire length of the oligonucleotide. In some embodiments, an oligonucleotide is at least 85% complementary to a SAMHD1 nucleic acid sequence over the entire length of the oligonucleotide. In some embodiments, an oligonucleotide is at least 80% complementary to a SAMHD1 nucleic acid sequence over the entire length of the oligonucleotide. In some embodiments, an oligonucleotide is between 80% and 100% complementary to a SAMHD1 nucleic acid sequence over the entire length of the oligonucleotide (*i.e.*, substantially complementary). In some embodiments, an oligonucleotide comprises a region that is perfectly complementary to a SAMHD1 nucleic acid sequence and is at least 80% complementary to the SAMHD1 nucleic acid sequence over the entire length of the oligonucleotide. In some embodiments, the region of perfect complementarity to a SAMHD1 nucleic acid sequence is from 6 to 20 nucleobases in length.

[0081] In some embodiments, an oligonucleotide is between 5 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 90 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 80 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 70 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 60 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 50 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 40 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 30 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 25 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 20 nucleotides in length. In some embodiments, an oligonucleotide is between 5 and 15 nucleotides in length. In some

embodiments, an oligonucleotide is between 5 and 10 nucleotides in length. In some embodiments, an oligonucleotide is between 10 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 15 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 20 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 25 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 30 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 40 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 50 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 60 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 70 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 90 and 100 nucleotides in length. In some embodiments, an oligonucleotide is between 8 and 30 nucleotides in length. In some embodiments, an oligonucleotide is 15 to 25 nucleotides in length. In some embodiments, an oligonucleotide is between 16 and 22 nucleotides in length. In some embodiments, an oligonucleotide is between 18 and 20 nucleotides in length. In some embodiments, an oligonucleotide is between 14 and 18 nucleotides in length. In some embodiments, an oligonucleotide is 8, 9, 10, 11, 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, an oligonucleotide is 20 nucleotides in length. In some embodiments, an oligonucleotide is 19 nucleotides in length. In some embodiments, an oligonucleotide is 18 nucleotides in length. In some embodiments, an oligonucleotide is 17 nucleotides in length. In some embodiments, an oligonucleotide is 16 nucleotides in length. In some embodiments, an oligonucleotide is 15 nucleotides in length.

[0082] In some embodiments, an oligonucleotide comprises a sequence having at least 80% identity to a sequence selected from a group consisting of SEQ ID NOs: 2-65, 135-151, and 169-203. In some embodiments, an oligonucleotide comprises a sequence having at least 85% identity to a sequence selected from a group consisting of SEQ ID NOs: 2-65, 135-151, and 169-203. In some embodiments, an oligonucleotide comprises a sequence having at least 90% identity to a sequence selected from a group consisting of SEQ ID NOs: 2-65, 135-151, and 169-203. In some embodiments, an oligonucleotide comprises a sequence selected from a group consisting of SEQ ID NOs: 2-65, 135-151, and 169-203. In some embodiments, an

oligonucleotide comprises a sequence selected from a group consisting of SEQ ID NOs: 2-65, 135-151, and 169-203.

[0083] In some embodiments, an oligonucleotide comprises a sequence having at least 80% identity to a sequence selected from a group consisting of SEQ ID NOs: 2-12. In some embodiments, an oligonucleotide comprises a sequence having at least 85% identity to a sequence selected from a group consisting of SEQ ID NOs: 2-12. In some embodiments, an oligonucleotide comprises a sequence having at least 90% identity to a sequence selected from a group consisting of SEQ ID NOs: 2-12. In some embodiments, an oligonucleotide comprises a sequence selected from a group consisting of SEQ ID NOs: 2-12. In some embodiments, an oligonucleotide comprises a sequence selected from a group consisting of SEQ ID NOs: 2-12.

[0084] In some embodiments, an oligonucleotide comprises a sequence having at least 80% identity to SEQ ID NO: 4. In some embodiments, an oligonucleotide comprises a sequence having at least 85% to SEQ ID NO: 4. In some embodiments, an oligonucleotide comprises a sequence having at least 90% identity to SEQ ID NO: 4. In some embodiments, an oligonucleotide comprises a sequence having at least 95% identity to SEQ ID NO: 4. In some embodiments, an oligonucleotide comprises SEQ ID NO: 4.

[0085] In some embodiments, an oligonucleotide comprises a sequence having at least 80% identity to SEQ ID NO: 6. In some embodiments, an oligonucleotide comprises a sequence having at least 85% to SEQ ID NO: 6. In some embodiments, an oligonucleotide comprises a sequence having at least 90% identity to SEQ ID NO: 6. In some embodiments, an oligonucleotide comprises a sequence having at least 95% identity to SEQ ID NO: 6. In some embodiments, an oligonucleotide comprises SEQ ID NO: 6.

[0086] In some embodiments, an oligonucleotide comprises a sequence having at least 80% identity to SEQ ID NO: 9. In some embodiments, an oligonucleotide comprises a sequence having at least 85% to SEQ ID NO: 9. In some embodiments, an oligonucleotide comprises a sequence having at least 90% identity to SEQ ID NO: 9. In some embodiments, an oligonucleotide comprises a sequence having at least 95% identity to SEQ ID NO: 9. In some embodiments, an oligonucleotide comprises SEQ ID NO: 9.

[0087] In some embodiments, an oligonucleotide comprises a sequence having at least 80% identity to SEQ ID NO: 10. In some embodiments, an oligonucleotide comprises a sequence having at least 85% to SEQ ID NO: 10. In some embodiments, an oligonucleotide comprises a sequence having at least 90% identity to SEQ ID NO: 10. In some embodiments, an oligonucleotide comprises a sequence having at least 95% identity to SEQ ID NO: 10. In some embodiments, an oligonucleotide comprises SEQ ID NO: 10.

[0088] In some embodiments, an oligonucleotide comprises a sequence having at least 80% identity to SEQ ID NO: 11. In some embodiments, an oligonucleotide comprises a sequence having at least 85% to SEQ ID NO: 11. In some embodiments, an oligonucleotide comprises a sequence having at least 90% identity to SEQ ID NO: 11. In some embodiments, an oligonucleotide comprises a sequence having at least 95% identity to SEQ ID NO: 11. In some embodiments, an oligonucleotide comprises SEQ ID NO: 11.

[0089] In some embodiments, an oligonucleotide comprises a sequence having at least 80% identity to SEQ ID NO: 12. In some embodiments, an oligonucleotide comprises a sequence having at least 85% to SEQ ID NO: 12. In some embodiments, an oligonucleotide comprises a sequence having at least 90% identity to SEQ ID NO: 12. In some embodiments, an oligonucleotide comprises a sequence having at least 95% identity to SEQ ID NO: 12. In some embodiments, an oligonucleotide comprises SEQ ID NO: 12.

[0090] In some embodiments, an oligonucleotide comprises a sequence that is at least 80%, 85%, 90%, 95%, or 100% identical to any one of SEQ ID NOs: 2-65 135-151, and 169-203 in the following **Table 1**. In some embodiments, an oligonucleotide comprises a sequence that differs by no more than 1, 2, 3, or 4 nucleotides from any one of the sequences listed below in **Table 1**. **Table 1** includes exemplary SAMHD1 oligonucleotide sequences and the corresponding coordinates of the target region within the SAMHD1 gene sequence (starting from the 5' end of SAMHD1 gene sequence as shown in SEQ ID NO: 1).

Table 1: Oligonucleotide Sequences, Corresponding Coordinates of Target Region on SAMHD1 Gene Sequence (SEQ ID NO: 1)

SEQ ID NO:	Oligonucleotide DNA Sequence (5' to 3')	Corresponding Coordinates within SEQ ID NO: 1
2	TCGAAGACGTTGAAATTGAG	21722-21741
3	CACCTCCCAGCTGTTTGATG	21744-21763
4	GTAACCACCTCCCAGCTGTT	21749-21768
5	AGTAACCACCTCCCAGCTGT	21750-21769
6	ATCGATTGTGTGAAGCTCCT	21780-21799
7	GCTCAAATCGATTGTGTGAA	21786-21805
8	GTCCATCAAACATGTGAGAA	29605-29624
9	GCGAGTGTGGAACATGTCAT	44308-44327
10	TGCGAGTGTGGAACATGTCA	44309-44328
11	TTGCGAGTGTGGAACATGTC	44310-44329
12	GTTGCGAGTGTGGAACATGT	44311-44330
13	ATCCACTTCCCTCCTTTTCC	44555-44574
14	TTTATCCACTTCCCTCCATC	44584-44603
15	TCATGTCTACCTCCCATTC	44714-44733
16	TTCATGTCTACCTCCCATTT	44715-44734
17	GACTCACACCCAGTGTGTTGA	44936-44955
18	TGACTCACACCCAGTGTGTTG	44937-44956
19	TTGACTCACACCCAGTGTGTT	44938-44957
20	TGTCGCAGGGCTTTGCATTC	45297-45316
21	CTGTTCGCAGGGCTTTGCATT	45298-45317
22	ACTGTTCGCAGGGCTTTGCAT	45299-45318
23	CACTGTTCGCAGGGCTTTGCA	45300-45319
24	GCACTGTTCGCAGGGCTTTGC	45301-45320
25	GGCACTGTTCGCAGGGCTTTG	45302-45321
26	AGGCACTGTTCGCAGGGCTTT	45303-45322
27	TCCAGGCACTGTTCGCAGGGC	45306-45325
28	TTCCAGGCACTGTTCGCAGGG	45307-45326
29	GTTCCAGGCACTGTTCGCAGG	45308-45327
30	TGTTCCAGGCACTGTTCGCAG	45309-45328
31	GTGTTCCAGGCACTGTTCGCA	45310-45329
32	TGTGTTCCAGGCACTGTTCGC	45311-45330
33	TCTGGCAGAAGTTGTGAAAC	58885-58904
34	CTGTCCACCTTCTTACAATA	58933-58952
35	TCTGTCCACCTTCTTACAAT	58934-58953
36	TTCTGTCCACCTTCTTACAA	58935-58954
37	TTTCTGTCCACCTTCTTACA	58936-58955
38	TGTCTGCACACCACTGAACA	58983-59002
39	CTGTCTGCACACCACTGAAC	58984-59003
40	TCGCCATCCTGCGGCTTGGT	59011-59022 and 63778-63785
41	ATCGCCATCCTGCGGCTTGG	59012-59022 and 63778-63786

42	CATCGCCATCCTGCGGCTTG	59013-59022 and 63778-63787
43	TACTGTCGTCCATTCCCTTT	63816-63835
44	GGAAAGTTCGAGTCCAAGCT	64243-64262
45	AGGAAAGTTCGAGTCCAAGC	64244-64263
46	CAGGAAAGTTCGAGTCCAAG	64245-64264
47	CCCAGGAAAGTTCGAGTCCA	64247-64266
48	GCCCAGGAAAGTTCGAGTCC	64248-64267
49	AGCCCAGGAAAGTTCGAGTC	64249-64268
50	CTCTCACCAGCGTGTGGAG	64616-64635
51	CCTCTCACCAGCGTGTGGGA	64617-64636
52	GCCTCTCACCAGCGTGTGG	64618-64637
53	GGCCTCTGGCCAGCTCTCCA	64885-64904
54	GGCAGTGCAGTGTGTGTCT	65149-65168
55	TCTGGCCACCACCAGCTTTG	65337-65356
56	CTCTGGCCACCACCAGCTTT	65338-65357
57	GCACCCTCTGGCCACCACCA	65343-65362
58	CCCCTCACTCCCAGTGTGCC	65443-65462
59	TGCCCCCTCACTCCCAGTGTG	65445-65464
60	CTGCCCCCTCACTCCCAGTGT	65446-65465
61	TCAGGCTGCCCCCTCACTCCC	65451-65470
62	GCTCAGGCTGCCCCCTCACTC	65453-65472
63	TGCTCAGGCTGCCCCCTCACT	65454-65473
64	TTGCTCAGGCTGCCCCCTCAC	65455-65474
65	TGCCATGGCTGACCTCACTT	65742-65761
135	AACATGTCATACAGATTTC	44298-44317
136	AATTATTTTGGATTCCAAGA	40026-40045
137	ACATGTCATACAGATTTC	44297-44316
138	AGTGTGGAACATGTCATACA	44305-44324
139	AGTTGCGAGTGTGGAACATG	44312-44331
140	ATGTCATACAGATTTC	44295-44314
141	ATTATTTTGGATTCCAAGAT	40025-40044
142	CATGTCATACAGATTTC	44296-44315
143	CGAGTGTGGAACATGTCATA	44307-44326
144	GAACATGTCATACAGATTTC	44299-44318
145	GAGTGTGGAACATGTCATAC	44306-44325
146	GGAACATGTCATACAGATT	44300-44319
147	GTGGAACATGTCATACAGAT	44302-44321
148	GTGTGGAACATGTCATACAG	44304-44323
149	TGGAACATGTCATACAGATT	44301-44320
150	TGTGGAACATGTCATACAGA	44303-44322
151	TTATTTTGGATTCCAAGATG	40024-40043
169	AACATGTCATACAGAT	44302-44317
170	AATTATTTTGGATTTC	40030-40045

171	ACATGTCATACAGATT	44301-44316
172	AGTGTGGAACATGTCA	44309-44324
173	AGTTGCGAGTGTGGA	44316-44331
174	ATGTCATACAGATTTC	44299-44314
175	ATTATTTTGGATTCCA	40029-40044
176	ATTTTGGATTCCAAGA	40026-40041
177	CAATCTGAACACAGAG	26048-26063
178	CATACAGATTTCCAAC	44295-44310
179	CATGTCATACAGATT	44300-44315
180	CCAAGGAACTTACTCC	333-348
181	CGAGTGTGGAACATGT	44311-44326
182	GAACATGTCATACAGA	44303-44318
183	GAGGTGTTATGAGTGG	63796-63811
184	GAGTGTGGAACATGTC	44310-44325
185	GCAATCTGAACACAGA	26049-26064
186	GCGAGTGTGGAACATG	44312-44327
187	GGAACATGTCATACAG	44304-44319
188	GTCATACAGATTTCCA	44297-44312
189	GTGGAACATGTCATAC	44306-44321
190	GTGTGGAACATGTCAT	44308-44323
191	GTTGCGAGTGTGGAAC	44315-44330
192	TATTTTGGATTCCAAG	40027-40042
193	TCATACAGATTTCCAA	44296-44311
194	TGCGAGTGTGGAACAT	44313-44328
195	TGGAACATGTCATACA	44305-44320
196	TGTCATACAGATTTCC	44298-44313
197	TGTGGAACATGTCATA	44307-44322
198	TTATTTTGGATTCCAA	40028-40043
199	TTGCGAGTGTGGAACA	44314-44329
200	TTGTACCCTTGTCTCA	64386-64401
201	TTTGGATTCCAAGATG	40024-40039
202	TTTGTACCCTTGTCTC	64387-64402
203	TTTTGGATTCCAAGAT	40025-40040

[0091] In some embodiments, an oligonucleotide comprises a sequence that is at least 80%, 85%, 90%, 95%, or 100% identical to any one of SEQ ID NOS: 9-12, 135, 137-140, and 142-150 in the following **Table 2**. In some embodiments, an oligonucleotide comprises a sequence that differs by no more than 1, 2, 3, or 4 nucleotides from any one of the sequences listed below in **Table 2**. **Table 2** includes exemplary SAMHD1 oligonucleotides that target a particular region on the SAMHD1 transcript within an identified “hotspot” region, or a region that when

targeted by an oligonucleotide described herein, decreases SAMHD1 RNA expression. **Table 2** includes exemplary SAMHD1 oligonucleotide sequences and the corresponding coordinates of the target region within the SAMHD1 gene sequence (starting from the 5' end of SAMHD1 gene sequence as shown in SEQ ID NO: 1).

Table 2: Oligonucleotide Sequences, Corresponding Coordinates of Another Target Region on SAMHD1 Gene Sequence (SEQ ID NO: 1)

SEQ ID NO:	Oligonucleotide DNA Sequence (5' to 3')	Corresponding Coordinates within SEQ ID NO: 1
140	ATGTCATACAGATTTCCAAC	44295-44314
142	CATGTCATACAGATTTCCAA	44296-44315
137	ACATGTCATACAGATTTCCA	44297-44316
135	AACATGTCATACAGATTTCC	44298-44317
144	GAACATGTCATACAGATTTTC	44299-44318
146	GGAACATGTCATACAGATTT	44300-44319
149	TGGAACATGTCATACAGATT	44301-44320
147	GTGGAACATGTCATACAGAT	44302-44321
150	TGTGGAACATGTCATACAGA	44303-44322
148	GTGTGGAACATGTCATACAG	44304-44323
138	AGTGTGGAACATGTCATACA	44305-44324
145	GAGTGTGGAACATGTCATAC	44306-44325
143	CGAGTGTGGAACATGTCATA	44307-44326
9	GCGAGTGTGGAACATGTCAT	44308-44327
10	TGCGAGTGTGGAACATGTCA	44309-44328
11	TTGCGAGTGTGGAACATGTC	44310-44329
12	GTTGCGAGTGTGGAACATGT	44311-44330
139	AGTTGCGAGTGTGGAACATG	44312-44331

[0092] In some embodiments, an oligonucleotide is complementary to a region of a SAMHD1 RNA transcript as illustrated in **FIG. 6**. In some embodiments, an oligonucleotide is complementary to a region of a SAMHD1 RNA transcript as illustrated in **Table 3**. In some

embodiments, an oligonucleotide sequence is complementary to a region within the SAMHD1 gene sequence (SEQ ID NO: 1).

[0093] In some embodiments, an oligonucleotide comprises a sequence that is complementary (*e.g.*, substantially complementary or perfectly complementary) to a SAMHD1 sequence, *e.g.*, SAMHD1 mRNA or pre-mRNA transcript (*e.g.*, complementary to a nucleotide sequence that is at least 80%, 85%, 90%, 95%, or 100% identical to a target region of SEQ ID NO: 131). In some embodiments, an oligonucleotide is complementary to 8 to 30 contiguous nucleotides of a SAMHD1 RNA transcript (*i.e.*, the target region), *e.g.*, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides long, although shorter and longer target regions are also contemplated.

[0094] In some embodiments, an oligonucleotide comprises a sequence that is complementary to a target region within corresponding coordinates 44295-44314, 44296-44315, 44297-44316, 44298-44317, 44299-44318, 44300-44319, 44301-44320, 44302-44321, 44303-44322, 44304-44323, 44305-44324, 44306-44325, 44307-44326, 44308-44327, 44309-44328, 44310-44329, 44311-44330, or 44312-44331 within SEQ ID NO: 1 of the SAMHD1 mRNA transcript. In some embodiments, a target region comprises a span of 8-30 contiguous nucleotides within the SAMHD1 mRNA transcript or SAMHD1 gene sequence comprising SEQ ID NOS: 9-12, 135, 137-140, 142-150.

[0095] In some embodiments, the 8 to 30 contiguous nucleotides on the SAMHD1 RNA transcript (*i.e.*, target region) comprises a sequence that is at least 80%, 85%, 90%, 95%, or 100% identical to any one of the sequences listed below in **Table 3**.

[0096] In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 80% identity to a sequence selected from a group consisting of SEQ ID NOS: 66-129, 152-168, and 204-238. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 85% identity to a sequence selected from a group consisting of SEQ ID NOS: 66-129, 152-168, and 204-238. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 90% identity to a sequence selected from a group consisting of SEQ ID NOS: 66-129, 152-168, and 204-238. In some embodiments, an

oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 95% identity to a sequence selected from a group consisting of SEQ ID NOs: 66-129, 152-168, and 204-238. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence selected from a group consisting of SEQ ID NOs: 66-129, 152-168, and 204-238.

[0097] In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 80% identity to a sequence selected from a group consisting of SEQ ID NOs: 66-76. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 85% identity to a sequence selected from a group consisting of SEQ ID NOs: 66-76. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 90% identity to a sequence selected from a group consisting of SEQ ID NOs: 66-76. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 95% identity to a sequence selected from a group consisting of SEQ ID NOs: 66-76. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence selected from a group consisting of SEQ ID NOs: 66-76.

[0098] In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 80% identity to SEQ ID NO: 68. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 85% to SEQ ID NO: 68. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 90% identity to SEQ ID NO: 68. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 95% identity to SEQ ID NO: 68. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises SEQ ID NO: 68.

[0099] In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 80% identity to SEQ ID NO: 70. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 85% to SEQ ID NO: 70. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 90% identity to SEQ ID NO: 70. In some embodiments, an oligonucleotides complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 95% identity to SEQ ID NO: 70. In some embodiments, an oligoribonucleotide complementary to a target region on the SAMHD1 RNA transcript that comprises SEQ ID NO: 70.

[00100] In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 80% identity to SEQ ID NO: 73. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 85% to SEQ ID NO: 73. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 90% identity to SEQ ID NO: 73. In some embodiments, an oligoribonucleotide complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 95% identity to SEQ ID NO: 73. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises SEQ ID NO: 73.

[00101] In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 80% identity to SEQ ID NO: 74. In some embodiments, an oligonucleotides complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 85% to SEQ ID NO: 74. In some embodiments, an oligonucleotide complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 90% identity to SEQ ID NO: 74. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 95% identity to SEQ ID NO: 74. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises SEQ ID NO: 74.

[00102] In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 80% identity to SEQ ID NO: 75. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 85% to SEQ ID NO: 75. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 90% identity to SEQ ID NO: 75. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 95% identity to SEQ ID NO: 75. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises SEQ ID NO: 75.

[00103] In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 80% identity to SEQ ID NO: 76. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 85% to SEQ ID NO: 76. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 90% identity to SEQ ID NO: 76. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1 RNA transcript that comprises a sequence having at least 95% identity to SEQ ID NO: 76. In some embodiments, an oligonucleotide is complementary to a target region on the SAMHD1@Dave RNA transcript that comprises SEQ ID NO: 76.

[00104] In some embodiments, an oligonucleotide comprises a sequence that is complementary (*e.g.*, substantially complementary or perfectly complementary, and/or includes no more than 1, 2, 3, or 4 nucleotide mismatches) to 8 to 30 contiguous nucleotides (*i.e.*, a target region) of a SAMHD1 RNA transcript (*e.g.*, SEQ ID NO: 131). In some embodiments, an oligonucleotide comprises a sequence that is complementary to 8 to 30 contiguous nucleotides (*i.e.*, a target region) within a region that corresponds to nucleotides 44295-44331 of SEQ ID NO: 1. In some embodiments, an oligonucleotide comprises a sequence that is complementary to 8 to 30 contiguous nucleotides (*i.e.*, a target region) of SEQ ID NO: 132. In some embodiments, an oligonucleotide is complementary to any one of the sequences listed below in **Table 3**.

Table 3: Target Sequence of SAMHD1

SEQ ID NO:	Target Sequence of SAMHD1 RNA Transcript (5' to 3')
66	CTCAATTTCAACGTCTTCGA
67	CATCAAACAGCTGGGAGGTG
68	AACAGCTGGGAGGTGGTTAC
69	ACAGCTGGGAGGTGGTTACT
70	AGGAGCTTCACACAATCGAT
71	TTCACACAATCGATTTGAGC
72	TTCTCACATGTTTGATGGAC
73	ATGACATGTTCCCACTCGC
74	TGACATGTTCCCACTCGCA
75	GACATGTTCCCACTCGCAA
76	ACATGTTCCCACTCGCAAC
77	GGAAAAGGAGGGAAGTGGAT
78	GATGGAGGGAAGTGGATAAA
79	GAATGGGAGGTAGGACATGA
80	AATGGGAGGTAGGACATGAA
81	TCAAACACTGGGTGTGAGTC
82	CAAACACTGGGTGTGAGTCA
83	AAACACTGGGTGTGAGTCAA
84	GAATGCAAAGCCCTGCGACA
85	AATGCAAAGCCCTGCGACAG
86	ATGCAAAGCCCTGCGACAGT
87	TGCAAAGCCCTGCGACAGTG
88	GCAAAGCCCTGCGACAGTGC
89	CAAAGCCCTGCGACAGTGCC
90	AAAGCCCTGCGACAGTGCCT
91	GCCCTGCGACAGTGCCTGGA
92	CCCTGCGACAGTGCCTGGAA
93	CCTGCGACAGTGCCTGGAAC
94	CTGCGACAGTGCCTGGAACA
95	TGCGACAGTGCCTGGAACAC
96	GCGACAGTGCCTGGAACACA
97	GTTTCACAACCTTCTGCCAGA
98	TATTGTAAGAAGGTGGACAG
99	ATTGTAAGAAGGTGGACAGA
100	TTGTAAGAAGGTGGACAGAA
101	TGTAAGAAGGTGGACAGAAA
102	TGTTCAAGTGGTGTGCAGACA
103	GTTCAAGTGGTGTGCAGACAG
104	ACCAAGCCGCAGGATGGCGA

105	CCAAGCCGCAGGATGGCGAT
106	CAAGCCGCAGGATGGCGATG
107	AAAGGAATGGAACGACAGTA
108	AGCTTGGA CT CGAACTTTCC
109	GCTTGGA CT CGAACTTTCCCT
110	CTTGGA CT CGAACTTTCCCTG
111	TGGACTCGAACTTTCCCTGGG
112	GGACTCGAACTTTCCCTGGGC
113	GACTCGAACTTTCCCTGGGCT
114	CTCCAACACGCTGGTGAGAG
115	TCCAACACGCTGGTGAGAGG
116	CCAACACGCTGGTGAGAGGC
117	TGGAGAGCTGGCCAGAGGCC
118	AGCACAAACACTGCACTGCC
119	CAAAGCTGGTGGTGGCCAGA
120	AAAGCTGGTGGTGGCCAGAG
121	TGGTGGTGGCCAGAGGGTGC
122	GGCACACTGGGAGTGAGGGG
123	CACACTGGGAGTGAGGGGCA
124	ACACTGGGAGTGAGGGGCAG
125	GGGAGTGAGGGGCAGCCTGA
126	GAGTGAGGGGCAGCCTGAGC
127	AGTGAGGGGCAGCCTGAGCA
128	GTGAGGGGCAGCCTGAGCAA
129	AAGTGAGGTCAGCCATGGCA
152	GGAAATCTGTATGACATGTT
153	TCTTGGAATCCAAAATAATT
154	TGGAAATCTGTATGACATGT
155	TGTATGACATGTTCCCACT
156	CATGTTCCCACTCGCAACT
157	GTTGGAATCTGTATGACAT
158	ATCTTGGAATCCAAAATAAT
159	TTGGAATCTGTATGACATG
160	TATGACATGTTCCCACTCG
161	GAAATCTGTATGACATGTTC
162	GTATGACATGTTCCCACTC
163	AAATCTGTATGACATGTTCC
164	ATCTGTATGACATGTTCCAC
165	CTGTATGACATGTTCCACAC
166	AATCTGTATGACATGTTCCA
167	TCTGTATGACATGTTCCACA
168	CATCTTGGAATCCAAAATAA
204	ATCTGTATGACATGTT

205	GGAATCCAAAATAATT
206	AATCTGTATGACATGT
207	TGACATGTTCCACACT
208	TTCCACACTCGCAACT
209	GAAATCTGTATGACAT
210	TGGAATCCAAAATAAT
211	TCTTGGAATCCAAAAT
212	CTCTGTGTTTCAGATTG
213	GTTGGAAATCTGTATG
214	AAATCTGTATGACATG
215	GGAGTAAGTTCCTTGG
216	ACATGTTCCACACTCG
217	TCTGTATGACATGTTC
218	CCACTCATAACACCTC
219	GACATGTTCCACACTC
220	TCTGTGTTTCAGATTGC
221	CATGTTCCACACTCGC
222	CTGTATGACATGTTCC
223	TGGAAATCTGTATGAC
224	GTATGACATGTTCCAC
225	ATGACATGTTCCACAC
226	GTTCCACACTCGCAAC
227	CTTGGAATCCAAAATA
228	TTGGAAATCTGTATGA
229	ATGTTCCACACTCGCA
230	TGTATGACATGTTCCA
231	GGAAATCTGTATGACA
232	TATGACATGTTCCACA
233	TTGGAATCCAAAATAA
234	TGTTCCACACTCGCAA
235	TGAGACAAGGGTACAA
236	CATCTTGGAATCCAAA
237	GAGACAAGGGTACAAA
238	ATCTTGGAATCCAAA

[00105] In some embodiments, a target region on the SAMHD1 RNA transcript comprises a sequence that corresponds to nucleotides 21722-21741, 21744-21763, 21749-21768, 21750-21769, 21780-21799, 21786-21805, 29605-29624, 44308-44327, 44309-44328, 44310-44329, 44311-44330, 44555-44574, 44584-44603, 44714-44733, 44715-44734, 44936-44955, 44937-44956, 44938-44957, 45297-45316, 45298-45317, 45299-45318, 45300-45319, 45301-45320, 45302-45321, 45303-45322, 45306-45325, 45307-45326, 45308-45327, 45309-45328, 45310-

45329, 45311-45330, 58885-58904, 58933-58952, 58934-58953, 58935-58954, 58936-58955, 58983-59002, 58984-59003, 59011-59022 and 63778-63785, 59012-59022 and 63778-63786, 59013-59022 and 63778-63787, 63816-63835, 64243-64262, 64244-64263, 64245-64264, 64247-64266, 64248-64267, 64249-64268, 64616-64635, 64617-64636, 64618-64637, 64885-64904, 65149-65168, 65337-65356, 65338-65357, 65343-65362, 65443-65462, 65445-65464, 65446-65465, 65451-65470, 65453-65472, 65454-65473, 65455-65474, 65742-65761, 44298-44317, 40026-40045, 44297-44316, 44305-44324, 44312-44331, 44295-44314, 40025-40044, 44296-44315, 44307-44326, 44299-44318, 44306-44325, 44300-44319, 44302-44321, 44304-44323, 44301-44320, 44303-44322, 40024-40043, 44302-44317, 40030-40045, 44301-44316, 44309-44324, 44316-44331, 44299-44314, 40029-40044, 40026-40041, 26048-26063, 44295-44310, 44300-44315, 333-348, 44311-44326, 44303-44318, 63796-63811, 44310-44325, 26049-26064, 44312-44327, 44304-44319, 44297-44312, 44306-44321, 44308-44323, 44315-44330, 40027-40042, 44296-44311, 44313-44328, 44305-44320, 44298-44313, 44307-44322, 40028-40043, 44314-44329, 64386-64401, 40024-40039, 64387-64402, or 40025-40040 of SEQ ID NO: 1.

[00106] In some embodiments, an oligonucleotide comprises a sequence that is complementary to a sequence that corresponds to nucleotides 21749-21768 of SEQ ID NO: 1. In some embodiments, an oligonucleotide comprises a sequence that is complementary to a sequence that corresponds to nucleotides 21780-21799 of SEQ ID NO: 1. In some embodiments, an oligonucleotide comprises a sequence that is complementary to a sequence that corresponds to nucleotides 44308-44327 of SEQ ID NO: 1. In some embodiments, an oligonucleotide comprises a sequence that is complementary to a sequence that corresponds to nucleotides 44309-44328 of SEQ ID NO: 1. In some embodiments, an oligonucleotide comprises a sequence that is complementary to a sequence that corresponds to nucleotides 44310-44329 of SEQ ID NO: 1. In some embodiments, an oligonucleotide comprises a sequence that is complementary to a sequence that corresponds to nucleotides 44311-44330 of SEQ ID NO: 1. In some embodiments, an oligonucleotide comprises a sequence that is complementary to a sequence that corresponds to nucleotides 44295-44314, 44296-44315, 44297-44316, 44298-44317, 44299-44318, 44300-44319, 44301-44320, 44302-44321, 44303-44322, 44304-44323, 44305-44324, 44306-44325, 44307-44326, 44308-44327, 44309-44328, 44310-44329, 44311-44330, or 44312-44331 of SEQ ID NO: 1.

[00107] In some embodiments, an oligonucleotide comprises a sequence that differs by no more than 1, 2, 3, or 4 nucleotides from any one of SEQ ID NOs: 2-12 and/or is complementary to a nucleotide sequence that differs by no more than 1, 2, 3, or 4 nucleotides from any one of SEQ ID NO: 66-76.

Modifications

[00108] In some embodiments, an oligonucleotide of the disclosure comprises a sequence based on a phosphodiester backbone (*i.e.*, an unmodified oligonucleotide sequence). In some embodiments, an oligonucleotide of the disclosure includes one or more modified nucleotides.

[00109] The use of naturally occurring nucleic acids (*e.g.*, unmodified DNA or RNA) is limited, for example, by their susceptibility to endo- and exo-nucleases. As such, various synthetic counterparts have been developed to circumvent these shortcomings. These include synthetic oligonucleotides that contain chemical modification, *e.g.*, base modifications, sugar modifications, backbone modifications, etc., which, among other things, render these molecules less susceptible to degradation and improve other properties of oligonucleotides. Chemical modifications may also lead to certain undesired effects, such as increased toxicities, etc.

[00110] Such as base sequence, chemical modifications (*e.g.*, modifications of sugar, base, and/or internucleotidic linkages, and patterns thereof), and/or stereochemistry (*e.g.*, stereochemistry of backbone chiral centers (chiral internucleotidic linkages), and/or patterns thereof), can have significant impact on properties, *e.g.*, stability, splicing-altering capabilities, etc. In some embodiments, oligonucleotide properties can be adjusted by optimizing chemical modifications (modifications of base, sugar, and/or internucleotidic linkage) and/or stereochemistry (pattern of backbone chiral centers).

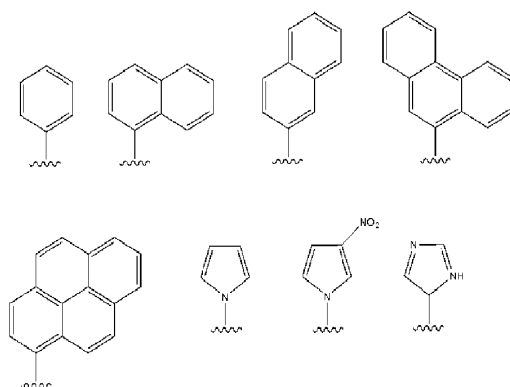
[00111] In some embodiments, a modified nucleotide comprises a base modification, a sugar or sugar phosphate modification, an internucleotidic linkage modification, or a combination thereof.

[00112] In some embodiments, an oligonucleotide of the disclosure includes one or more natural nucleobase and/or one or more modified nucleobases derived from a natural nucleobase. Examples include, but are not limited to, uracil, thymine, adenine, cytosine, and guanine having their respective amino groups protected by acyl protecting groups, 2-fluorouracil, 2-

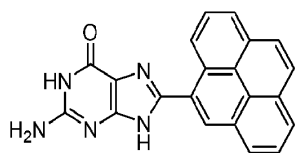
fluorocytosine, 5-bromouracil, 5-iodouracil, 2,6-diaminopurines, azacytosine, pyrimidine analogs such as pseudoisocytosine and pseudouracil and other modified nucleobases such as 8-substituted purines, xanthine, or hypoxanthine (the latter two being the natural degradation products).

[00113] Modified nucleobases also include expanded-size nucleobases in which one or more aryl rings, such as phenyl rings, have been added.

[00114] In some embodiments, modified nucleobases comprise any one of the following substituents, each of which is optionally substituted:



[00115] For example, a pyrene-modified guanine base can have the structure



[00116] A person skilled in the art would understand where and how a nucleobase can be modified with any of the foregoing groups.

[00117] In some embodiments, a modified nucleobase is unsubstituted. In some embodiments, a modified nucleobase is substituted. In some embodiments, a modified nucleobase is substituted such that it contains, e.g., heteroatoms, alkyl groups, or linking moieties connected to fluorescent moieties, biotin or avidin moieties, or other protein or peptides. In some embodiments, a modified nucleobase is a “universal base” that is not a

nucleobase in the most classical sense, but that functions similarly to a nucleobase. One representative example of such a universal base is 3-nitropyrrole.

[00118] In some embodiments, an oligonucleotide described herein includes nucleosides that incorporate modified nucleobases and/or nucleobases covalently bound to modified sugars (i.e., a “base modification”). Some examples of nucleosides that incorporate modified nucleobases include 4-acetylcytidine; 5-(carboxyhydroxymethyl)uridine; 2'-*O*-methylcytidine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; dihydrouridine; 2'-*O*-methylpseudouridine; beta,D-galactosylqueosine; 2'-*O*-methylguanosine; *N*⁶-isopentenyladenosine; 1-methyladenosine; 1-methylpseudouridine; 1-methylguanosine; 1-methylinosine; 2,2-dimethylguanosine; 2-methyladenosine; 2-methylguanosine; *N*⁷-methylguanosine; 3-methylcytidine; 5-methylcytidine; 5-hydroxymethylcytidine; 5-methylcytosine, 5-formylcytosine; 5-carboxylcytosine; *N*⁶-methyladenosine; 7-methylguanosine; 5-methylaminoethyluridine; 5-methoxyaminomethyl-2-thiouridine; beta,D-mannosylqueosine; 5-methoxycarbonylmethyluridine; 5-methoxyuridine; 2-methylthio-*N*⁶-isopentenyladenosine; *N*-((9-beta,D-ribofuranosyl-2-methylthiopurine-6-yl)carbamoyl)threonine; *N*-((9-beta,D-ribofuranosylpurine-6-yl)-*N*-methylcarbamoyl)threonine; uridine-5-oxyacetic acid methylester; uridine-5-oxyacetic acid; pseudouridine; queosine; 2-thiocytidine; 5-methyl-2-thiouridine; 2-thiouridine; 4-thiouridine; 5-methyluridine; 2'-*O*-methyl-5-methyluridine; and 2'-*O*-methyluridine. In some embodiments, an oligonucleotide described herein comprises at least one G-clamp modification.

[00119] In some embodiments, nucleosides include 6'-modified bicyclic nucleoside analogs that have either (*R*) or (*S*)-chirality at the 6'-position and include the analogs described in US Patent No. 7,399,845. In other embodiments, nucleosides include 5'-modified bicyclic nucleoside analogs that have either (*R*) or (*S*)-chirality at the 5'-position and include the analogs described in U.S. Publ. No. 20070287831. In some embodiments, a nucleobase or modified nucleobase is 5-bromouracil, 5-iodouracil, or 2,6-diaminopurine. In some embodiments, a nucleobase or modified nucleobase is modified by substitution with a fluorescent moiety.

[00120] In some embodiments, an oligonucleotide described herein includes one or more modified nucleotides wherein a phosphate group or linkage phosphorus in the nucleotides are

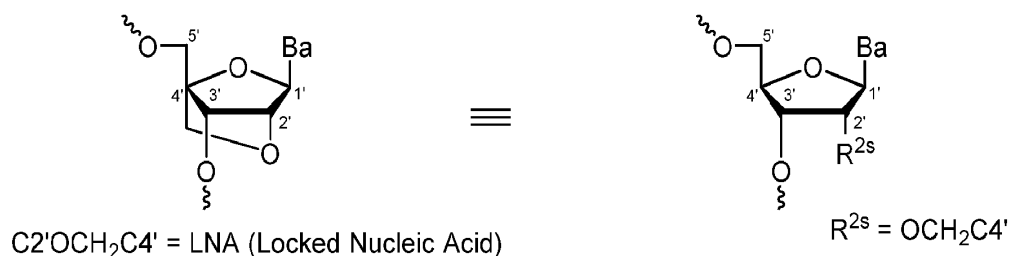
linked to various positions of a sugar or modified sugar. As non-limiting examples, the phosphate group or linkage phosphorus can be linked to the 2', 3', 4' or 5' hydroxyl moiety of a sugar or modified sugar. Nucleotides that incorporate modified nucleobases as described herein are also contemplated in this context. In some embodiments, the sugar or sugar phosphate modification comprises a 2'-O-methoxyethyl (2'-MOE) modification, a 2'-fluoro (2'-F) modification, a 2'-O-methyl (2'-O-Me) modification, a phosphorodiamidate morpholino (PMO) modification, a peptide nucleic acid (PNA) modification, a glycol nucleic acid (GNA), an unlocked nucleic acid (UNA), or a locked nucleic acid (LNA).

[00121] Other modified sugars can also be incorporated within an oligonucleotide molecule. In some embodiments, a modified sugar contains one or more groups at the 2' position selected from -F, -CF₃, -CN, -N₃, -NO, -NO₂, -OR', -SR', or -N(R')₂, wherein each R' is independently hydrogen or optionally substituted C₁-C₁₀ aliphatic. In some embodiments, a modified sugar contains one or more groups at the 2' position selected from -F, -CF₃, -CN, -N₃, -NO, -NO₂, -O-(C₁-C₁₀ alkyl), -S-(C₁-C₁₀ alkyl), -NH-(C₁-C₁₀ alkyl), -N(C₁-C₁₀ alkyl)₂, -O-(C₂-C₁₀ alkenyl), -S-(C₂-C₁₀ alkenyl), -NH-(C₂-C₁₀ alkenyl), -N(C₂-C₁₀ alkenyl)₂, -O-(C₂-C₁₀ alkynyl), -S-(C₂-C₁₀ alkynyl), -NH-(C₂-C₁₀ alkynyl), -N(C₂-C₁₀ alkynyl)₂, -O-(C₁-C₁₀ alkylene)-O-(C₁-C₁₀ alkyl), -O-(C₁-C₁₀ alkylene)-NH-(C₁-C₁₀ alkyl), -O-(C₁-C₁₀ alkylene)-N(C₁-C₁₀ alkyl)₂, -NH-(C₁-C₁₀ alkylene)-O-(C₁-C₁₀ alkyl), or -N(C₁-C₁₀ alkyl)-(C₁-C₁₀ alkylene)-O-(C₁-C₁₀ alkyl), wherein each alkyl, alkylene, alkenyl and alkynyl may be substituted or unsubstituted. In some embodiments, an alkyl, alkenyl, or alkynyl is substituted by a group selected from -O(CH₂)_nOCH₃ or -O(CH₂)_nNH₂, wherein n is from 1 to about 10, MOE, DMAOE, and DMAEOE.

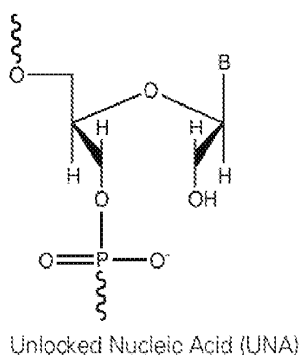
[00122] In some embodiments, the 2'-OH of a ribose is replaced with a group selected from -H, -F, -CF₃, -CN, -N₃, -NO, -NO₂, -OR', -SR', or -N(R')₂, wherein each R' is independently hydrogen or optionally substituted C₁-C₁₀ aliphatic. In some embodiments, a modified sugar contains one or more groups at the 2' position selected from -F, -CF₃, -CN, -N₃, -NO, -NO₂, -O-(C₁-C₁₀ alkyl), -S-(C₁-C₁₀ alkyl), -NH-(C₁-C₁₀ alkyl), -N(C₁-C₁₀ alkyl)₂, -O-(C₂-C₁₀ alkenyl), -S-(C₂-C₁₀ alkenyl), -NH-(C₂-C₁₀ alkenyl), -N(C₂-C₁₀ alkenyl)₂, -O-(C₂-C₁₀ alkynyl), -S-(C₂-C₁₀ alkynyl), -NH-(C₂-C₁₀ alkynyl), -N(C₂-C₁₀ alkynyl)₂, -O-(C₁-C₁₀ alkylene)-O-(C₁-C₁₀ alkyl), -O-(C₁-C₁₀ alkylene)-NH-(C₁-C₁₀ alkyl), -O-(C₁-C₁₀ alkylene)-

$N(C_1-C_{10} \text{ alkyl})_2$, $-NH-(C_1-C_{10} \text{ alkylene})-O-(C_1-C_{10} \text{ alkyl})$, or $-N(C_1-C_{10} \text{ alkyl})-(C_1-C_{10} \text{ alkylene})-O-(C_1-C_{10} \text{ alkyl})$, wherein each alkyl, alkylene, alkenyl and alkynyl may be substituted or unsubstituted. In some embodiments, the 2'-OH is replaced with -H (i.e., deoxyribose). In some embodiments, the 2'-OH is replaced with -F. In some embodiments, the 2'-OH is replaced with -OR'. In some embodiments, the 2'-OH is replaced with -OMe. In some embodiments, the 2'-OH is replaced with $-OCH_2CH_2OMe$ (i.e., MOE).

[00123] Modified sugars also include locked nucleic acids (LNAs). In some embodiments, the locked nucleic acid has the structure indicated below. In some embodiments, a locked nucleic acid comprises the structure below, wherein Ba represents a nucleobase or modified nucleobase as described herein, and wherein R^{2s} is $-OCH_2C4'$ —

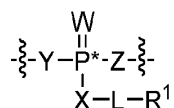


[00124] Modified sugars also include unlocked nucleic acids (UNAs). In some embodiments, an unlocked nucleic acid has the structure indicated below (see *e.g.*, Fluiters, Kees, et al., *Molecular BioSystems* 5.8 (2009): 838-843, which is herein incorporated by reference in its entirety). In some embodiments, a locked nucleic acid comprises the structure below.



[00125] In some embodiments, an oligonucleotide described herein comprises at least one modified internucleotidic linkage. In some embodiments, an internucleotidic linkage modification comprises a phosphorothioate or phosphodithioate linkage modification.

[00126] In some embodiments, the present invention provides an oligonucleotide comprising one or more modified internucleotidic linkages independently having the structure of formula I:



(I)

wherein:

P* is an asymmetric phosphorus atom and is either *Rp* or *Sp*;

W is O, S or Se;

each of X, Y and Z is independently -O-, -S-, -N(-L-R¹)-, or L;

L is a covalent bond or an optionally substituted, linear or branched, saturated or unsaturated C₁-C₁₀ aliphatic, wherein one or more methylene units of L are optionally and independently replaced by -C(R')₂-, -Cy-, -O-, -S-, -S-S-, -N(R')-, -C(O)-, -C(S)-, -C(NR')-, -C(O)N(R')-, -N(R')C(O)N(R'), -N(R')C(O)-, -N(R')C(O)O-, -OC(O)N(R')-, -S(O)-, -S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)₂-, -SC(O)-, -C(O)S-, -OC(O)-, or -C(O)O-;

R¹ is halogen, R, or an optionally substituted, linear or branched, saturated or unsaturated C₁-C₅₀ aliphatic wherein one or more methylene units are optionally and independently replaced by -C(R')₂-, -Cy-, -O-, -S-, -S-S-, -N(R')-, -C(O)-, -C(S)-, -C(NR')-, -C(O)N(R')-, -N(R')C(O)N(R'), -N(R')C(O)-, -N(R')C(O)O-, -OC(O)N(R')-, -S(O)-, -S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)₂-, -SC(O)-, -C(O)S-, -OC(O)-, or -C(O)O-;

each R' is independently -R, C(O)R, CO₂R, or -SO₂R, or:

[00128] Among other things, the present disclosure provides oligonucleotides of various designs, which may comprise various nucleobases and patterns thereof, sugars and patterns thereof, internucleotidic linkages and patterns thereof, and/or additional chemical moieties and patterns thereof as described in the present disclosure. In some embodiments, provided oligonucleotides can decrease the level of SAMHD1 protein, SAMHD1 mRNA expression and/or SAMHD1 activity in a cell of a subject. In some embodiments, such an oligonucleotide has a base sequence which consists of, comprises, or comprises a portion (*e.g.*, a span of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more contiguous bases) of the base sequence of an oligonucleotide disclosed herein, wherein each T can be independently substituted with U and vice versa, and the oligonucleotide comprises at least one non-naturally-occurring modification of a base, sugar and/or internucleotidic linkage.

[00129] According to certain embodiments, various nucleotide modifications or nucleotide modification patterns may be in any of oligonucleotides described herein.

[00130] In some embodiments, an oligonucleotide comprises two or more chemically distinct regions, wherein the regions confer distinct properties on the compound. In some embodiments, at least one region is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid and at least one additional region of the oligonucleotide can serve as a substrate for enzymes (*e.g.*, RNase H) capable of cleaving RNA:DNA or RNA:RNA hybrids. In some embodiments, at least one region of the oligonucleotide can serve as a substrate for enzymes (*e.g.*, RNase H) capable of cleaving RNA:DNA or RNA:RNA hybrids and at least one region can inhibit translation by steric blocking.

[00131] In some embodiments, an oligonucleotide comprises at least one (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) phosphorothioate (PS) internucleotide bond. In some embodiments, an oligonucleotide comprises a sequence where each internucleotidic linkage comprises a phosphorothioate (PS) internucleotide bond. In some embodiments, an oligonucleotide comprises at least one (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) phosphodithioate bond. In some embodiments, an oligonucleotide comprises a sequence where each internucleotidic linkage comprises a phosphodithioate bond.

[00132] In some embodiments, an oligonucleotide comprises at least one (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) 2'-MOE modification.

[00133] In some embodiments, an oligonucleotide comprises five nucleotides at the 5'-end and five nucleotides at the 3'-end which contain a 2'-MOE modification.

[00134] In some embodiments, an oligonucleotide is modified so that each nucleotide comprises a 2'-MOE modification.

[00135] In some embodiments, an oligonucleotide described herein (*e.g.*, any one of the sequences listed in **Table 1**, or a sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to any one of the sequences listed in **Table 1**) comprises one of the following modification patterns or a portion thereof:

X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS} ("5-6-5" 16-mer)

X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS} ("4-8-4" 16-mer)

X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS} ("3-10-3" 16-mer)

X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS} ("5-8-5" 18-mer)

X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS} ("5-9-4" 18-mer)

X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS} ("4-9-5" 18-mer)

X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS} ("5-10-5" 20-mer)

X_{MS}

[00136] where "X" represents any nucleotide; a "M" represents a 2'-O-MOE group; and an "S" represents a phosphorothioate bond.

[00137] When DNA-based antisense oligonucleotides (ASO) bind to their cognate mRNA transcripts, the endogenous RNase H enzyme RNASEH1 recognizes RNA–DNA heteroduplex substrates that are formed and further cleaves at the site of ASO binding and results in degradation of the target RNA, thereby silencing target gene expression. Gapmer antisense oligonucleotides (ASOs), consisting of a DNA-based internal 'gap' and RNA-like flanking

regions (often consisting of 2'-O-methyl (2'-OMe) or 2'-O-methoxyethyl(2'-MOE) modified bases) bind to target transcripts with high affinity. In some embodiments, oligonucleotides comprise a Gapmer modification pattern.

[00138] In some embodiments, an oligonucleotide comprises any one of the sequences listed in **Table 1**, or a sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to any one of the sequences listed in **Table 1** and comprises the following modification pattern:

$X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}[X_S]_{6-10}X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}$

[00139] where “X” represents any nucleotide; a “M” represents a 2'-O-MOE group; and an “S” represents a phosphorothioate bond.

[00140] In some embodiments, an oligonucleotide comprises any one of the sequences listed in **Table 1**, or a sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to any one of the sequences listed in **Table 1** and comprises the following modification pattern:

$[X_{MS}]_{16-20}$

[00141] where “X” represents any nucleotide; a “M” represents a 2'-O-MOE group; and an “S” represents a phosphorothioate bond.

[00142] In some embodiments, oligonucleotides are provided and/or utilized in salt forms. In some embodiments, oligonucleotides are provided as salts comprising negatively charged internucleotidic linkages (*e.g.*, phosphorothioate internucleotidic linkages, natural phosphate linkages, etc.) existing as their salt forms. In some embodiments, oligonucleotides are provided as pharmaceutically acceptable salts. In some embodiments, oligonucleotides are provided as metal salts. In some embodiments, metal salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using the appropriate hydroxide or amine base. In some embodiments, oligonucleotides are provided as sodium salts. In some embodiments, oligonucleotides are provided as metal salts, *e.g.*, sodium salts, wherein each negatively charged internucleotidic linkage is independently in a salt form (*e.g.*, for sodium salts, $-O-P(O)(SNa)-O-$ for a phosphorothioate internucleotidic linkage, $-O-P(O)(ONa)-O-$ for a

natural phosphate linkage, etc.). In some embodiments, oligonucleotides are provided as ammonium salts.

[00143] In some embodiments, an oligonucleotide can be modified according to any one of the modifications and modification patterns described herein and can also be conjugated to a ligand, *e.g.*, as described herein. In some such embodiments, a ligand can be attached to any of the 3' or 5' terminus of the oligonucleotide sequence.

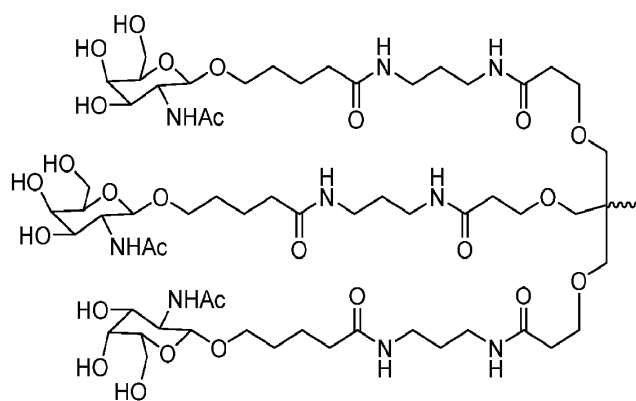
[00144] In some embodiments, the ligand targets the nucleic acid molecule to hepatocytes. For example, in some embodiments the ligand binds to hepatocyte-specific asialoglycoprotein receptor (ASGPR), *e.g.*, the ligand comprises a galactose derivative, *e.g.*, GalNAc.

[00145] In some embodiments, an oligonucleotide is conjugated to or otherwise physically associated with one or more moieties that modulate, *e.g.*, enhance, the activity, stability, cellular distribution, and/or cellular uptake of the oligonucleotide and/or alter one or more physical properties of the oligonucleotide, such as charge or solubility. In some embodiments, a moiety may comprise an antibody or ligand. A ligand may be a carbohydrate, lectin, protein, glycoprotein, lipid, cholesterol, steroid, bile acid, nucleic acid hormone, growth factor, or receptor. In some embodiments a biologically inactive variant of a naturally occurring hormone, growth factor, or other ligand may be used. In some embodiments, the moiety comprises a targeting moiety that targets the oligonucleotide to a specified cell type, *e.g.*, a hepatocyte. In some embodiments a targeting moiety binds to hepatocyte-specific asialoglycoprotein receptor (ASGPR).

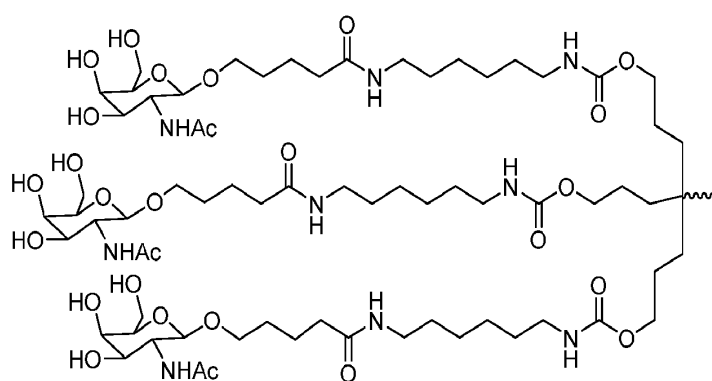
[00146] In some embodiments, a moiety is attached to an oligonucleotide via a reversible linkage. A “reversible linkage” is a linkage that comprises a reversible bond. A “reversible bond” (also referred to as a labile bond or cleavable bond) is a covalent bond other than a covalent bond to a hydrogen atom that is capable of being selectively broken or cleaved more rapidly than other bonds in a molecule under selected conditions, the bond is capable of being selectively broken or cleaved under conditions that substantially will not break or cleave other covalent bonds in the same molecule. Cleavage or lability of a bond may be described in terms of the half-life ($t_{1/2}$) of bond cleavage (the time required for half of the bonds to cleave).

[00147] In some embodiments a moiety attached to an oligonucleotide comprises a carbohydrate. Representative carbohydrates include mono-, di-, tri- and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units. In certain embodiments the carbohydrate comprises galactose or a galactose derivative such as galactosamine, N-formyl-galactosamine, N-acetylgalactosamine, N-propionyl-galactosamine, N-n-butanoyl-galactosamine, and N-iso-butanoylgalactos-amine. In certain embodiments of particular interest the galactose derivative comprises N-acetylgalactosamine (GalNAc). In certain embodiments, the moiety comprises multiple instances of the galactose or galactose derivative, *e.g.*, multiple N-acetylgalactosamine moieties, *e.g.*, 3 GalNAc moieties. A terminal galactose derivative may be attached to another moiety through the C-1 carbon of the galactose derivative. In some embodiments two or more, *e.g.*, three, galactose derivatives are attached to a moiety that serves as a branch point and that can be attached to an oligonucleotide. In some embodiments, a galactose derivative is linked to the moiety that serves as a branch point via a linker or spacer. In some embodiments, the moiety that serves as a branch point may be attached to an oligonucleotide via a linker or spacer. For example, in some embodiments, a galactose derivative is attached to a branch point via a linker or spacer that comprises an amide, carbonyl, alkyl, oligoethylene glycol moiety, or combination thereof. In some embodiments, at least 3 nucleoside–GalNAc monomers or at least 3 non-nucleoside–GalNAc monomers are incorporated site-specifically into an oligonucleotide. In some embodiments, such incorporation may occur during solid-phase synthesis using phosphoramidite chemistry or via post synthetic conjugation. In some embodiments, the galactose derivative-containing monomeric units are joined via phosphodiester bonds to each other and/or to nucleosides of the oligonucleotide that do not have a galactose derivative attached.

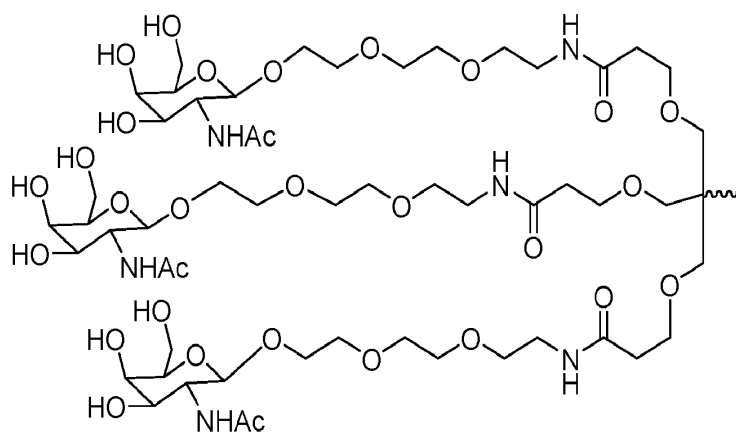
[00148] Exemplary galactose clusters are depicted below.



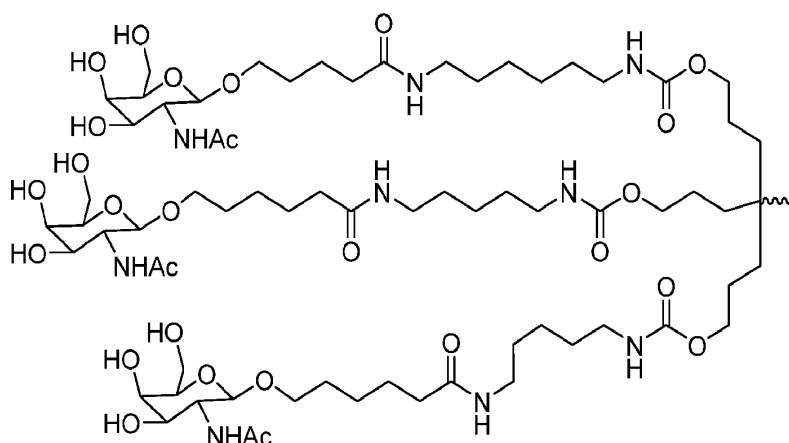
Formula I



Formula II



Formula III



Formula IV

[00149] In some embodiments, a GalNAc moiety (*e.g.*, a GalNAc moiety as represented in Formulas I-IV) is conjugated to the 5' end of an oligonucleotide described herein (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151 or 169-203).

[00150] In some embodiments, a GalNAc moiety (*e.g.*, a GalNAc moiety as represented in Formulas I-IV) is conjugated to the 3' end of an oligonucleotide described herein (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151 or 169-203).

[00151] Methods of conjugating oligonucleotides to a GalNAc moiety are known in the art and exemplary methods are disclosed in Østergaard, Michael E., et al., "Efficient synthesis and biological evaluation of 5'-GalNAc conjugated antisense oligonucleotides." *Bioconjugate chemistry* 26.8 (2015): 1451-1455, which is herein incorporated by reference in its entirety.

[00152] In some embodiments, a 2' deoxyadenosine phosphodiester is inserted between the oligonucleotide and the GalNAc conjugate to facilitate metabolic cleavage. Accordingly, in some embodiments, an oligonucleotide sequence contains an additional adenine (A) nucleotide residue at the 5' or 3' end where a GalNAc moiety is conjugated (see *e.g.*, Østergaard, Michael E., et al., 2015) and the additional A contains a phosphate bond between the A and the 5' or 3' nucleotide of the oligonucleotide. Exemplary modification patterns are shown below:

AoX_{MS}X_{MS}X_{MS}X_{MS}X_{MS}[X_S]₆₋₁₀X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}

X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}[X_S]₆₋₁₀X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}Ao

$$Ao[X_{MS}]_{16-20}$$

$$[X_{MS}]_{16-20}Ao$$

$$Ao[X_{MS}]_{16-20}Ao$$

[00153] where “A” represents an adenine; an “X” represents any nucleotide; a “M” represents a 2'-O-MOE group; an “S” represents a phosphorothioate bond; and an “O” represents a phosphate linkage.

[00154] In some embodiments, an oligonucleotide comprises any one of the sequences listed in Table 1, or a sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to any one of the sequences listed in Table 1 and comprises the following modification pattern:

$$AoX_{MS}X_{MS}X_{MS}X_{MS}X_{MS}[X_S]_{6-10}X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}$$

$$X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}[X_S]_{6-10}X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}Ao$$

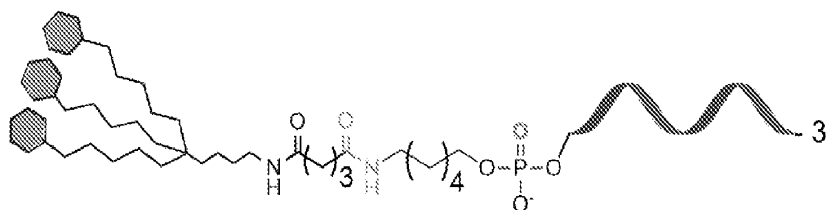
$$Ao[X_{MS}]_{16-20}$$

$$[X_{MS}]_{16-20}Ao$$

$$Ao[X_{MS}]_{16-20}Ao$$

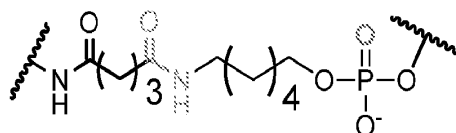
[00155] where “A” represents an adenine; an “X” represents any nucleotide; a “M” represents a 2'-O-MOE group; an “S” represents a phosphorothioate bond; and an “O” represents a phosphate linkage.

[00156] In some embodiments, a linking moiety connects an oligonucleotide described herein (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151 or 169-203) to a GalNAc moiety (*e.g.*, as shown in Formulas I-IV). In some embodiments, an oligonucleotide described herein is conjugated to GalNAc as depicted below:



5'-triantennary GalNAc-ASO conjugate

[00157] In some embodiments, a linking moiety comprises a structure as depicted below:



Formula A

[00158] In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) is conjugated to a GalNAc moiety as shown in Formula I at its 5' end via a linker as shown in Formula A. In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) is conjugated to a GalNAc moiety as shown in Formula I at its 3' end via a linker as shown in Formula A. In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) additionally comprises a 2' deoxyadenosine phosphodiester inserted between the oligonucleotide and the GalNAc/Linker moiety.

[00159] In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) is conjugated to a GalNAc moiety as shown in Formula II at its 5' end via a linker as shown in Formula A. In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) is conjugated to a GalNAc moiety as shown in Formula II at its 3' end via a linker as shown in Formula A. In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) additionally comprises a 2'

deoxyadenosine phosphodiester inserted between the oligonucleotide and the GalNAc/Linker moiety.

[00160] In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) is conjugated to a GalNAc moiety as shown in Formula III at its 5' end via a linker as shown in Formula A. In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) is conjugated to a GalNAc moiety as shown in Formula III at its 3' end via a linker as shown in Formula A. In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) additionally comprises a 2' deoxyadenosine phosphodiester inserted between the oligonucleotide and the GalNAc/Linker moiety.

[00161] In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) is conjugated to a GalNAc moiety as shown in Formula IV at its 5' end via a linker as shown in Formula A. In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) is conjugated to a GalNAc moiety as shown in Formula IV at its 3' end via a linker as shown in Formula A. In some embodiments, an oligonucleotide (*e.g.*, an oligonucleotide represented in any one of SEQ ID NOs: 2-65, 135-151, or 169-203) additionally comprises a 2' deoxyadenosine phosphodiester inserted between the oligonucleotide and the GalNAc/Linker moiety.

[00162] In some embodiments a moiety attached to an oligonucleotide comprises a lipophilic moiety. In some embodiments, the lipophilic moiety comprises a tocopherol, *e.g.*, alpha-tocopherol. In some embodiments, the lipophilic moiety comprises cholesterol. In some embodiments, the lipophilic compound comprises an alkyl or heteroalkyl group. In some embodiments the lipophilic compound comprises palmitoyl, hexadec-8-enoyl, oleyl, (9E,12E)-octadeca-9,12-dienoyl, dioctanoyl, or C₁₆-C₂₀ acyl. In some embodiments, the lipophilic moiety comprises at least 16 carbon atoms. In some embodiments the lipophilic moiety comprises – (CH_y)_n-NH-(C=O)-(CH_x)_m-CH₃, wherein each of m and n is independently 0-20; and each of x

and y is independently 0-2. In some embodiments, n and m are each independently an integer from 1 to 20. In some embodiments, n + m is at least 10, 12, 14, or 16.

[00163] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

Compositions and Administration

[00164] In some embodiments, one or more oligonucleotides as described herein may be formulated in an oligonucleotide composition. In some embodiments, an oligonucleotide composition comprises oligonucleotides comprising the same nucleotide sequence (e.g., any one of the sequences provided in **Table 1**). In some embodiments, an oligonucleotide composition comprises oligonucleotides comprising more than one nucleotide sequence (e.g., more than one of the sequences provided in **Table 1**).

[00165] In some embodiments, provided oligonucleotide compositions may be or include pure preparations of individual stereochemically isomeric forms of a compound (e.g., comprising a chirally pure oligonucleotide). In some embodiments, provided oligonucleotide compositions may be or include mixtures of two or more stereochemically isomeric forms of the compound. In some embodiments, such mixtures contain equal amounts of different stereochemically isomeric forms. In some embodiments, such mixtures contain different amounts of at least two different stereochemically isomeric forms. In some embodiments, an oligonucleotide

composition may contain all diastereomers and/or enantiomers of the compound. In some embodiments, an oligonucleotide composition may contain less than all diastereomers and/or enantiomers of a compound. In some embodiments, if a particular enantiomer of an oligonucleotide is desired, it may be prepared, for example, by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, diastereomeric salts are formed with an appropriate optically-active acid, and resolved, for example, by fractional crystallization.

Pharmaceutical Compositions

[00166] In some embodiments, the present disclosure provides pharmaceutical compositions comprising one or more oligonucleotides. In some embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable carrier.

[00167] In some embodiments, a pharmaceutical composition is formulated for systemic or localized administration. In some embodiments, a pharmaceutical composition is for delivery route selected from intrathecal, oral, intramuscular, or intravenous administration.

[00168] Pharmaceutically acceptable compositions of this disclosure may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents. In some embodiments, an intranasal composition is an intranasal drop or spray (fine mist) in a liquid form such as, for example, a solution, emulsion or suspension.

[00169] Pharmaceutically acceptable compositions of this disclosure may also be adapted for pulmonary administration, such as an inhalation composition to be inhaled by the patient. The inhalation composition can be in the form of a dry powder inhalation composition, a pressurized aerosol inhalation composition or a nebulized inhalation composition (e.g., an aqueous suspension or solution).

[00170] In some embodiments, an oligonucleotide is associated with a delivery agent. “Delivery agent” refers to a substance or entity that is non-covalently or covalently associated with an oligonucleotide or is co-administered with an oligonucleotide and serves one or more functions that increase the stability and/or efficacy of the biologically active agent beyond that which would result if the biologically active agent was delivered (*e.g.*, administered to a subject) in the absence of the delivery agent. For example, a delivery agent may protect an oligonucleotide from degradation, may facilitate entry of an oligonucleotide into cells or into a cellular compartment of interest (*e.g.*, the cytoplasm or mitochondria), and/or may enhance associations with particular cells containing the molecular target to be modulated. Those of ordinary skill in the art are aware of numerous delivery agents that may be used to deliver oligonucleotide (see Dhuri, Karishma, et al., *Journal of clinical medicine* 9.6 (2020), which is herein incorporated by reference in its entirety). In some embodiments, *e.g.*, for administering an oligonucleotide systemically, the oligonucleotide may be associated with a delivery agent such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Lipids (*e.g.*, cationic lipids, or neutral lipids), dendrimers, or polymers may be bound to an oligonucleotide or may form a vesicle or micelle that encapsulates an oligonucleotide.

[00171] In some embodiments an oligonucleotide is administered in association with a lipid or lipid-containing particle (*e.g.*, a lipid nanoparticle (LNP)). In some embodiments an oligonucleotide is administered in association with a cationic polymer (which may be a polypeptide or a non-polypeptide polymer), a lipid, a peptide, PEG, cyclodextrin, or combination thereof, which may be in the form of a nanoparticle or microparticle. The lipid or peptide may be cationic. “Nanoparticle” refers to particles with lengths in two or three dimensions greater than 1 nanometer (nm) and smaller than about 150 nm *e.g.*, 20 nm – 50 nm or 50 nm -100 nm. “Microparticle” refers to particles with lengths in two or three dimensions greater than 150 nm and smaller than about 1000 nm. A nanoparticle may have a targeting moiety and/or cell-penetrating moiety or membrane active moiety covalently or noncovalently attached thereto. Nanoparticles, such as lipid nanoparticles, are described in, *e.g.*, Tatiparti et al., *Nanomaterials* 7:77 (2017), which is herein incorporated by reference in its entirety.

[00172] In some embodiments, a delivery agent comprises one or more amino acid lipids. Amino acid lipids are molecules containing an amino acid residue (*e.g.*, arginine, homoarginine,

norarginine, nor-norarginine, ornithine, lysine, homolysine, histidine, 1-methylhistidine, pyridylalanine, asparagine, N-ethylasparagine, glutamine, 4-aminophenylalanine, the N-methylated versions thereof, and side chain modified derivatives thereof) and one or more lipophilic tails. In some embodiments, a delivery agent comprises a lipopeptide compound comprising a central peptide and having lipophilic groups attached at each terminus. In some embodiments lipophilic groups can be derived from a naturally occurring lipid. In some embodiments a lipophilic group may comprise a C(1-22)alkyl, C(6-12)cycloalkyl, C(6-12)cycloalkyl-alkyl, C(3-18)alkenyl, C(3-18)alkynyl, C(1-5)alkoxy-C(1-5)alkyl, or a sphinganine, or (2R,3R)-2-amino-1,3-octadecanediol, icosasphinganine, sphingosine, phytosphingosine, or cis-4-sphingenine. The central peptide may comprise a cationic or amphipathic amino acid sequence. Examples of such lipopeptides and their use to deliver nucleic acids are described in, *e.g.*, U.S. Pat. No. 9,220,785, which is herein incorporated by reference.

[00173] In some embodiments, an oligonucleotide is conjugated to a delivery agent that is a polymer. Useful delivery polymers include, *e.g.*, poly(acrylate) polymers (see., *e.g.*, US Pat. Pub. No. 20150104408), poly(vinyl ester) polymers (see., *e.g.*, US Pat. Pub. No. 20150110732) and certain polypeptides.

[00174] In some embodiments, an oligonucleotide may be administered in “naked” form, *i.e.*, administered in the absence of a delivery agent. The naked oligonucleotide may be in a suitable buffer solution. The buffer solution may, for example, comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In some embodiments, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution can be adjusted such that it is suitable for administering to a subject. In some embodiments, an oligonucleotide is administered not in physical association with a lipid or lipid-containing particle. In some embodiments, an oligonucleotide is administered not in physical association with a nanoparticle or microparticle. In some embodiments, an oligonucleotide is administered not in physical association with a cationic polymer.

[00175] Oligonucleotides described herein, can be incorporated into pharmaceutical compositions. Such pharmaceutical compositions are useful for, among other things,

administration and delivery to a subject *in vivo* or *ex vivo*. In some embodiments, pharmaceutical compositions also contain a pharmaceutically acceptable carrier or excipient. Such excipients include any pharmaceutical agent, *e.g.*, a pharmaceutical agent that does not itself induce an immune response harmful to the individual receiving the composition, and which may be administered without undue toxicity. As used herein the terms “pharmaceutically acceptable” and “physiologically acceptable” mean a biologically acceptable formulation, gaseous, liquid or solid, or mixture thereof, which is suitable for one or more routes of administration, *in vivo* delivery or contact. Pharmaceutically acceptable excipients include, but are not limited to, liquids such as water, saline, glycerol, sugars and ethanol. Pharmaceutically acceptable salts can also be included therein, for example, mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such vehicles.

[00176] Pharmaceutical compositions may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding, free base forms. In some embodiments, a pharmaceutical composition may be a lyophilized powder.

[00177] Pharmaceutical compositions can include solvents (aqueous or non-aqueous), solutions (aqueous or non-aqueous), emulsions (*e.g.*, oil-in-water or water-in-oil), suspensions, syrups, elixirs, dispersion and suspension media, coatings, isotonic and absorption promoting or delaying agents, compatible with pharmaceutical administration or *in vivo* contact or delivery. Aqueous and non-aqueous solvents, solutions and suspensions may include suspending agents and thickening agents. Such pharmaceutically acceptable carriers include tablets (coated or uncoated), capsules (hard or soft), microbeads, powder, granules and crystals. Supplementary active compounds (*e.g.*, preservatives, antibacterial, antiviral and antifungal agents) can also be incorporated into the compositions.

[00178] Pharmaceutical compositions can be formulated to be compatible with a particular route of administration or delivery, as set forth herein or known to one of skill in the art. Thus, pharmaceutical compositions include carriers, diluents, or excipients suitable for administration by various routes.

[00179] Compositions suitable for parenteral administration can comprise aqueous and non-aqueous solutions, suspensions or emulsions of the active compound, which preparations are typically sterile and can be isotonic with the blood of the intended recipient. Non-limiting illustrative examples include water, buffered saline, Hanks' solution, Ringer's solution, dextrose, fructose, ethanol, animal, vegetable or synthetic oils. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oil injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility to allow for the preparation of highly concentrated solutions.

[00180] Cosolvents and adjuvants may be added to the formulation. Non-limiting examples of cosolvents contain hydroxyl groups or other polar groups, for example, alcohols, such as isopropyl alcohol; glycols, such as propylene glycol, polyethyleneglycol, polypropylene glycol, glycol ether; glycerol; polyoxyethylene alcohols and polyoxyethylene fatty acid esters. Adjuvants include, for example, surfactants such as, soy lecithin and oleic acid; sorbitan esters such as sorbitan trioleate; and polyvinylpyrrolidone.

[00181] After pharmaceutical compositions have been prepared, they may be placed in an appropriate container and labeled for treatment. Such labeling can include amount, frequency, and method of administration.

[00182] Pharmaceutical compositions and delivery systems appropriate for the compositions, methods and uses of the disclosure are known in the art (see, *e.g.*, Remington: The Science and Practice of Pharmacy. 21st Edition. Philadelphia, PA. Lippincott Williams & Wilkins, 2005, which is herein incorporated by reference).

Dosing and Administration

[00183] Oligonucleotides described herein, or a vector comprising a nucleotide sequence encoding an oligonucleotide described herein, can be used to treat cancer or a metabolic disease or disorder, e.g., subjects suffering from or susceptible to a metabolic disease or disorder (*e.g.*, a mt DNA depletion syndrome) described herein. The mode of administration of pharmaceutical compositions described herein can vary depending upon the desired results. One with skill in the art, *i.e.*, a physician, is aware that dosage regimens can be adjusted to provide the desired response, *e.g.*, a therapeutic response.

[00184] Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intrathecal (*e.g.*, intracisternal or via a lumbar puncture), intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. In some embodiments, compositions of oligonucleotides are delivered to the central nervous system (CNS), *e.g.*, delivered via intracerebroventricular administration.

[00185] In some embodiments, a pharmaceutical composition described herein is delivered to the liver. In some embodiments, a pharmaceutical composition described herein is delivered to the muscle. In some embodiments, a pharmaceutical composition described herein is delivered to the CNS (*e.g.*, via intrathecal administration). In some embodiments, a pharmaceutical composition described herein is delivered to the cerebrospinal fluid.

[00186] Delivery of an oligonucleotide to a cell may be achieved in a number of different ways. In vivo delivery may be performed by administering a composition comprising an oligonucleotide to a subject, *e.g.*, by parenteral administration route, *e.g.*, subcutaneous or intravenous or intramuscular administration.

[00187] The disclosure also provides methods for administering an oligonucleotide, or a vector comprising a nucleotide sequence encoding an oligonucleotide described herein, into a cell or an animal. In some embodiments, such methods include contacting a subject (*e.g.*, a cell or tissue of a subject) with, or administering to a subject (*e.g.*, a subject such as a mammal), an oligonucleotide described herein (or a vector comprising a nucleotide sequence encoding an

oligonucleotide described herein), such that the oligonucleotide is expressed in the subject (*e.g.*, in a cell or tissue of a subject).

[00188] Compositions of oligonucleotides described herein (or a vector comprising a nucleotide sequence encoding an oligonucleotide described herein) can be administered in a sufficient or effective amount to a subject in need thereof. Doses can vary and depend upon the type, onset, progression, severity, frequency, duration, or probability of the disease to which treatment is directed, the clinical endpoint desired, previous or simultaneous treatments, the general health, age, gender, race or immunological competency of the subject and other factors that will be appreciated by the skilled artisan. The dose amount, number, frequency or duration may be proportionally increased or reduced, as indicated by any adverse side effects, complications or other risk factors of the treatment or therapy and the status of the subject. The skilled artisan will appreciate the factors that may influence the dosage and timing required to provide an amount sufficient for providing a therapeutic or prophylactic benefit.

[00189] All publications, patent applications, patents, and other references mentioned herein, including GenBank Accession Numbers, are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described herein.

[00190] The disclosure is further illustrated by the following examples. The examples are provided for illustrative purposes only. They are not to be construed as limiting the scope or content of the disclosure in any way.

EXAMPLES

Example 1: Knockdown of SAMHD1 Expression in Human 143B cells

[00191] This example illustrates the design and production of exemplary oligonucleotides that target the SAMHD1 RNA transcript and are capable of altering mRNA expression of SAMHD1 in human 143B cells.

[00192] The exemplary oligonucleotide sequences, the target region on the SAMHD1 RNA transcript, and the corresponding coordinates of the target region within the full SAMHD1 gene sequence (SEQ ID NO: 1) are shown in **Table 4** below.

Table 4

Oligo SEQ ID NO:	Oligonucleotide sequence (5' to 3')	SEQ ID NO:	SAMHD1 RNA Sequence (5' to 3')	Corresponding coordinates within SEQ ID NO: 1
2	TCGAAGACGTTGAAATTGAG	66	CTCAATTTCAACGTCTTCGA	21722-21741
3	CACCTCCCAGCTGTTTGATG	67	CATCAAACAGCTGGGAGGTG	21744-21763
4	GTAACCACCTCCCAGCTGTT	68	AACAGCTGGGAGGTGGTTAC	21749-21768
5	AGTAACCACCTCCCAGCTGT	69	ACAGCTGGGAGGTGGTTACT	21750-21769
6	ATCGATTGTGTGAAGCTCCT	70	AGGAGCTTCACACAATCGAT	21780-21799
7	GCTCAAATCGATTGTGTGAA	71	TTACACAAATCGATTTGAGC	21786-21805
8	GTCCATCAAACATGTGAGAA	72	TTCTCACATGTTTGATGGAC	29605-29624
9	GCGAGTGTGGAACATGTCAT	73	ATGACATGTTCCACACTCGC	44308-44327
10	TGCGAGTGTGGAACATGTCA	74	TGACATGTTCCACACTCGCA	44309-44328
11	TTGCGAGTGTGGAACATGTC	75	GACATGTTCCACACTCGCAA	44310-44329
12	GTTGCGAGTGTGGAACATGT	76	ACATGTTCCACACTCGCAAC	44311-44330
13	ATCCACTTCCCTCCTTTTCC	77	GGAAAAGGAGGGAAGTGGAT	44555-44574
14	TTTATCCACTTCCCTCCATC	78	GATGGAGGGAAGTGGATAAA	44584-44603
15	TCATGTCCTACCTCCCATT	79	GAATGGGAGGTAGGACATGA	44714-44733
16	TTCATGTCCTACCTCCCATT	80	AATGGGAGGTAGGACATGAA	44715-44734
17	GA CTCACACCCAGTGT TGA	81	TCAAACACTGGGTGTGAGTC	44936-44955
18	TGACTCACACCCAGTGT TGA	82	CAAACACTGGGTGTGAGTCA	44937-44956
19	TTGACTCACACCCAGTGT TTT	83	AAACACTGGGTGTGAGTCAA	44938-44957
20	TGTCGCAGGGCTTTGCATT	84	GAATGCAAAGCCCTGCGACA	45297-45316
21	CTGTGCGAGGGCTTTGCATT	85	AATGCAAAGCCCTGCGACAG	45298-45317
22	ACTGTGCGAGGGCTTTGCAT	86	ATGCAAAGCCCTGCGACAGT	45299-45318
23	CACTGTGCGAGGGCTTTGCA	87	TGCAAAGCCCTGCGACAGTG	45300-45319
24	GCACTGTGCGAGGGCTTTGCA	88	GCAAAGCCCTGCGACAGTGC	45301-45320
25	GGCACTGTGCGAGGGCTTTG	89	CAAAGCCCTGCGACAGTGCC	45302-45321
26	AGGCACTGTGCGAGGGCTTT	90	AAAGCCCTGCGACAGTGCC	45303-45322
27	TCCAGGCACTGTGCGAGGGC	91	GCCCTGCGACAGTGCCTGGA	45306-45325
28	TTCCAGGCACTGTGCGAGGG	92	CCCTGCGACAGTGCCTGGAA	45307-45326
29	GTTCCAGGCACTGTGCGAGG	93	CCTGCGACAGTGCCTGGAAC	45308-45327
30	TGTTCCAGGCACTGTGCGAG	94	CTGCGACAGTGCCTGGAACA	45309-45328
31	GTGTTCCAGGCACTGTGCGA	95	TGCGACAGTGCCTGGAACAC	45310-45329
32	TGTGTTCCAGGCACTGTGCGC	96	GCGACAGTGCCTGGAACACA	45311-45330
33	TCTGGCAGAAGTTGTGAAAC	97	GTTTCACAACCTTCTGCCAGA	58885-58904
34	CTGTCCACCTTCTTACAATA	98	TATTGTAAGAAGGTGGACAG	58933-58952

35	TCTGTCCACCTTCTTACAAT	99	ATTGTAAGAAGGTGGACAGA	58934-58953
36	TTCTGTCCACCTTCTTACAA	100	TTGTAAGAAGGTGGACAGAA	58935-58954
37	TTTCTGTCCACCTTCTTACA	101	TGTAAGAAGGTGGACAGAAA	58936-58955
38	TGTCTGCACACCACTGAACA	102	TGTTCAAGTGGTGTGCAGACA	58983-59002
39	CTGTCTGCACACCACTGAAC	103	GTTCAAGTGGTGTGCAGACAG	58984-59003
40	TCGCCATCCTGCGGCTTGGT	104	ACCAAGCCGCAGGATGGCGA	59011-59022 and 63778-63785
41	ATCGCCATCCTGCGGCTTGG	105	CCAAGCCGCAGGATGGCGAT	59012-59022 and 63778-63786
42	CATCGCCATCCTGCGGCTTG	106	CAAGCCGCAGGATGGCGATG	59013-59022 and 63778-63787
43	TACTGTTCGTTCCATTCTTT	107	AAAGGAATGGAACGACAGTA	63816-63835
44	GGAAAGTTCGAGTCCAAGCT	108	AGCTTGACTCGAACTTTCC	64243-64262
45	AGGAAAGTTCGAGTCCAAGC	109	GCTTGACTCGAACTTTCTCT	64244-64263
46	CAGGAAAGTTCGAGTCCAAG	110	CTTGACTCGAACTTTCTCTG	64245-64264
47	CCCAGGAAAGTTCGAGTCCA	111	TGGACTCGAACTTTCTCTGGG	64247-64266
48	GCCCAGGAAAGTTCGAGTCC	112	GGACTCGAACTTTCTCTGGGC	64248-64267
49	AGCCCAGGAAAGTTCGAGTC	113	GACTCGAACTTTCTCTGGGCT	64249-64268
50	CTCTCACCAGCGTGTGGAG	114	CTCCAACACGCTGGTGAGAG	64616-64635
51	CCTCTCACCAGCGTGTGGA	115	TCCAACACGCTGGTGAGAGG	64617-64636
52	GCCTCTCACCAGCGTGTGG	116	CCAACACGCTGGTGAGAGGC	64618-64637
53	GGCCTCTGGCCAGCTCTCCA	117	TGGAGAGCTGGCCAGAGGCC	64885-64904
54	GGCAGTGCAGTGTGTGCT	118	AGCACAAACACTGCACTGCC	65149-65168
55	TCTGGCCACCACCAGCTTTG	119	CAAAGCTGGTGGTGGCCAGA	65337-65356
56	CTCTGGCCACCACCAGCTTT	120	AAAGCTGGTGGTGGCCAGAG	65338-65357
57	GCACCCTCTGGCCACCACCA	121	TGGTGGTGGCCAGAGGGTGC	65343-65362
58	CCCCTCACTCCCACTGTGCC	122	GGCACACTGGGAGTGAGGGG	65443-65462
59	TGCCCCCTCACTCCCACTGTG	123	CACACTGGGAGTGAGGGGCA	65445-65464
60	CTGCCCCCTCACTCCCACTGT	124	ACACTGGGAGTGAGGGGCAG	65446-65465
61	TCAGGCTGCCCCCTCACTCCC	125	GGGAGTGAGGGGCAGCCTGA	65451-65470
62	GCTCAGGCTGCCCCCTCACTC	126	GAGTGAGGGGCAGCCTGAGC	65453-65472
63	TGCTCAGGCTGCCCCCTCACT	127	AGTGAGGGGCAGCCTGAGCA	65454-65473
64	TTGCTCAGGCTGCCCCCTCAC	128	GTGAGGGGCAGCCTGAGCAA	65455-65474
65	TGCCATGGCTGACCTCACTT	129	AAGTGAGGTGAGCCATGGCA	65742-65761

Oligonucleotide Synthesis

[00193] Exemplary oligonucleotide were synthesized using phosphoramidite synthesis methods that begin with the 3'-most nucleotide and proceed through multiple cycles of the following steps: deprotection (trityl group is removed from the 5' carbon by trichloroacetic acid (TCA) resulting in a reactive hydroxyl group for the next base to be added), coupling (using

tetrazole activation to produce an intermediate that reacts with the hydroxyl group), capping (acetylating reagent is added to react with free hydroxyl groups of oligonucleotides where coupling failed), and stabilization (iodine and water are added to cause oxidation of the phosphite into phosphate leaving a stabilized phosphor-triester bond), until the 5'-most nucleotide is attached. Where phosphorothioate bonds are produced in exemplary oligonucleotides, a sulfurizing agent is used in place of iodine/water in the stabilize step, for example, dibenzyl tetrasulfide, Beaucage Reagent (3*H*-1,2-benzodithiol-3-one 1,1-dioxide), 3-ethoxy-1,2,4-dithiazolidin-5-one (EDITH), 1,2,4-dithiazolidine-3,5-dione (DtsNH), 3-amino-1,2,4-dithiazole-5-thione.

[00194] The remaining trityl groups were removed from completed synthesis and from the CPG resulting in a hydroxyl group on both the 3' and 5' ends. The oligo was deprotected using ammonium hydroxide to promote base hydrolysis. The remaining contaminants were removed through desalting. The oligonucleotides were purified via PAGE or HPLC and quality is confirmed using Mass Spectrometry (using either Matrix Assisted Laser Desorption Ionization – Time of Flight (MALDI-TOF) or Electrospray Ionization (ESI)) (see <https://eu.idtdna.com/pages/products/functional-genomics/antisense-oligos>).

[00195] In this experiment, oligonucleotides contained modifications that included the following modification pattern:

[00196] X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS}X_{MS}

[00197] where “X” represents any nucleotide; a “M” represents a 2'-O-MOE group; and an “S” represents a phosphorothioate bond.

Oligonucleotide Transfection

[00198] Human 143B cells (ATCC CRL-8303) were grown at 37 °C with 5% (v/v) CO₂ in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% foetal bovine serum (FBS).

[00199] 1.5 µl of each oligonucleotide (100µM) was added to 8 µL of DharmaFECT 1 (horizondiscovery, T-2001-02), 1 ml Opti-MEM media (Thermo Fisher Scientific, Cat#11058021), and mixed well. Oligonucleotides were tested at 25 nM. The mixture was

incubated for 15 min at room temperature. 5 mL of 5×10^4 /mL 143B cells were added to the mixture and mixed well. The cells and oligonucleotide mixture were seeded (2 mL per well) in a 6-well plate and grown for 24 hours.

RT-PCR Protocol

[00200] The following RT-PCR protocol was performed:

1. Transfer 143B cells to eppendorf tubes, pellet cells by centrifuging 500 x g 5 min, and remove remaining media. Wash the cell pellet with 1 x Phosphate Buffered Saline (PBS). Add 1 mL of trizol solution (Thermo Fisher Scientific, Cat# 15596026) to the 143B cell pellet. Resuspend the cells completely by vortexing.
2. Incubate tubes at room temperature for 5 min.
3. Add 200 µl chloroform. Vortex for 10 seconds.
4. Incubate for 5 min at room temperature to permit nucleoprotein dissociation.
5. Centrifuge the tubes at 12,000 x g for 15 min at 4 °C.
6. Transfer the upper phase to a new microcentrifuge tube without disturbing the interphase.
7. Add 500 µL of isopropanol to the sample, invert 5 times to mix and incubate 30 min at -20 °C.
8. Centrifuge at a minimum of 12,000 x g for 15 min at 4 °C and remove the supernatant. The RNA will appear as a white pellet in the tube.
9. Wash the pellet with 500 µL of ice-cold 75% ethanol (made with deionized, diethylpyrocarbonate (DEPC) treated and 0.22 µm membrane-filtered H₂O).
10. Remove the ethanol, air dry for 5 minutes at room temperature (do not completely dry the RNA) and resuspend the RNA in 100 µL of DEPC-H₂O.
11. Incubate 5 µg RNA with 1 unit of turbo DNase (TURBO DNA-free Kit, Thermo Fisher Scientific, Cat# AM1907) at room temperature for 15 minutes and stop reaction following the manufacturer's instructions.
12. Purify RNA using a Quick-RNA miniprep kit (ZYMO, Cat# R1055).
13. Perform reverse transcription using 1 µg RNA and the iScript cDNA Synthesis Kit (Biorad, 170-8891).
14. Dilute 20 µl of cDNA to a final volume of 200 µl using H₂O. The cDNA is now ready for PCR quantification.

[00201] The iTaq Universal SYBR Green Supermix (Bio-Rad, Cat# #1725121) was used together with primers ordered from Eurofins genomics (shown below in **Table 5**) to detect expression of SAMHD1, CytB and 18S rRNA genes. Quantification was performed using the Biorad CFX96 PCR system. The reaction mixtures in each well contained 1 μ L forward primer (conc. 5 μ M) and 1 μ L reverse primer (conc. 5 μ M), 2 μ L cDNA, 9.5 μ L H₂O and 12.5 μ L SYBR supermix.

Table 5:

Primer	Supplier	Sequence	SEQ ID NO:	Storage
Human 18S_qPCR_F	Eurofins	AGAAACGGCTACCACATCCA	239	-20 °C
Human 18S_qPCR_R	Eurofins	CCCTCCAATGGATCCTCGTT	240	-20 °C
SAMHD1_RT_F	Eurofins	TCACAGGCGCATTACTGCC	241	-20 °C
SAMHD1_RT_R	Eurofins	GGATTTGAACCAATCGCTGGA	242	-20 °C

Results – SAMHD1 Expression

[00202] SAMHD1 expression in 143B cells transfected with the exemplary oligonucleotides are shown in **FIG. 1**. A scrambled oligonucleotide (not a perfect match to any human transcripts) was used as a negative control. All results were normalized by 18S expression.

[00203] Of the oligonucleotides tested at 25 nM concentration (*i.e.*, oligonucleotides represented in SEQ ID NOs: 2-65), all oligonucleotide sequences showed a reduction of relative SAMHD1 expression at 25 nM (**FIG. 1**).

[00204] The results in **FIG. 1** show that oligonucleotides represented in SEQ ID NOs: 2-12 showed excellent inhibition of SAMHD1 expression. Additionally, a subset of these (oligonucleotides corresponding to SEQ ID NOs: 9-12) targeting a region within a region that corresponds to nucleotides 44295-44331 of SEQ ID NO: 1 (*i.e.*, a region within the target region defined by SEQ ID NO: 132) showed particularly good inhibition of SAMHD1 expression. **FIG. 6** shows the particular region on the SAMHD1 transcript targeted by oligonucleotides represented in SEQ ID NOs: 9-12.

[00205] These results show that the inhibition activity of the oligonucleotide depends on the region of the SAMHD1 transcript targeted.

Example 2: Selection and Testing of Cross-Reactive Oligonucleotides in Human and Mouse cells

[00206] This example demonstrates oligonucleotides capable of SAMHD1 expression knockdown in human and mouse cells.

[00207] The oligonucleotides tested in Example 1 were screened for cross-reactivity in mouse cells. First, sequences of the targeting regions of the oligonucleotides tested in Example 1 were analyzed for the sequence conservation with the same targeting region of the mouse SAMHD1 transcript.

[00208] Oligonucleotides represented in SEQ ID NOs: 2-12 were selected for potential cross-reactivity in mouse and humans. These selected oligonucleotides were tested for their ability to knockdown SAMHD1 expression in both human and mouse cells.

Oligonucleotide Transfection

[00209] Mouse WT MEFs (Karolinska Institute) and Human 143B cells (ATCC # CRL-8303) were grown at 37 °C with 5% (v/v) CO₂ in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% foetal bovine serum (FBS).

[00210] 1.5 µl of each oligonucleotide (100 µM) was serially diluted (1:2) in PBS to 8 different final concentrations between 0-25 µM. 2 µl of each diluted oligonucleotides were added to 2 µL of DharmaFECT 1 (horizondiscovery, T-2001-02), and 330 µL of Opti-MEM media (Thermo Fisher Scientific, Cat#11058021). The mixtures were incubated for 15 min at room temperature. 1.67 mL of 5 × 10⁴/mL mouse WT MEFs were added to the oligonucleotide/media/DharmaFECT mixture and mixed well. The cells and oligonucleotide mixture were seeded (2 mL per well) in a 6-well plate and grown for 24 hours.

RT-PCR Protocol

[00211] The RT-PCR protocol is performed according to Example 1 in order to measure relative SAMHD1 mRNA expression levels.

Results

[00212] Table 6 below shows a comparison of SAMHD1 mRNA levels normalized to vehicle control in human 143B cells and mouse WT MEFs transfected with the same four oligonucleotides (represented in SEQ ID NOs: 9-12) at a concentration of 25nM. These results show that the four oligonucleotides tested were cross-reactive in human and mouse cells. Additionally, when compared with other oligonucleotides, oligonucleotides represented in SEQ ID NOs: 9-12 showed better cross-reactivity than other oligonucleotides targeting different regions of the SAMHD1 transcript (see **FIG. 4**).

Table 6

Oligo SEQ ID NO	cross species match	SamHD1 mRNA level (normalized to vehicle)	
		143B (Human)	WT MEF (Mouse)
2	-	0.15	0.72
3	-	0.15	0.72
4	-	0.06	0.49
5	-	0.15	0.47
6	-	0.08	0.72
7	-	0.18	0.72
8	-	0.17	0.51
9	perfect match	0.114	0.259
10	perfect match	0.139	0.081
11	perfect match	0.202	0.14
12	perfect match	0.178	0.159

[00213] Dose response curves for each oligonucleotides represented in SEQ ID NOs: 9-12 transfected in mouse WT MEFs are shown in **Figure 2** (panels A-D) and a scrambled control (panel E). Dose response curves for each oligonucleotide represented in SEQ ID NOs: 9-12 transfected in human 143B cells are shown in **Figure 3** (panels A-D) and a scrambled control (panel E).

[00214] **Table 7** below shows a comparison of IC50 values for SAMHD1 knockdown in mouse and human cells transfected with oligonucleotides represented by SEQ ID NOs: 9-12.

Table 7

Oligo SEQ ID NO	IC50 Wt MEF (nM)	IC50 143B (nM)
9	3.46 (4.10/2.82)	0.92
10	3.36	1.89
11	2.36	1.75
12	2.51	1.93

[00215] The results from this experiment demonstrate that oligonucleotides represented in SEQ ID NOs: 9-12 are effective at inhibiting both human and mouse SAMHD1 expression.

Example 3: Design and Testing of Additional Cross-Reactive Oligonucleotides targeting particular region of SAMHD1 gene sequence

[00216] This example illustrates the design of additional exemplary oligonucleotides that target human and mouse SAMHD1.

[00217] 81 oligonucleotides were selected by first generating oligonucleotides (20mers, 18mers, and 16mers) covering the longest transcript of human and mouse SAMHD1. Oligonucleotides were then selected that had identical sequences between human and mouse. Finally, oligonucleotide sequences containing motifs that diminish antisense activity were filtered out.

[00218] Of these 81 selected oligonucleotides, 21 were selected for testing in human 143B cells (which include oligonucleotides represented in SEQ ID NOs: 9-12), which are shown in **Table 8** below.

Table 8

Oligo SEQ ID NO:	Oligonucleotide sequence (5' to 3')	SEQ ID NO:	SAMHD1 RNA Sequence (5' to 3')	Corresponding coordinates within SEQ ID NO: 1
9	GCGAGTGTGGAACATGTCAT	73	ATGACATGTTCCACACTCGC	44308-44327
10	TGCGAGTGTGGAACATGTCA	74	TGACATGTTCCACACTCGCA	44309-44328
11	TTGCGAGTGTGGAACATGTC	75	GACATGTTCCACACTCGCAA	44310-44329
12	GTTGCGAGTGTGGAACATGT	76	ACATGTTCCACACTCGCAAC	44311-44330
135	AACATGTCATACAGATTTC	152	GGAAATCTGTATGACATGTT	44298-44317
136	AATTATTTTGGATTCCAAGA	153	TCTTGAATCCAAAATAATT	40026-40045
137	ACATGTCATACAGATTTC	154	TGGAAATCTGTATGACATGT	44297-44316
138	AGTGTGGAACATGTCATACA	155	TGTATGACATGTTCCACACT	44305-44324
139	AGTTGCGAGTGTGGAACATG	156	CATGTTCCACACTCGCAACT	44312-44331
140	ATGTCATACAGATTTC	157	GTTGGAAATCTGTATGACAT	44295-44314
141	ATTATTTTGGATTCCAAGAT	158	ATCTTGAATCCAAAATAAT	40025-40044
142	CATGTCATACAGATTTC	159	TTGGAAATCTGTATGACATG	44296-44315
143	CGAGTGTGGAACATGTCATA	160	TATGACATGTTCCACACTCG	44307-44326
144	GAACATGTCATACAGATTTC	161	GAAATCTGTATGACATGTTT	44299-44318
145	GAGTGTGGAACATGTCATAC	162	GTATGACATGTTCCACACTC	44306-44325
146	GGAACATGTCATACAGATTT	163	AAATCTGTATGACATGTTCC	44300-44319
147	GTGGAACATGTCATACAGAT	164	ATCTGTATGACATGTTCCAC	44302-44321
148	GTGTGGAACATGTCATACAG	165	CTGTATGACATGTTCCACAC	44304-44323
149	TGGAACATGTCATACAGATT	166	AATCTGTATGACATGTTCCA	44301-44320
150	TGTGGAACATGTCATACAGA	167	TCTGTATGACATGTTCCACA	44303-44322
151	TTATTTTGGATTCCAAGATG	168	CATCTTGAATCCAAAATAA	40024-40043

Oligonucleotide synthesis

[00219] Oligonucleotides were synthesized according to the protocol performed in Example 1. The oligonucleotides were chosen based on target regions of the oligonucleotides that were shown to have the greatest activity in Example 1. The targeting region for each of these oligonucleotides is shown in **FIG. 6**.

[00220] In this experiment, oligonucleotides contained modifications that included the following modification pattern:

X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS}X_{MS} (for 20-mers)

$X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS}X_{MS}$ (for 18-mers)

$X_{MS}X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS}X_{MS}$ (for 16-mers)

[00221] where “X” represents any nucleotide; a “M” represents a 2'-O-MOE group; and an “S” represents a phosphorothioate bond.

Oligonucleotide Transfection

[00222] Human 143B cells were transfected with each of the 21 oligonucleotides according to the protocol performed in Example 1.

RT-PCR Protocol

[00223] The RT-PCR protocol is performed according to Example 1 in order to measure relative SAMHD1 mRNA expression levels.

Results

[00224] Relative SAMHD1 expression levels and toxicity in cells transfected with each of the 21 oligonucleotides is shown in **FIG. 5**. The region of the SAMHD1 transcript targeted by these 21 oligonucleotides is shown in **FIG. 6**. Oligonucleotides that target this region are shown.

[00225] These results confirm that oligonucleotides targeting different regions within the SAMHD1 transcript show knockdown activity. These oligonucleotides were active and were targeting the same “hotspot” region as oligonucleotides represented in SEQ ID NOs: 9-12 previously identified in Example 1 (*i.e.*, within a region that corresponds to nucleotides 44295-44331 of SEQ ID NO: 1). This data suggests that this target region may have a functional role in SAMHD1 expression. Without wishing to be bound by any theory, such activity in this region may be a result of the region being a predicted mRNA hairpin site (*i.e.*, folding) site within the SAMHD1 transcript.

Example 4: Design and Testing of Additional SAMHD1-targeting Oligonucleotides

[00226] This example illustrates the design and testing of additional exemplary oligonucleotides that target human SAMHD1.

[00227] The additional oligonucleotides were selected by first generating oligonucleotides (16-mers) covering the longest transcript of human and mouse SAMHD1. Oligonucleotide sequences containing motifs that diminish antisense activity were filtered out. The oligonucleotide sequences designed and tested in this example are shown in **Table 9** below.

Table 9

Oligo SEQ ID NO:	Oligonucleotide sequence (5' to 3')	SEQ ID NO:	SAMHD1 RNA Sequence (5' to 3')	Corresponding coordinates within SEQ ID NO: 1
169	AACATGTCATACAGAT	204	ATCTGTATGACATGTT	44302-44317
170	AATTATTTTGGATTCC	205	GGAATCCAAAATAATT	40030-40045
171	ACATGTCATACAGATT	206	AATCTGTATGACATGT	44301-44316
172	AGTGTGGAACATGTCA	207	TGACATGTTCCACACT	44309-44324
173	AGTTGCGAGTGTGGAA	208	TTCCACACTCGCAACT	44316-44331
174	ATGTCATACAGATTTC	209	GAAATCTGTATGACAT	44299-44314
175	ATTATTTTGGATTCCA	210	TGGAATCCAAAATAAT	40029-40044
176	ATTTTGGATTCCAAGA	211	TCTTGAATCCAAAAT	40026-40041
177	CAATCTGAACACAGAG	212	CTCTGTGTTCAGATTG	26048-26063
178	CATACAGATTTC AAC	213	GTTGGAATCTGTATG	44295-44310
179	CATGTCATACAGATT	214	AAATCTGTATGACATG	44300-44315
180	CCAAGGAACCTACTCC	215	GGAGTAAGTTCCTTGG	333-348
181	CGAGTGTGGAACATGT	216	ACATGTTCCACACTCG	44311-44326
182	GAACATGTCATACAGA	217	TCTGTATGACATGTTT	44303-44318
183	GAGGTGTTATGAGTGG	218	CCACTCATAACACCTC	63796-63811
184	GAGTGTGGAACATGTC	219	GACATGTTCCACACTC	44310-44325
185	GCAATCTGAACACAGA	220	TCTGTGTTTCCAGATTG	26049-26064
186	GCGAGTGTGGAACATG	221	CATGTTCCACACTCGC	44312-44327
187	GGAACATGTCATACAG	222	CTGTATGACATGTTCC	44304-44319
188	GTCATACAGATTTC CA	223	TGGAAATCTGTATGAC	44297-44312
189	GTGGAACATGTCATAC	224	GTATGACATGTTCCAC	44306-44321
190	GTGTGGAACATGTCAT	225	ATGACATGTTCCACAC	44308-44323
191	GTTGCGAGTGTGGAAC	226	GTTCCACACTCGCAAC	44315-44330
192	TATTTTGGATTCCAAG	227	CTTGAATCCAAAATA	40027-40042
193	TCATACAGATTTC CA	228	TTGGAAATCTGTATGA	44296-44311
194	TGCGAGTGTGGAACAT	229	ATGTTCCACACTCGCA	44313-44328
195	TGGAACATGTCATACA	230	TGTATGACATGTTCCA	44305-44320
196	TGTCATACAGATTTC C	231	GGAAATCTGTATGACA	44298-44313
197	TGTGGAACATGTCATA	232	TATGACATGTTCCACA	44307-44322
198	TTATTTTGGATTTC CA	233	TTGGAATCCAAAATAA	40028-40043

199	TTGCGAGTGTGGAACA	234	TGTTCCACACTCGCAA	44314-44329
200	TTGTACCCTTGTCTCA	235	TGAGACAAGGGTACAA	64386-64401
201	TTTGGATTCCAAGATG	236	CATCTTGAATCCAAA	40024-40039
202	TTTGTACCCTTGTCTC	237	GAGACAAGGGTACAAA	64387-64402
203	TTTTGGATTCCAAGAT	238	ATCTTGAATCCAAAA	40025-40040

Oligonucleotide synthesis

[00228] Oligonucleotides were synthesized according to the protocol performed in Example 1. In this experiment, oligonucleotides contained modifications that included the following modification pattern:

X_{MS}X_{MS}X_{MS}X_{MS}X_SX_SX_SX_SX_SX_SX_SX_SX_{MS}X_{MS}X_{MS}X_{MS} (for 16-mers)

[00229] where “X” represents any nucleotide; a “M” represents a 2'-O-MOE group; and an “S” represents a phosphorothioate bond.

Oligonucleotide Transfection

[00230] Mouse WT NIH3T3 and Human 143B cells (ATCC # CRL-8303) were grown at 37 °C with 5% (v/v) CO₂ in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% foetal bovine serum (FBS).

[00231] 1.5 µl of each oligonucleotide (100 µM) was serially diluted (1:2) in PBS to 8 different final concentrations between 0-25 µM. 2 µl of each diluted oligonucleotides were added to 2 µL of DharmaFECT 1 (horizondiscovery, T-2001-02), and 330 µL of Opti-MEM media (Thermo Fisher Scientific, Cat#11058021). The mixtures were incubated for 15 min at room temperature. 1.67 mL of 5 × 10⁴/mL mouse WT NIH3T3s or human 143B cells were added to the oligonucleotide/media/DhamaFECT mixture and mixed well. The cells and oligonucleotide mixture were seeded (2 mL per well) in a 6-well plate and grown for 24 hours.

RT-PCR Protocol

[00232] The RT-PCR protocol is performed according to Example 1 in order to measure relative SAMHD1 mRNA expression levels.

Results

[00233] Relative SAMHD1 mRNA expression levels (expressed as a % change in expression compared to a control) in human 143B cells transfected with each of the oligonucleotides in Table 9 is shown in **FIG. 7**. Relative SAMHD1 mRNA expression levels (expressed as a % change in expression compared to a control) in mouse NIH3T3 cells transfected with each of the oligonucleotides in Table 9 is shown in **FIG. 8**.

[00234] **Table 10** below shows a comparison of SAMHD1 mRNA levels normalized to vehicle control in human 143B and mouse NIH3T3 cells transfected for each oligonucleotide in Table 9 at a concentration of 31.6nM. These results show that several of the oligonucleotides tested were cross-reactive in human and mouse cells. Additionally, oligonucleotides targeting certain regions on the SAMHD1 transcript sequence were more effective at knocking down expression of SAMHD1. For example, oligonucleotides represented in SEQ ID NOs: 171, 172, and 173, target the SAMHD1 transcript in a region that corresponds to positions 44301-44331 on the SAMHD1 gene sequence (SEQ ID NO: 1) showed significant knockdown in SAMHD1 mRNA expression in human and mouse cells. However, shifting the target region slightly (e.g., to target positions 40029-40044 of SEQ ID NO: 1, using oligonucleotide of SEQ ID NO: 175) showed a significantly different effect.

Table 10

Oligo SEQ ID NO	SamHD1 mRNA level (normalized to vehicle)	
	143B (Human)	WT MEF (Mouse)
169	0.89	0.86
170	0.84	0.75
171	0.74	0.69
172	0.61	0.76
173	0.51	0.80
174	0.85	0.83
175	1.05	0.73
176	0.98	0.79
177	0.98	0.86

178	0.99	0.71
179	0.84	0.71
180	0.91	0.70
181	0.82	0.54
182	0.80	0.80
183	0.76	0.75
184	0.68	0.65
185	0.90	0.84
186	0.77	0.81
187	0.93	0.69
188	1.08	0.74
189	0.86	0.59
190	0.89	0.70
191	0.75	0.75
192	1.13	0.82
193	0.98	0.96
194	0.88	0.69
195	0.96	0.82
196	1.01	0.81
197	0.92	0.84
198	1.03	0.92
199	1.02	0.81
200	1.01	0.80
201	0.87	0.84
202	0.97	0.87
203	0.93	0.89

EXEMPLARY SEQUENCES

Human SAMHD1 gene sequence (NG_017059.1 Homo sapiens SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1 (SAMHD1), RefSeqGene (LRG_281) on chromosome 20 (SEQ ID NO: 1)

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Human SAMHD1 Wildtype Protein sequence (SEQ ID NO: 130; UniProt Q9Y3Z3-1)

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***Human SAMHD1 mRNA Transcript (SEQ ID NO: 131; ENST00000646673.2 SAMHD1-221,
NM 15474.4)***

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 AACAGCTGCAATAAGCTTCGTGAATATA

SAMHD1 Exemplary "Hotspot" region (SEQ ID NO: 132)

GTGGAAATCTGTATGACATGTTCCACACTCGCAACT

Table 11: SAMHD1 Oligonucleotide Sequences

SEQ ID NO:	Oligo DNA Sequence (5' to 3')
2	TCGAAGACGTTGAAATTGAG
3	CACCTCCCAGCTGTTTGATG
4	GTAACCACCTCCCAGCTGTT
5	AGTAACCACCTCCCAGCTGT
6	ATCGATTGTGTGAAGCTCCT
7	GCTCAAATCGATTGTGTGAA
8	GTCCATCAAACATGTGAGAA
9	GCGAGTGTGGAACATGTCAT
10	TGCGAGTGTGGAACATGTCA
11	TTGCGAGTGTGGAACATGTC
12	GTTGCGAGTGTGGAACATGT
13	ATCCACTTCCCTCCTTTTCC
14	TTTATCCACTTCCCTCCATC
15	TCATGTCCTACCTCCCATT
16	TTCATGTCCTACCTCCCATT
17	GACTCACACCCAGTGTGTTGA
18	TGACTCACACCCAGTGTGTTG
19	TTGACTCACACCCAGTGTGTT
20	TGTCGCAGGGCTTTGCATT
21	CTGTCGCAGGGCTTTGCATT
22	ACTGTCGCAGGGCTTTGCAT
23	CACTGTCGCAGGGCTTTGCA
24	GCACTGTCGCAGGGCTTTGC
25	GGCACTGTCGCAGGGCTTTG
26	AGGCACTGTCGCAGGGCTTT
27	TCCAGGCACTGTCGCAGGGC
28	TTCCAGGCACTGTCGCAGGG
29	GTTCCAGGCACTGTCGCAGG
30	TGTTCCAGGCACTGTCGCAG
31	GTGTTCCAGGCACTGTCGCA
32	TGTGTTCCAGGCACTGTCGC
33	TCTGGCAGAAGTTGTGAAAC
34	CTGTCCACCTTCTTACAATA
35	TCTGTCCACCTTCTTACAAT
36	TTCTGTCCACCTTCTTACAA
37	TTTCTGTCCACCTTCTTACA
38	TGTCTGCACACCACTGAACA
39	CTGTCTGCACACCACTGAAC
40	TCGCCATCCTGCGGCTTGGT
41	ATCGCCATCCTGCGGCTTGG

42	CATCGCCATCCTGCGGCTTG
43	TACTGTCGTTCATTCTTT
44	GGAAAGTTCGAGTCCAAGCT
45	AGGAAAGTTCGAGTCCAAGC
46	CAGGAAAGTTCGAGTCCAAG
47	CCCAGGAAAGTTCGAGTCCA
48	GCCCAGGAAAGTTCGAGTCC
49	AGCCCAGGAAAGTTCGAGTC
50	CTCTCACCAGCGTGTGGAG
51	CCTCTCACCAGCGTGTGGGA
52	GCCTCTCACCAGCGTGTGG
53	GGCCTCTGGCCAGCTCTCCA
54	GGCAGTGCAGTGTGTGCT
55	TCTGGCCACCACCAGCTTTG
56	CTCTGGCCACCACCAGCTTT
57	GCACCCTCTGGCCACCACCA
58	CCCCTCACTCCCAGTGTGCC
59	TGCCCCCTCACTCCCAGTGTG
60	CTGCCCCCTCACTCCCAGTGT
61	TCAGGCTGCCCCCTCACTCCC
62	GCTCAGGCTGCCCCCTCACTC
63	TGCTCAGGCTGCCCCCTCACT
64	TTGCTCAGGCTGCCCCCTCAC
65	TGCCATGGCTGACCTCACTT
135	AACATGTCATACAGATTTCC
136	AATTATTTTGGATTCCAAGA
137	ACATGTCATACAGATTTCCA
138	AGTGTGGAACATGTCATACA
139	AGTTGCGAGTGTGGAACATG
140	ATGTCATACAGATTTCCAAC
141	ATTATTTTGGATTCCAAGAT
142	CATGTCATACAGATTTCCAA
143	CGAGTGTGGAACATGTCATA
144	GAACATGTCATACAGATTTTC
145	GAGTGTGGAACATGTCATAC
146	GGAACATGTCATACAGATTT
147	GTGGAACATGTCATACAGAT
148	GTGTGGAACATGTCATACAG
149	TGGAACATGTCATACAGATT
150	TGTGGAACATGTCATACAGA
151	TTATTTTGGATTCCAAGATG
169	AACATGTCATACAGAT
170	AATTATTTTGGATTCC

171	ACATGTCATACAGATT
172	AGTGTGGAACATGTCA
173	AGTTGCGAGTGTGGAA
174	ATGTCATACAGATTTC
175	ATTATTTTGGATTCCA
176	ATTTTGGATTCCAAGA
177	CAATCTGAACACAGAG
178	CATACAGATTTCCAAC
179	CATGTCATACAGATTT
180	CCAAGGAACTTACTCC
181	CGAGTGTGGAACATGT
182	GAACATGTCATACAGA
183	GAGGTGTTATGAGTGG
184	GAGTGTGGAACATGTC
185	GCAATCTGAACACAGA
186	GCGAGTGTGGAACATG
187	GGAACATGTCATACAG
188	GTCATACAGATTTCCA
189	GTGGAACATGTCATAC
190	GTGTGGAACATGTCAT
191	GTTGCGAGTGTGGAAC
192	TATTTTGGATTCCAAG
193	TCATACAGATTTCCAA
194	TGCGAGTGTGGAACAT
195	TGGAACATGTCATACA
196	TGTCATACAGATTTCC
197	TGTGGAACATGTCATA
198	TTATTTTGGATTCCAA
199	TTGCGAGTGTGGAACA
200	TTGTACCCTTGTCTCA
201	TTTGGATTCCAAGATG
202	TTTGTACCCTTGTCTC
203	TTTGTGGATTCCAAGAT

Table 12: SAMHD1 RNA Target Region Sequences

SEQ ID NO:	SAMHD1 RNA Sequence (5' to 3') (represented as a DNA sequence)
66	CTCAATTTCAACGTCTTCGA
67	CATCAAACAGCTGGGAGGTG
68	AACAGCTGGGAGGTGGTTAC
69	ACAGCTGGGAGGTGGTTACT
70	AGGAGCTTCACACAATCGAT

71	TTCACACAATCGATTGAGC
72	TTCTCACATGTTTGATGGAC
73	ATGACATGTTCCCACTCGC
74	TGACATGTTCCCACTCGCA
75	GACATGTTCCCACTCGCAA
76	ACATGTTCCCACTCGCAAC
77	GGAAAAGGAGGGAAGTGGAT
78	GATGGAGGGAAGTGGATAAA
79	GAATGGGAGGTAGGACATGA
80	AATGGGAGGTAGGACATGAA
81	TCAAACACTGGGTGTGAGTC
82	CAAACACTGGGTGTGAGTCA
83	AAACACTGGGTGTGAGTCAA
84	GAATGCAAAGCCCTGCGACA
85	AATGCAAAGCCCTGCGACAG
86	ATGCAAAGCCCTGCGACAGT
87	TGCAAAGCCCTGCGACAGTG
88	GCAAAGCCCTGCGACAGTGC
89	CAAAGCCCTGCGACAGTGCC
90	AAAGCCCTGCGACAGTGCCT
91	GCCCTGCGACAGTGCCTGGA
92	CCCTGCGACAGTGCCTGGAA
93	CCTGCGACAGTGCCTGGAAC
94	CTGCGACAGTGCCTGGAACA
95	TGCGACAGTGCCTGGAACAC
96	GCGACAGTGCCTGGAACACA
97	GTTTCACAACTTCTGCCAGA
98	TATTGTAAGAAGGTGGACAG
99	ATTGTAAGAAGGTGGACAGA
100	TTGTAAGAAGGTGGACAGAA
101	TGTAAGAAGGTGGACAGAAA
102	TGTTCAAGTGGTGTGCAGACA
103	GTTCAAGTGGTGTGCAGACAG
104	ACCAAGCCGCAGGATGGCGA
105	CCAAGCCGCAGGATGGCGAT
106	CAAGCCGCAGGATGGCGATG
107	AAAGGAATGGAACGACAGTA
108	AGCTTGGAATCGAACTTTCC
109	GCTTGGAATCGAACTTTCCCT
110	CTTGGAATCGAACTTTCCCTG
111	TGGACTCGAACTTTCCCTGGG
112	GGACTCGAACTTTCCCTGGGC
113	GACTCGAACTTTCCCTGGGCT

114	CTCCAACACGCTGGTGAGAG
115	TCCAACACGCTGGTGAGAGG
116	CCAACACGCTGGTGAGAGGC
117	TGGAGAGCTGGCCAGAGGCC
118	AGCACAAACACTGCACTGCC
119	CAAAGCTGGTGGTGGCCAGA
120	AAAGCTGGTGGTGGCCAGAG
121	TGGTGGTGGCCAGAGGGTGC
122	GGCACACTGGGAGTGAGGGG
123	CACACTGGGAGTGAGGGGCA
124	ACACTGGGAGTGAGGGGCAG
125	GGGAGTGAGGGGCAGCCTGA
126	GAGTGAGGGGCAGCCTGAGC
127	AGTGAGGGGCAGCCTGAGCA
128	GTGAGGGGCAGCCTGAGCAA
129	AAGTGAGGTCAGCCATGGCA
152	GGAAATCTGTATGACATGTT
153	TCTTGGAATCCAAAATAATT
154	TGGAAATCTGTATGACATGT
155	TGTATGACATGTTCCACACT
156	CATGTTCCACACTCGCAACT
157	GTTGGAAATCTGTATGACAT
158	ATCTTGGAATCCAAAATAAT
159	TTGGAAATCTGTATGACATG
160	TATGACATGTTCCACACTCG
161	GAAATCTGTATGACATGTTC
162	GTATGACATGTTCCCACTC
163	AAATCTGTATGACATGTTCC
164	ATCTGTATGACATGTTCCAC
165	CTGTATGACATGTTCCACAC
166	AATCTGTATGACATGTTCCA
167	TCTGTATGACATGTTCCACA
168	CATCTTGGAATCCAAAATAA
204	ATCTGTATGACATGTT
205	GGAATCCAAAATAATT
206	AATCTGTATGACATGT
207	TGACATGTTCCCACT
208	TTCCCACTCGCAACT
209	GAAATCTGTATGACAT
210	TGGAATCCAAAATAAT
211	TCTTGGAATCCAAAAT
212	CTCTGTGTTTCAGATTG
213	GTTGGAAATCTGTATG

214	AAATCTGTATGACATG
215	GGAGTAAGTTCCTTGG
216	ACATGTTCCACACTCG
217	TCTGTATGACATGTTC
218	CCACTCATAACACCTC
219	GACATGTTCCACACTC
220	TCTGTGTTTCAGATTGC
221	CATGTTCCACACTCGC
222	CTGTATGACATGTTCC
223	TGGAAATCTGTATGAC
224	GTATGACATGTTCCAC
225	ATGACATGTTCCACAC
226	GTTCCACACTCGCAAC
227	CTTGGAATCCAAAATA
228	TTGGAAATCTGTATGA
229	ATGTTCCACACTCGCA
230	TGTATGACATGTTCCA
231	GGAAATCTGTATGACA
232	TATGACATGTTCCACA
233	TTGGAATCCAAAATAA
234	TGTTCCACACTCGCAA
235	TGAGACAAGGGTACAA
236	CATCTTGGAATCCAAA
237	GAGACAAGGGTACAAA
238	ATCTTGGAATCCAAAA

EQUIVALENTS

[00236] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the following claims:

CLAIMS

1. An oligonucleotide comprising a sequence that is substantially complementary to 8 to 30 contiguous nucleotides of a SAMHD1 RNA transcript.
2. The oligonucleotide of claim 1, wherein the oligonucleotide comprises a sequence that is at least 85%, at least 90%, or at least 95% complementary to 8 to 30 contiguous nucleotides of a SAMHD1 RNA transcript.
3. The oligonucleotide of claim 1, wherein the oligonucleotide comprises a sequence that is perfectly complementary to 8 to 30 contiguous nucleotides of a SAMHD1 RNA transcript.
4. The oligonucleotide of claim 1, wherein the 8 to 30 contiguous nucleotides is 15 to 25 contiguous nucleotides.
5. The oligonucleotide of claim 1, wherein the oligonucleotide is 8 to 30 nucleotides in length.
6. This oligonucleotide of claim 1, wherein the oligonucleotide is 16 to 22 nucleotides in length.
7. The oligonucleotide of claim 1, wherein the oligonucleotide is 20 nucleotides in length.
8. The oligonucleotide of claim 1, wherein the oligonucleotide is 16 nucleotides in length.
9. The oligonucleotide of claim 1, wherein the SAMHD1 RNA transcript is a human SAMHD1 RNA transcript.
10. The oligonucleotide of claim 9, wherein the human SAMHD1 RNA transcript comprises SEQ ID NO: 131.

11. The oligonucleotide of claim 1, wherein the 8 to 30 contiguous nucleotides of the SAMHD1 RNA transcript is within or includes an exon region of the SAMHD1 RNA transcript.

12. The oligonucleotide of claim 1, wherein the 8 to 30 contiguous nucleotides comprises a sequence that corresponds to nucleotides 21722-21741, 21744-21763, 21749-21768, 21750-21769, 21780-21799, 21786-21805, 29605-29624, 44308-44327, 44309-44328, 44310-44329, 44311-44330, 44555-44574, 44584-44603, 44714-44733, 44715-44734, 44936-44955, 44937-44956, 44938-44957, 45297-45316, 45298-45317, 45299-45318, 45300-45319, 45301-45320, 45302-45321, 45303-45322, 45306-45325, 45307-45326, 45308-45327, 45309-45328, 45310-45329, 45311-45330, 58885-58904, 58933-58952, 58934-58953, 58935-58954, 58936-58955, 58983-59002, 58984-59003, 59011-59022 and 63778-63785, 59012-59022 and 63778-63786, 59013-59022 and 63778-63787, 63816-63835, 64243-64262, 64244-64263, 64245-64264, 64247-64266, 64248-64267, 64249-64268, 64616-64635, 64617-64636, 64618-64637, 64885-64904, 65149-65168, 65337-65356, 65338-65357, 65343-65362, 65443-65462, 65445-65464, 65446-65465, 65451-65470, 65453-65472, 65454-65473, 65455-65474, 65742-65761, 44298-44317, 40026-40045, 44297-44316, 44305-44324, 44312-44331, 44295-44314, 40025-40044, 44296-44315, 44307-44326, 44299-44318, 44306-44325, 44300-44319, 44302-44321, 44304-44323, 44301-44320, 44303-44322, 40024-40043, or 44302-44317, 40030-40045, 44301-44316, 44309-44324, 44316-44331, 44299-44314, 40029-40044, 40026-40041, 26048-26063, 44295-44310, 44300-44315, 333-348, 44311-44326, 44303-44318, 63796-63811, 44310-44325, 26049-26064, 44312-44327, 44304-44319, 44297-44312, 44306-44321, 44308-44323, 44315-44330, 40027-40042, 44296-44311, 44313-44328, 44305-44320, 44298-44313, 44307-44322, 40028-40043, 44314-44329, 64386-64401, 40024-40039, 64387-64402, or 40025-40040 of SEQ ID NO: 1.

13. The oligonucleotide of claim 1, wherein the 8 to 30 contiguous nucleotides comprises a sequence that corresponds to nucleotides 44295-44314, 44296-44315, 44297-44316, 44298-44317, 44299-44318, 44300-44319, 44301-44320, 44302-44321, 44303-44322, 44304-44323, 44305-44324, 44306-44325, 44307-44326, 44308-44327, 44309-44328, 44310-44329, 44311-44330, or 44312-44331 of SEQ ID NO: 1.

14. The oligonucleotide of claim 1, wherein the oligonucleotide is substantially complementary to 8 to 30 contiguous nucleotides of a sequence that corresponds to nucleotides 44295-44331 of SEQ ID NO: 1.

15. The oligonucleotide of claim 1, wherein the oligonucleotide is perfectly complementary to 8 to 30 contiguous nucleotides of a sequence that corresponds to nucleotides 44295-44331 of SEQ ID NO: 1.

16. An oligonucleotide comprising a sequence having at least 80% identity to a sequence selected from a group consisting of SEQ ID NOS: 9-12, 135, 137-140, 142-150, and 169-203.

17. The oligonucleotide of claim 16, wherein the oligonucleotide comprises a sequence having at least 90% identity to a sequence selected from a group consisting of SEQ ID NOS: 9-12, 135, 137-140, 142-150, and 169-203.

18. The oligonucleotide of claim 16, wherein the oligonucleotide comprises a sequence selected from a group consisting of SEQ ID NOS: 9-12, 135, 137-140, 142-150, and 169-203.

19. An oligonucleotide comprising a sequence that is substantially complementary to a sequence selected from a group consisting of SEQ ID NOs: 73-76, 152, 154-157, 159-167, and 204-238.

20. The oligonucleotide of claim 19, wherein the oligonucleotide is at least 85%, at least 90%, or at least 95% complementary to a sequence selected from a group consisting of SEQ ID NOs: 73-76, 152, 154-157, 159-167, and 204-238.

21. The oligonucleotide of claim 19, wherein the oligonucleotide is perfectly complementary to a sequence selected from a group consisting of SEQ ID NOs: 73-76, 152, 154-157, 159-167, and 204-238.

22. The oligonucleotide of claim 19, wherein the oligonucleotide is perfectly complementary to SEQ ID NO: 167.
23. The oligonucleotide of claim 19, wherein the oligonucleotide is perfectly complementary to SEQ ID NO: 166.
24. The oligonucleotide of claim 19, wherein the oligonucleotide is perfectly complementary to SEQ ID NO: 73.
25. The oligonucleotide of claim 19, wherein the oligonucleotide is perfectly complementary to SEQ ID NO: 74.
26. The oligonucleotide of claim 19, wherein the oligonucleotide is perfectly complementary to SEQ ID NO: 75.
27. The oligonucleotide of claim 19, wherein the oligonucleotide is perfectly complementary to SEQ ID NO: 76.
28. The oligonucleotide of claim 1, wherein the oligonucleotide is a chirally pure oligonucleotide.
29. The oligonucleotide of claim 1, wherein the oligonucleotide comprises at least one modified nucleotide.
30. The oligonucleotide of claim 29, wherein the modified nucleotide comprises a base modification, a sugar modification, a sugar phosphate modification, an internucleotidic linkage modification, or a combination thereof.
31. The oligonucleotide of claim 30, wherein the internucleotidic linkage modification comprises a phosphorothioate or phosphodithioate linkage modification.

32. The oligonucleotide of claim 30, wherein the sugar modification comprises a 2'-O-methoxyethyl (2'-MOE) modification, a 2'-Fluoro (2'-F) modification, a 2'-O-methyl (2'-O-Me) modification, an unlocked nucleic acid (UNA), or a locked nucleic acid (LNA).
33. The oligonucleotide of claim 30, wherein the sugar phosphate modification comprises a phosphorodiamidate morpholino (PMO) modification and/or a peptide nucleic acid (PNA) modification.
34. The oligonucleotide of claim 30, wherein the base modification comprises a 5'-methylcytosine modification or a G-clamp modification.
35. The oligonucleotide of claim 31, wherein each nucleotide comprises a phosphorothioate (PS) internucleotide linkage.
36. The oligonucleotide of claim 32, wherein the oligonucleotide comprises five nucleotides at the 5'-end and five nucleotides at the 3'-end of the oligonucleotide sequence which contain a 2'-MOE modification.
37. The oligonucleotide of claim 32, wherein each nucleotide contains a 2'-MOE modification.
38. The oligonucleotide of claim 1, further comprising at least one ligand attached to the 5' end and/or the 3' end.
39. The oligonucleotide of claim 38, wherein the ligand comprises at least one lipid, peptide, and/or sugar.
40. The oligonucleotide of claim 39, wherein the sugar comprises N-acetylgalactosamine (GalNAc) moiety.