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(54) Title: HUNTINGTIN (HTT) iRNA AGENT COMPOSITIONS AND METHODS OF USE THEREOF

(57) Abstract: The disclosure relates to double stranded ribonucleic acid (dsRNAi) agents and compositions targeting a Huntingtin (HTT) gene, as well as methods of inhibiting expression of an HTT gene and methods of treating subjects having an HTT-associated disease or disorder, e.g., Huntington's disease, using such dsRNAi agents and compositions.

HUNTINGTIN (HTT) iRNA AGENT COMPOSITIONS AND METHODS OF USE THEREOF

RELATED APPLICATONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/273,200, filed on October 29, 2021, and U.S. Provisional Application No. 63/285,550, filed on December 3, 2021. The entire contents of each of the foregoing applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Huntington's disease is a progressive neurodegenerative disorder characterized by motor disturbance, cognitive loss and psychiatric manifestations (Martin and Gusella (1986) *N. Engl. J. Med.* 315:1267-1276). It is inherited in an autosomal dominant fashion, and affects about 1/10,000 individuals in most populations of European origin (Harper, P. S. *et al.*, in *Huntington's Disease*, W. B. Saunders, Philadelphia, 1991). The hallmark of Huntington's disease is a distinctive choreic movement disorder that typically has a subtle, insidious onset in the fourth to fifth decade of life and gradually worsens over a course of 10 to 20 years until death. Occasionally, Huntington's disease is expressed in juveniles typically manifesting with more severe symptoms including rigidity and a more rapid course. Juvenile onset of Huntington's disease is associated with a preponderance of paternal transmission of the disease allele. The neuropathology of Huntington's disease also displays a distinctive pattern, with selective loss of neurons that is most severe in the caudate and putamen regions of the brain.

[0003] Huntington's disease has been shown to be caused by an expanding glutamine repeat in exon 1 of a gene termed IT15 or Huntingtin (HTT). Although this gene is widely expressed and is required for normal development, the pathology of Huntington's disease is restricted to the brain, for reasons that remain poorly understood. In patients having HD (an autosomal dominant disease), the expansion of the polyglutamine repeat results in a full-length mutant transcript encoding an expanded polyglutamine repeat, as well as a truncated mutant transcript which retains intron 1 and encodes an expanded polyglutamine repeat. The other allele produces a wild-type transcript. It has been shown that, although the Huntingtin gene product is expressed at similar levels in patients and controls, it is the expansion of the polyglutamine repeat and the presence of the full-length mutant transcript and the truncated mutant transcript that induces toxicity.

[0004] Effective treatment for Huntington's disease is currently not available. The choreic movements and agitated behaviors may be suppressed, usually only partially, by antipsychotics (*e.g.*, chlorpromazine) or reserpine until adverse effects of lethargy, hypotension, or parkinsonism occur. In addition, despite significant advances in the field of RNAi and Huntington's disease treatment, there remains a need for an agent that can selectively and efficiently silence the HD gene using the cell's own RNAi machinery that has both high biological activity and *in vivo* stability, and that can effectively inhibit expression of a target Huntingtin gene.

BRIEF SUMMARY OF THE INVENTION

[0005] The present disclosure provides RNAi agent compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a mutant huntingin (HTT) gene. In particular, the RNAi agent compositions of the invention target intron 1 retained in the truncated mutant HTT gene, thereby inhibiting expression of the truncated mutant HTT transcript encoding an expanded polyglutamine repeat while sparing full-length wild-type HTT. The HTT gene may be within a cell, *e.g.,* a cell within a subject, such as a human. The present disclosure also provides methods of using the RNAi agent compositions of the disclosure for inhibiting the expression of an HTT gene or for treating a subject who would benefit from inhibiting or reducing the expression of an HTT gene, *e.g.,* a subject suffering or prone to suffering from an HTT-associated disease.

[0006] In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Huntingtin (HTT), in a cell, wherein the dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to intron 1 retained in mutant HTT mRNA, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3, *e.g.,* 3, 2, 1, or 0. nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-3 and 5-6.

[0007] In one embodiment, the dsRNA agent comprises a sense strand comprising a contiguous nucleotide sequence which has at least 85%, *e.g.*, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, nucleotide sequence identity over its entire length to any one of the nucleotide sequences of the sense strands in any one of Tables 2-3 and 5-6 and an antisense strand comprising a contiguous nucleotide sequence which has at least 85%, *e.g.*, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, nucleotide sequence identity over its entire length to any one of the nucleotide sequences of the antisense strands in any one of Tables 2-3 and 5-6.

[0008] In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-3 and 5-6 and an antisense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-3 and 5-6.

[0009] In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-3 and 5-6 and an antisense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-3 and 5-6.

[00010] In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the sense strands in any one of Tables 2-3 and

5-6 and an antisense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-3 and 5-6.

[00011] In one embodiment, the dsRNA agent comprises a sense strand comprising or consisting of a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the sense strands in any one of Tables 2-3 and 5-6 and an antisense strand comprising or consisting of a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the antisense strands in any one of Tables 2-3 and 5-6.

[00012] In one embodiment, the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 5790-5810; 5791-5811; 5924-5944; 5925-5945; 5998-6018; 6063-6083; 6064-6084; 6194-6214; 6195-6215; or 6211-6231 of SEQ ID NO:11.

[00013] In one embodiment, the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of nucleotides 5790-5810; 5791-5811; 5924-5944; 6064-6084; or 6194-6214 of SEQ ID NO:11.

[00014] In one embodiment, the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more that three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1640384; AD-1640458; AD-1640457; AD-1640461; AD-1640628; AD-1640629; AD-1640498; AD-1640651; AD-1640631; AD-1640497; AD-1640382; or AD-1640467.

[00015] In one embodiment, the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more that three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1640384; AD-1640458; AD-1640457; AD-1640628; AD-1640629; AD-1640498; or AD-1640382.

[0010] In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Huntingtin (HTT) in a cell, wherein the dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more that three nucleotides from any one of the nucleotide sequences of nucleotides 5922-5944, 6059-6106; 6059-6084; 6068-6092; 6076-6106; 6191-6231; 6191-6215; 6191-6214; 6192-6215; 6198-6231; or 6198-6224 of SEQ ID NO:11.

[0011] In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Huntingtin (HTT) in a cell, wherein the dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more that three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-

1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

[0012] In some embodiments, the dsRNA agent comprises a sense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than three nucleotides from any one of the sense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721, and an antisense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

[0013] In some embodiments, the dsRNA agent comprises a sense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than two nucleotides from any one of the sense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721, and an antisense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than two nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

[0014] In some embodiments, the dsRNA agent comprises a sense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than one nucleotide from any one of the sense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721, and an antisense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than one nucleotide from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-

1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

[0015] In some embodiments, the dsRNA agent comprises a sense strand comprising a nucleotide sequence selected from any one of the sense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721, and an antisense strand comprising a nucleotide sequence selected from any one of the antisense strand nucleotide sequences of a duplex elected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

[0016] In one embodiment, the dsRNA agent comprises a sense strand comprising a contiguous nucleotide sequence which has at least 85%, *e.g.*, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, nucleotide sequence identity over its entire length to any one of the nucleotide sequences of the sense strands of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721, and an antisense strand comprising a contiguous nucleotide sequence which has at least 85%, *e.g.*, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, nucleotide sequence identity over its entire length to any one of the nucleotide sequences of the antisense strands of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

[0017] The sense strand, the antisense strand, or both the sense strand and the antisense strand may be conjugated to one or more lipophilic moieties. In some embodiments, the lipophilic moiety is conjugated to one or more internal positions in the double stranded region of the dsRNA agent, *e.g.,* the one or more lipophilic moieties may be conjugated to one or more internal positions on the antisense strand. In some embodiments, the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand *via* a linker or carrier.

[0018] In some embodiments, lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

[0019] In some embodiments, the hydrophobicity of the dsRNA agent, measured by the unbound fraction in a plasma protein binding assay of the dsRNA agent, exceeds 0.2. In some embodiments,

the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

[0020] In some embodiments, the internal positions include all positions except the terminal two positions from each end of the sense strand or the antisense strand. In other embodiments, the internal positions include all positions except the terminal three positions from each end of the sense strand or the antisense strand.

[0021] In some embodiments, the internal positions exclude a cleavage site region of the sense strand, such as the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand or the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.

[0022] In some embodiments, the internal positions exclude a cleavage site region of the antisense strand. In other embodiments, the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand. In some embodiments, the internal positions include all positions except positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.

[0023] In some embodiments, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5'end of each strand.

[0024] In some embodiments, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand.

[0025] In some embodiments, the positions in the double stranded region exclude a cleavage site region of the sense strand.

[0026] In some embodiments, the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.

[0027] In other embodiments, the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.

[0028] In some embodiments, the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

[0029] In some embodiments, the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

[0030] In some embodiments, the lipophilic moiety contains a saturated or unsaturated C4-C30 hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

[0031] In some embodiments, the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

[0032] In some embodiments, the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain. In some embodiments, the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

[0033] In some embodiments, the lipophilic moiety is conjugated *via* a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region. In some embodiments, the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

[0034] In some embodiments, the lipophilic moiety is conjugated to the dsRNA agent *via* a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

[0035] In some embodiments, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

[0036] In some embodiments, the dsRNA agent comprises at least one modified nucleotide. In some embodiments, no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides. In other embodiments, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

[0037] In some embodiments, at least one of the modified nucleotides is selected from the group a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofurane-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a

terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

[0038] In other embodiments, the modified nucleotide is selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, 3'-terminal deoxy-thymine nucleotides (dT), a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

[0039] In some embodiments, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), and, a vinyl-phosphonate nucleotide; and combinations thereof.

[0040] In some embodiments, at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification. In some embodiments, the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acids (UNA), and a glycerol nucleic acid (GNA)

[0041] In some embodiments, the modified nucleotide comprises a short sequence of 3'-terminal deoxy-thymine nucleotides (dT).

[0042] In some embodiments, the modifications on the nucleotides are 2'-O-methyl, GNA and 2'fluoro modifications.

[0043] In some embodiments, the dsRNA comprises at least one, *e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, 2'-fluoro nucleotide modifications.

[0044] In some embodiments, the antisense strand comprises at least one, *e.g.*, 2, 3, 4, 5 or more 2'-fluoro nucleotidemodification.

[0045] In some embodiments, the antisense strand comprises a 2'-fluoro nucleotide at positions 2, 14 and 16, counting from the 5'-end of the antisense strand.

[0046] In some embodiments, the antisense strand comprises a 2'-fluoro nucleotide at positions 2, 6, 14 and 16, counting from the 5'-end of the antisense strand.

[0047] In some embodiments, the antisense strand comprises a 2'-fluoro nucleotide at positions 2, 6, 9, 14 and 16, counting from the 5'-end of the antisense strand.

[0048] In some embodiments,wherein the antisense strand comprises a 2'-fluoro nucleotide at positions 2, 6, 8, 9, 14 and 16, counting from the 5'-end of the antisense strand.

[0049] In some embodiments, the antisense strand comprises at least one, e.g., 2, 3, 4, 5 or more 2'-fluoro nucleotides.

[0050] In some embodiments, the sense strand comprises a 2'-fluoro nucleotide at positions 7, 9 and 11, counting from the 5'-end of the sense strand or at positions 11, 13 and 15, counting from the 3'-end of the sense strand.

[0051] In some embodiments, the sense strand comprises a 2'-fluoro nucleotide at positions 7, 9, 10 and 11, counting from the 5'-end of the sense strand or at positions 11, 12, 13 and 15, counting from the 3'-end of the sense strand.

[0052] In some embodiments, the sense strand comprises a 2'-fluoro nucleotide at positions 9, 10, and 11, counting from the 5'-end of the sense strand or at positions 11, 12, and 13 counting from the 3'-end of the sense strand.

[0053] In some embodiments, the antisense strand comprises at least one, e.g., 2, 3, 4, 5, 6, 7 or more DNA nucleotides.

[0054] In some embodiments, the antisense strand comprises a DNA nucleotide at positions 2, 5, 7, and 12, counting from the 5'-end of the antisense strand.

[0055] In some embodiments, the antisense strand comprises a DNA nucleotide at positions 2, 5, 7, 12, and 14 counting from the 5'-end of the antisense strand.

[0056] In some embodiments,the antisense strand a DNA nucleotide at positions 2, 5, 7, and 12, and a 2'-fluoro nucleotide at position 14 counting from the 5'-end of the antisense strand.

[0057] In some embodiments, the antisense strand a DNA nucleotide at positions 2, 5, 7, 12, 14 and 16 counting from the 5'-end of the antisense strand.

[0058] In some embodiments, the dsRNA comprises at least one thermally destabilizing modification.

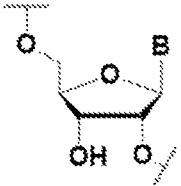
[0059] In some embodiments, the antisense strand comprises at least one thermally destabilizing modification.

[0060] In some embodiments, the antisense strand comprises at least one thermally destabilizing modification in the seed region (i.e., positions 2-9 from the 5'-end) of the antisense strand.

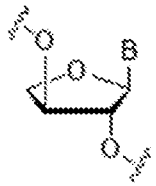
[0061] In some embodiments,he antisense strand comprises a thermally destabilizing modification at least at one of positions 6, 7 or 8, counting from the 5'-end of the strand.

[0062] In some embodiments,the antisense strand comprises a thermally destabilizing modification at position 7, counting from the 5'-end of the strand.

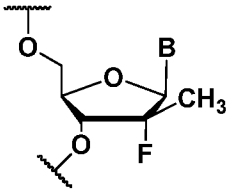
[0063] In some embodiments, the thermally destabilizing modification is an abasic nucleotide, 2'-deoxy nucleotides, acyclic nucleotide (e.g., unlocked nucleic acid (UNA), glycol nucleic acid (GNA) or (S)-glycol nucleic acid (S-GNA)), a 2'-5' linked nucleotide (3'-RNA), threose nucleotide (TNA), 2' gem Me/F nucleotide or mismatch with an opposing nucleotide in the other strand.



3'RNA:



TNA:

2' gem Me/F nucleotide: 

[0064] In some embodiments, any nucleotide not otherwise defined is 2'-OMe.

[0065] In some embodiments, the dsRNA agent further comprises at least one phosphorothioate internucleotide linkage. In some embodiments, the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages. In one embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. Optionally, the strand is the antisense strand. In another embodiment, the strand is the sense strand. In a related embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. Optionally, the strand is the antisense strand. In another embodiment, the strand is the sense strand. In another embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand. Optionally, the strand is the antisense strand. In another embodiment, the strand is the sense strand.

[0066] In some embodiments, each strand is no more than 30 nucleotides in length.

[0067] In some embodiments, at least one strand comprises a 3' overhang of at least 1 nucleotide or a 3' overhang of at least 2 nucleotides.

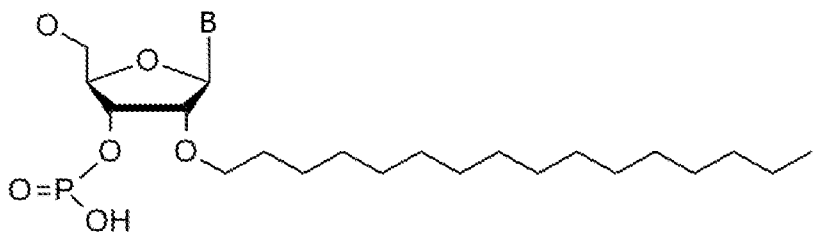
[0068] The double stranded region may be 15-30 nucleotide pairs in length; 17-23 nucleotide pairs in length; 17-25 nucleotide pairs in length; 23-27 nucleotide pairs in length; 19-21 nucleotide pairs in length; or 21-23 nucleotide pairs in length.

[0069] Each strand may be 19-30 nucleotides; 19-23 nucleotides; or 21-23 nucleotides.

[0070] In some embodiments, the dsRNA agent further comprises a targeting ligand that targets a liver tissue. In some embodiments, the targeting ligand is a GalNAc conjugate. In other embodiments, the dsRNA agent does not comprise a targeting ligand that targets a liver tissue, such as a GalNAc conjugate.

[0071] In certain embodiments, the double-stranded RNAi agent further includes a targeting ligand that targets a receptor which mediates delivery to a CNS tissue, *e.g.*, a hydrophilic ligand.

[0072] In certain embodiments, the targeting ligand is a C16 ligand. In one embodiment, the ligand is



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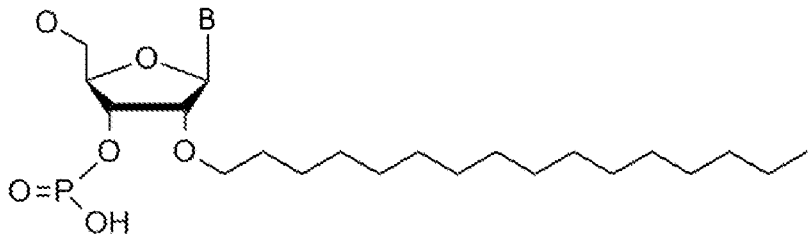
where B is a nucleotide base or a nucleotide base analog, optionally where B is adenine, guanine, cytosine, thymine or uracil.

[0073] In some embodiments, the dsRNA agent further includes a targeting ligand that targets a receptor which mediates delivery to a CNS tissue, *e.g.*, a hydrophilic ligand, such as a C16 ligand, *e.g.*,



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where B is a nucleotide base or a nucleotide base analog, optionally where B is adenine, guanine, cytosine, thymine or uracil and does not comprise a targeting ligand that targets a liver tissue, such as a GalNAc conjugate.

[0074] In some embodiments, the lipophilic moeity or targeting ligand is conjugated *via* a bio-clevable linker selected from the group consisting of DNA, RNA, disulfide, amide, funtionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

[0075] In some embodiments, the 3' end of the sense strand is protected *via* an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.

[0076] In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.

[0077] In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

[0078] In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral

modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

[0079] In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

[0080] In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

[0081] In some embodiments, the dsRNA agent further comprises a phosphate or phosphate mimic at the 5'-end of the antisense strand. In some embodiments, the phosphate mimic is a 5'-vinyl phosphonate (VP).

[0082] In some embodiments, the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

[0083] In some embodiments, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

[0084] The present invention further provides cells containing any of the dsRNA agents of the invention and pharmaceutical compositions for inhibiting expression of a gene encoding HTT, comprising any of the dsRNA agents of the invention.

[0085] In one embodiment, the double stranded RNAi agent is in an unbuffered solution. Optionally, the unbuffered solution is saline or water. In another embodiment, the double stranded RNAi agent is in a buffer solution. Optionally, the buffer solution includes acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof. In another embodiment, the buffer solution is phosphate buffered saline (PBS). Another aspect of the disclosure provides a pharmaceutical composition that includes a double stranded RNAi agent of the instant disclosure and a lipid formulation. In one embodiment, the lipid formulation includes a lipid nanoparticle (LNP).

[0086] An additional aspect of the disclosure provides a method of inhibiting expression of an HTT gene in a cell, the method including (a) contacting the cell with a double stranded RNAi agent of the instant disclosure, or a pharmaceutical composition of of the instant disclosure; and (b)

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

[0087] In one embodiment, the cell is within a subject. Optionally, the subject is a human.

[0088] In certain embodiments, the subject is a rhesus monkey, a cynomolgous monkey, a mouse, or a rat. In certain embodiments HTT expression is inhibited by at least about 50% by the RNAi agent.

[0089] In certain embodiments, the human subject has been diagnosed with an HTT-associated disease, *e.g.,* Huntington's disease.

[0090] Another aspect of the disclosure provides a method of treating a subject diagnosed with an HTT-associated disease, *e.g.*, Huntington's disease, the method including administering to the subject a therapeutically effective amount of a double stranded RNAi agent of the disclosure, or a pharmaceutical composition of the disclosure, thereby treating the subject.

[0091] In one embodiment, treating comprises amelioration of at least on sign or symptom of the disease. In another embodiment, treating comprises prevention of progression of the disease.

[0092] In some embodiments, the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

[0093] In some embodiments, the dsRNA agent is administered to the subject intrathecally. In one embodiment, the method reduces the expression of an HTT gene in a brain (*e.g.,* striatum) or spine tissue. Optionally, the brain or spine tissue is striatum, cortex, cerebellum, cervical spine, lumbar spine, or thoracic spine.

[0094] In some embodiments, the method further comprises measuring a level of HTT in a sample obtained from the subject.

[0095] Another aspect of the instant disclosure provides a method of inhibiting the expression of huntingtin (HTT) in a subject, the method involving: administering to the subject a therapeutically effective amount of a double stranded RNAi agent of the disclosure or a pharmaceutical composition of the disclosure, thereby inhibiting the expression of HTT in the subject.

[0096] In some embodiment, the method further comprises administering to the subject an additional agent suitable for treatment or prevention of an HTT-associated disorder.

[0097] The present invention also provides an RNA-induced silencing complex (RISC) comprising an antisense strand of any of the dsRNA agents of the present invention.

[0098] In one embodiment, the dsRNA agent is a pharmaceutically acceptable salt thereof. "Pharmaceutically acceptable salts" of each of dsRNA agents herein include, but are not limited to, a sodium salt, a calcium salt, a lithium salt, a potassium salt, an ammonium salt, a magnesium salt, an mixtures thereof. One skilled in the art will appreciate that the dsRNA agent, when provided as a polycationic salt having one cation per free acid group of the optionally modified phosophodiester backbone and/or any other acidic modifications (*e.g.*, 5'-terminal phosphonate groups). For example, an oligonucleotide of "n" nucleotides in length contains n-1 optionally modified phosophodiesters, so that an oligonucleotide of 21 nt in length may be provided as a salt having up to 20 cations (*e.g*, 20 sodium cations). Similarly, an RNAi agentshaving a sense strand of 21 nt in length and an antisense

strand of 23 nt in length may be provided as a salt having up to 42 cations (*e.g*, 42 sodium cations). In the preceding example, where the dsRNA agent also includes a 5'-terminal phosphate or a 5'-terminal vinylphosphonate group, the dsRNA agent may be provided as a salt having up to 44 cations (*e.g*, 44 sodium cations).

DETAILED DESCRIPTION OF THE INVENTION

[0099] The present disclosure provides RNAi compositions, which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a huntingtin (HTT) gene. The HTT gene may be within a cell, *e.g.,* a cell within a subject, such as a human. The use of these iRNAs enables the targeted degradation of mRNAs of the corresponding gene (HTT gene) in mammals.

[00100] The iRNAs of the invention have been designed to target intron 1 retained in the truncated mutant HTT gene, thereby inhibiting expression of the truncated mutant HTT transcript encoding an expanded polyglutamine repeat while sparing full-length wild-type HTT. Without intending to be limited by theory, it is believed that a combination or sub-combination of the foregoing properties and the specific target sites, or the specific modifications in these iRNAs confer to the iRNAs of the invention improved efficacy, stability, potency, durability, and safety.

[00101] Accordingly, the present disclosure also provides methods of using the RNAi compositions of the disclosure, including., compositions comprising one or more, *e.g.*, 2, 3, or 4, dsRNA agents of the invention, for inhibiting the expression of an HTT gene or for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of an HTT gene, *e.g.,* an HTT-associated disesase, for example, Huntington's disease (HD).

[00102] The RNAi agents of the disclosure include an RNA strand (the antisense strand) having a region which is about 30 nucleotides or less in length, *e.g.*, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of an HTT gene. In certain embodiments, the RNAi agents of the disclosure include an RNA strand (the antisense strand) having a region which is about 21-23 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of an HTT gene.

[00103] In certain embodiments, the RNAi agents of the disclosure include an RNA strand (the antisense strand) which can include longer lengths, for example up to 66 nucleotides, *e.g.*, 36-66, 26-36, 25-36, 31-60, 22-43, 27-53 nucleotides in length with a region of at least 19 contiguous nucleotides that is substantially complementary to at least a part of an mRNA transcript of an HTT gene. These RNAi agents with the longer length antisense strands preferably include a second RNA strand (the sense strand) of 20-60 nucleotides in length wherein the sense and antisense strands form a duplex of 18-30 contiguous nucleotides.

[00104] The use of these RNAi agents enables the targeted degradation of mRNAs of an HTT gene in mammals. Thus, methods and compositions including these RNAi agents are useful for treating a subject who would benefit by a reduction in the levels or activity of an HTT protein, such as a subject having an HTT-associated disease, such as Huntington's disease (HD).

[00105] The following detailed description discloses how to make and use compositions containing RNAi agents to inhibit the expression of an HTT gene, as well as compositions and methods for treating subjects having diseases and disorders that would benefit from inhibition or reduction of the expression of the genes.

I. Definitions

[00106] In order that the present disclosure may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this disclosure.

[00107] The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element, *e.g.*, a plurality of elements.

[00108] The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to". The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise.

[00109] The term "about" is used herein to mean within the typical ranges of tolerances in the art. For example, "about" can be understood as about 2 standard de*via*tions from the mean. In certain embodiments, about means ±10%. In certain embodiments, about means ±5%. When about is present before a series of numbers or a range, it is understood that "about" can modify each of the numbers in the series or range.

[00110] The term "at least", "no less than", or "or more"prior to a number or series of numbers is understood to include the number adjacent to the term "at least", and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleotides in a nucleic acid molecule must be an integer. For example, "at least 18 nucleotides of a 21 nucleotide nucleic acid molecule" means that 18, 19, 20, or 21 nucleotides have the indicated property. When at least is present before a series of numbers or a range, it is understood that "at least" can modify each of the numbers in the series or range.

[00111] As used herein, "no more than" or "less than" is understood as the value adjacent to the phrase and logical lower values or intergers, as logical from context, to zero. For example, a duplex with an overhang of "no more than 2 nucleotides" has a 2, 1, or 0 nucleotide overhang. When "no more than" is present before a series of numbers or a range, it is understood that "no more than" can modify each of the numbers in the series or range.

[00112] As used herein, methods of detection can include determination that the amount of analyte present is below the level of detection of the method.

[00113] In the event of a conflict between an indicated target site and the nucleotide sequence for a sense or antisense strand, the indicated sequence takes precedence.

[00114] In the event of a conflict between a chemical structure and a chemical name, the chemical structure takes precedence.

[00115] The term "HTT" or "huntingtin", also known as "Huntingtin," "Huntington Disease Protein," "IT15," "HD," HD Protein," or "LOMARS," refers to the well-known gene that encodes the protein, HTT, that is widely expressed, required for normal development and the disease gene linked to Huntington's disease, a neurodegenerative disorder characterized by loss of striatal neurons caused by an expanded, unstable trinucleotide (CAG) repeat in the huntingtin gene, which translates as a polyglutamine repeat in the protein product.

[00116] Exemplary nucleotide and amino acid sequences of HTT can be found, for example, at GenBank Accession No. NM_002111.8 (Homo sapiens HTT, SEQ ID NO: 1, reverse complement, SEQ ID NO: 6); GenBank Accession No. NM_010414.3 (Mus musculus HTT, SEQ ID NO: 2; reverse complement, SEQ ID NO: 7); GenBank Accession No.: NM_024357.3 (Rattus norvegicus HTT, SEQ ID NO: 3, reverse complement, SEQ ID NO: 8); GenBank Accession No.: XM_015449989.1 (Macaca fascicularis HTT, SEQ ID NO: 4, reverse complement, SEQ ID NO: 9); GenBank Accession No.: XM_028848247.1 (Macaca mulatta HTT, SEQ ID NO: 5, reverse complement, SEQ ID NO: 10);

[00117] GenBank Accession No.: NG_009378.1 (Homo sapiens huntingtin (HTT), RefSeqGene (LRG_763) on chromosome 4, SEQ ID NO:11, reverse complement, SEQ ID NO:12); and Gen Bank Accession No.: NC_000004.12 (Homo sapiens chromosome 4, GRCh38.p13 Primary Assembly).

[00118] Additional examples of HTT sequences can be found in publically available databases, for example, GenBank, OMIM, and UniProt.

[00119] Further information on HTT can be found, for example, at www.ncbi.nlm.nih.gov/gene/3064.

[00120] The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

[00121] The term HTT, as used herein, also refers to variations of the HTT gene including variants provided in the SNP database. Numerous seuqnce variations within the HTT gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, *e.g.*, www.ncbi.nlm.nih.gov/snp/?LinkName=gene_snp&from_uid=3064, the entire contents of which is incorporated herein by reference as of the date of filing this application.

[00122] As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of an HTT gene, including mRNA that is a product of RNA processing of a primary transcription product. In one embodment, the target portion of the sequence will be at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of an HTT gene.

[00123] The target sequence is about 15-30 nucleotides in length. For example, the target sequence can be from about 15-30 nucleotides, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length. In certain embodiments, the target sequence is 19-23 nucleotides in length, optionally 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

[00124] As used herein, the term "strand comprising a sequence" refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature.

[00125] "G," "C," "A," "T", and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine, and uracil as a base, respectively in the context of a modified or unmodified nucleotide. However, it will be understood that the term "ribonucleotide" or "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety (see, *e.g.*, Table 1). The skilled person is well aware that guanine, cytosine, adenine, thymidine, and uracil can be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base can base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine can be replaced in the nucleotide sequences of dsRNA featured in the disclosure by a nucleotide containing, for example, inosine. In another example, adenine and cytosine anywhere in the oligonucleotide can be replaced with guanine and uracil, respectively to form G-U Wobble base pairing with the target mRNA. Sequences containing such replacement moieties are suitable for the compositions and methods featured in the disclosure.

[00126] The terms "iRNA", "RNAi agent," "iRNA agent," "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. RNA interference (RNAi) is a process that directs the sequence-specific degradation of mRNA. RNAi modulates, *e.g.*, inhibits, the expression of HTT in a cell, *e.g.*, a cell within a subject, such as a mammalian subject.

[00127] In one embodiment, an RNAi agent of the disclosure includes a single stranded RNAi that interacts with a target RNA sequence, *e.g.*, an HTT target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory it is believed that long double stranded RNA introduced into cells is broken down into double-stranded short interfering RNAs (siRNAs) comprising a sense strand and an antisense strand by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) Genes Dev. 15:485). Dicer, a ribonuclease-III-like enzyme, processes these dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) Nature 409:363). These siRNAs are then incorporated into an RNA-induced silencing complex

(RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al*., (2001) Cell 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al*., (2001) Genes Dev. 15:188). Thus, in one aspect the disclosure relates to a single stranded RNA (ssRNA) (the antisense strand of a siRNA duplex) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.*, an HTT gene. Accordingly, the term "siRNA" is also used herein to refer to an RNAi as described above.

[00128] In another embodiment, the RNAi agent may be a single-stranded RNA that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents bind to the RISC endonuclease, Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are chemically modified. The design and testing of single-stranded RNAs are described in U.S. Patent No. 8,101,348 and in Lima *et al*., (2012) Cell 150:883-894, the entire contents of each of which are hereby incorporated herein by reference. Any of the antisense nucleotide sequences described herein may be used as a single-stranded siRNA as described herein or as chemically modified by the methods described in Lima *et al*., (2012) Cell 150:883-894.

[00129] In another embodiment, a "RNAi agent" for use in the compositions and methods of the disclosure is a double stranded RNA and is referred to herein as a "double stranded RNAi agent," "double stranded RNA (dsRNA) molecule," "dsRNA agent," or "dsRNA". The term "dsRNA" refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having "sense" and "antisense" orientations with respect to a target RNA, *i.e.*, an HTT gene. In some embodiments of the disclosure, a double stranded RNA (dsRNA) triggers the degradation of a target RNA, *e.g.*, an mRNA, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

[00130] In general, a dsRNA molecule can include ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide, a modified nucleotide. In addition, as used in this specification, an "RNAi agent" may include ribonucleotides with chemical modifications; an RNAi agent may include substantial modifications at multiple nucleotides. As used herein, the term "modified nucleotide" refers to a nucleotide having, independently, a modified sugar moiety, a modified internucleotide linkage, or a modified nucleobase. Thus, the term modified nucleotide encompasses substitutions, additions or removal of, *e.g.*, a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. The modifications suitable for use in the agents of the disclosure include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by "RNAi agent" for the purposes of this specification and claims.

[0100] In certain embodiments of the instant disclosure, inclusion of a deoxy-nucleotide if present within an RNAi agent can be considered to constitute a modified nucleotide.

[0101] The duplex region may be of any length that permits specific degradation of a desired target RNA through a RISC pathway, and may range from about 15-36 base pairs in length, for example, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36

base pairs in length, such as about 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain embodiments, the duplex region is 19-21 base pairs in length, *e.g.*, 21 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

[0102] The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting RNA chain is referred to as a "hairpin loop." A hairpin loop can comprise at least one unpaired nucleotide. In some embodiments, the hairpin loop can comprise at at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 23 or more unpaired nucleotides or nucleotides not directed to the target site of the dsRNA. In some embodiments, the hairpin loop can be 10 or fewer nucleotides. In some embodiments, the hairpin loop can be 8 or fewer unpaired nucleotides. In some embodiments, the hairpin loop can be 4-10 unpaired nucleotides. In some embodiments, the hairpin loop can be 4-8 nucleotides.

[0103] Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. In certain embodiments where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a "linker" (though it is noted that certain other structures defined elsewhere herein can also be referred to as a "linker"). The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi may comprise one or more nucleotide overhangs. In one embodiment of the RNAi agent, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In other embodiments, at least one strand of the RNAi agent comprises a 5' overhang of at least 1 nucleotide. In certain embodiments, at least one strand comprises a 5' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In still other embodiments, both the 3' and the 5' end of one strand of the RNAi agent comprise an overhang of at least 1 nucleotide.

[0104] In one embodiment, an RNAi agent of the disclosure is a dsRNA, each strand of which independently comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, an HTT target mRNA sequence, to direct the cleavage of the target RNA.

[0105] As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an RNAi agent, *e.g.*, a dsRNA. For example, when a 3'-end

of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively, the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, at least five nucleotides or more. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a dsRNA.

[0106] In one embodiment, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

[0107] In certain embodiments, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, 0-3, 1-3, 2-4, 2-5, 4-10, 5-10, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

[0108] In certain embodiments, the overhang on the sense strand or the antisense strand, can include extended lengths longer than 10 nucleotides, *e.g.*, 1-30 nucleotides, 2-30 nucleotides, 10-30 nucleotides, or 10-15 nucleotides in length. In certain embodiments, an extended overhang is on the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 3'end of the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 5'end of the sense strand of the duplex. In certain embodiments, an extended overhang is on the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 3'end of the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 5'end of the antisense strand of the duplex. In certain embodiments, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate. In certain embodiments, the overhang includes a self-complementary portion such that the overhang is capable of forming a hairpin structure that is stable under physiological conditions.

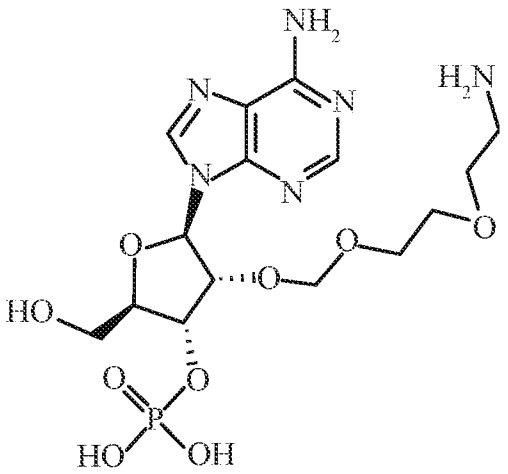
[0109] In certain embodiments, at least one end of at least one strand is extended beyond a duplex targeting region, including structures where one of the strands includes a thermodynamically -stabilizing tetraloop structure (see, *e.g.*, U.S. Patent Nos. 8,513,207 and 8,927,705, as well as W02010033225, the entire contents of each of which are incorporated by reference herein). Such structures may include single-stranded extensions (on one or both sides of the molecule)as well as double-stranded extensions.

[0110] In certain embodiments, the 3' end of the sense strand and the 5' end of the antisense strand are joined by a polynucleotide sequence comprising ribonucleotides, deoxyribonucleotides or

both, optionally wherein the polynucleotide sequence comprises a tetraloop sequence. In certain embodiments, the sense strand is 25-35 nucleotides in length.

[0111] A tetraloop may contain ribonucleotides, deoxyribonucleotides, modified nucleotides, and combinations thereof. Typically, a tetraloop has 4 to 5 nucleotides. In some embodiments, the loop comprises a sequence set forth as GAAA. In some embodiments, at least one of the nucleotide of the loop (GAAA) comprises a nucleotide modification. In some embodiments, the modified nucleotide comprises a 2'-modification. In some embodiments, the 2 '-modification is a modification selected from the group consisting of 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, 2'-aminodiethoxymethanol, 2'- adem, and 2'-deoxy-2'-fhioro- -d-arabinonucleic acid. In some embodiments, all of the nucleotides of the loop are modified. In some embodiments, the G in the GAAA sequence comprises a 2'-OH. In some embodiments, each of the nucleotides in the GAAA sequence comprises a 2'-O-methyl modification. In some embodiments, each of the A in the GAAA sequence comprises a 2'-OH and the G in the GAAA sequence comprises a 2'-O-methyl modification. In preferred embodiments, In some embodiments, each of the A in the GAAA sequence comprises a 2'-O-methoxyethyl (MOE) modification and the G in the GAAA sequence comprises a 2'-O-methyl modification; or each of the A in the GAAA sequence comprises a 2'- adem modification and the G in the GAAA sequence comprises a 2'-O-methyl modification. See, *e.g.*, PCT Publication No. WO 2020/206350, the entire contents of which are incorporated herein by reference.

[0112] An exemplary 2'adem modified nucleotide is shown below:



[0113] The terms "blunt" or "blunt ended" as used herein in reference to a dsRNA mean that there are no unpaired nucleotides or nucleotide analogs at a given terminal end of a dsRNA, *i.e.*, no nucleotide overhang. One or both ends of a dsRNA can be blunt. Where both ends of a dsRNA are blunt, the dsRNA is said to be blunt ended. To be clear, a "blunt ended" dsRNA is a dsRNA that is blunt at both ends, *i.e.*, no nucleotide overhang at either end of the molecule. Most often such a molecule will be double stranded over its entire length.

[0114] The term “antisense strand” or "guide strand" refers to the strand of an RNAi agent, *e.g.*, a dsRNA, which includes a region that is substantially complementary to a target sequence, *e.g.*, an HTT mRNA.

[0115] As used herein, the term “region of complementarity” refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence, *e.g.,* an HTT nucleotide sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can be in the internal or terminal regions of the molecule. Generally, the most tolerated mismatches are in the terminal regions, *e.g.*, within 5, 4, 3, or 2 nucleotides of the 5’- or 3’-terminus of the RNAi agent. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the antisense strand. In some embodiments, the antisense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the target mRNA, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the target mRNA. In some embodiments, the antisense strand double stranded RNA agent of the invention includes no more than 4 mismatches with the sense strand, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the sense strand. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the sense strand. In some embodiments, the sense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the antisense strand, *e.g.*, the sense strand includes 4, 3, 2, 1, or 0 mismatches with the antisense strand. In some embodiments, the nucleotide mismatch is, for example, within 5, 4, 3 nucleotides from the 3’-end of the iRNA. In another embodiment, the nucleotide mismatch is, for example, in the 3’-terminal nucleotide of the iRNA agent. In some embodiments, the mismatch(s) is not in the seed region.

[0116] Thus, an RNAi agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, an RNAi agent as described herein contains no more than 3 mismatches (*i.e.,* 3, 2, 1, or 0 mismatches). In one embodiment, an RNAi agent as described herein contains no more than 2 mismatches. In one embodiment, an RNAi agent as described herein contains no more than 1 mismatch. In one embodiment, an RNAi agent as described herein contains 0 mismatches. In certain embodiments, if the antisense strand of the RNAi agent contains mismatches to the target sequence, the mismatch can optionally be restricted to be within the last 5 nucleotides from either the 5’- or 3’-end of the region of complementarity. For example, in such embodiments, for a 23 nucleotide RNAi agent, the strand which is complementary to a region of an HTT gene, generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an RNAi agent containing a mismatch to a target sequence is effective in inhibiting the expression of an HTT gene. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of an HTT gene is important, especially if the particular region of complementarity in an HTT gene is known to have polymorphic sequence variation within the population.

[0117] The term “sense strand” or "passenger strand" as used herein, refers to the strand of an RNAi agent that includes a region that is substantially complementary to a region of the antisense strand as that term is defined herein.

[0118] As used herein, the term “cleavage region” refers to a region that is located immediately adjacent to the cleavage site. The cleavage site is the site on the target at which cleavage occurs. In some embodiments, the cleavage region comprises three bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage site specifically occurs at the site bound by nucleotides 10 and 11 of the antisense strand, and the cleavage region comprises nucleotides 11, 12 and 13.

[0119] As used herein, and unless otherwise indicated, the term “complementary,” when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person.

[0120] Complementary sequences within an RNAi agent, *e.g.*, within a dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as “fully complementary” with respect to each other herein. However, where a first sequence is referred to as “substantially complementary” with respect to a second sequence herein, the two sequences can be fully complementary, or they can form one or more, but generally not more than 5, 4, 3 or 2 mismatched base pairs upon hybridization for a duplex up to 30 base pairs, while retaining the ability to hybridize under the conditions most relevant to their ultimate application, *e.g.*, inhibition of gene expression *via* a RISC pathway. However, where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, can yet be referred to as “fully complementary” for the purposes described herein.

[0121] “Complementary” sequences, as used herein, can also include, or be formed entirely from, non-Watson-Crick base pairs or base pairs formed from non-natural and modified nucleotides, in so far as the above 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 Hoogstein base pairing.

[0122] The terms “complementary,” “fully complementary” and “substantially complementary” herein can be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between the antisense strand of an RNAi agent and a target sequence, as will be understood from the context of their use.

[0123] As used herein, a polynucleotide that is "substantially complementary to at least part of" a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.*, an mRNA encoding HTT). For example, a polynucleotide is complementary to at least a part of an HTT mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding HTT.

[0124] Accordingly, in some embodiments, the antisense polynucleotides disclosed herein are fully complementary to the target HTT sequence. In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target HTT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to the equivalent region of the nucleotide sequence of any one of SEQ ID NOs:1-5 and 11, or a fragment of any one of SEQ ID NOs:1-5 and 11, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

[0125] In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target HTT sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of any one of Tables 2-3 and 5-6, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 2-3 and 5-6, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

[0126] In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target HTT sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 6-10 and 12, or a fragment of any one of SEQ ID NOs:6-10 and 12, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

[0127] In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target HTT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 11 selected from the group of nucleotides 5922-5944, 6059-6106; 6059-6084; 6068-6092; 6076-6106; 6191-6231; 6191-6215; 6191-6214; 6192-6215; 6198-6231; or 6198-6224 of SEQ ID NO: 11, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

[0128] In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target HTT sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 2-3 and 5-6, or a fragment of any one of

the antisense strand nucleotide sequences in any one of Tables 2-3 and 5-6, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

[0129] In some embodiments, the sense and antisense strand are selected from any one of the duplexes AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

[0130] In one embodiment, at least partial suppression of the expression of an HTT gene, is assessed by a reduction of the amount of HTT mRNA which can be isolated from or detected in a first cell or group of cells in which an HTT gene is transcribed and which has or have been treated such that the expression of an HTT gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells). The degree of inhibition may be expressed in terms of:

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} \bullet 100\%$$

[0131] The phrase "contacting a cell with an RNAi agent," such as a dsRNA, as used herein, includes contacting a cell by any possible means. Contacting a cell with an RNAi agent includes contacting a cell *in vitro* with the RNAi agent or contacting a cell *in vivo* with the RNAi agent. The contacting may be done directly or indirectly. Thus, for example, the RNAi agent may be put into physical contact with the cell by the individual performing the method, or alternatively, the RNAi agent may be put into a situation that will permit or cause it to subsequently come into contact with the cell.

[0132] Contacting a cell *in vitro* may be done, for example, by incubating the cell with the RNAi agent. Contacting a cell *in vivo* may be done, for example, by injecting the RNAi agent into or near the tissue where the cell is located, or by injecting the RNAi agent into another area, *e.g.*, the central nervous system (CNS), optionally *via* intrathecal, intravitreal or other injection, or to the bloodstream or the subcutaneous space, such that the agent will subsequently reach the tissue where the cell to be contacted is located. For example, the RNAi agent may contain or be coupled to a ligand, *e.g.*, a lipophilic moiety or moieties as described below and further detailed, *e.g.*, in PCT/US2019/031170, which is incorporated herein by reference, that directs or otherwise stabilizes the RNAi agent at a site of interest, *e.g.*, the CNS. Combinations of *in vitro* and *in vivo* methods of contacting are also possible. For example, a cell may also be contacted *in vitro* with an RNAi agent and subsequently transplanted into a subject.

[0133] In one embodiment, contacting a cell with an RNAi agent includes "introducing" or "delivering the RNAi agent into the cell" by facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an RNAi agent can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. Introducing an RNAi agent into a cell may be *in vitro* or *in vivo*. For example, for *in vivo* introduction, an RNAi agent can be injected into a tissue site or

administered systemically. *In vitro* introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below or are known in the art.

[0134] The term "lipophile" or "lipophilic moiety" broadly refers to any compound or chemical moiety having an affinity for lipids. One way to characterize the lipophilicity of the lipophilic moiety is by the octanol-water partition coefficient, $\log K_{ow}$, where K_{ow} is the ratio of a chemical's concentration in the octanol-phase to its concentration in the aqueous phase of a two-phase system at equilibrium. The octanol-water partition coefficient is a laboratory-measured property of a substance. However, it may also be predicted by using coefficients attributed to the structural components of a chemical which are calculated using first-principle or empirical methods (see, for example, Tetko *et al.*, *J. Chem. Inf. Comput. Sci.* 41:1407-21 (2001), which is incorporated herein by reference in its entirety). It provides a thermodynamic measure of the tendency of the substance to prefer a non-aqueous or oily milieu rather than water (*i.e.* its hydrophilic/lipophilic balance). In principle, a chemical substance is lipophilic in character when its $\log K_{ow}$ exceeds 0. Typically, the lipophilic moiety possesses a $\log K_{ow}$ exceeding 1, exceeding 1.5, exceeding 2, exceeding 3, exceeding 4, exceeding 5, or exceeding 10. For instance, the $\log K_{ow}$ of 6-amino hexanol, for instance, is predicted to be approximately 0.7. Using the same method, the $\log K_{ow}$ of cholesteryl N-(hexan-6-ol) carbamate is predicted to be 10.7.

[0135] The lipophilicity of a molecule can change with respect to the functional group it carries. For instance, adding a hydroxyl group or amine group to the end of a lipophilic moiety can increase or decrease the partition coefficient (*e.g.*, $\log K_{ow}$) value of the lipophilic moiety.

[0136] Alternatively, the hydrophobicity of the double-stranded RNAi agent, conjugated to one or more lipophilic moieties, can be measured by its protein binding characteristics. For instance, in certain embodiments, the unbound fraction in the plasma protein binding assay of the double-stranded RNAi agent could be determined to positively correlate to the relative hydrophobicity of the double-stranded RNAi agent, which could then positively correlate to the silencing activity of the double-stranded RNAi agent.

[0137] In one embodiment, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. An exemplary protocol of this binding assay is illustrated in detail in, *e.g.*, PCT/US2019/031170. The hydrophobicity of the double-stranded RNAi agent, measured by fraction of unbound siRNA in the binding assay, exceeds 0.15, exceeds 0.2, exceeds 0.25, exceeds 0.3, exceeds 0.35, exceeds 0.4, exceeds 0.45, or exceeds 0.5 for an enhanced *in vivo* delivery of siRNA.

[0138] Accordingly, conjugating the lipophilic moieties to the internal position(s) of the double-stranded RNAi agent provides optimal hydrophobicity for the enhanced *in vivo* delivery of siRNA.

[0139] The term "lipid nanoparticle" or "LNP" is a vesicle comprising a lipid layer encapsulating a pharmaceutically active molecule, such as a nucleic acid molecule, *e.g.,* a rNAi agent or a plasmid from which an RNAi agent is transcribed. LNPs are described in, for example, U.S. Patent Nos.

6,858,225, 6,815,432, 8,158,601, and 8,058,069, the entire contents of which are hereby incorporated herein by reference.

[0140] As used herein, a "subject" is an animal, such as a mammal, including a primate (such as a human, a non-human primate, *e.g.*, a monkey, and a chimpanzee), or a non-primate (such as a a rat, or a mouse). In a preferred embodiment, the subject is a human, such as a human being treated or assessed for a disease, disorder, or condition that would benefit from reduction in HTT expression; a human at risk for a disease, disorder, or condition that would benefit from reduction in HTT expression; a human having a disease, disorder, or condition that would benefit from reduction in HTT expression; or human being treated for a disease, disorder, or condition that would benefit from reduction in HTT expression as described herein. In some embodiments, the subject is a female human. In other embodiments, the subject is a male human. In one embodiment, the subject is an adult subject. In one embodiment, the subject is a pediatric subject. In another embodiment, the subject is a juvenile subject, *i.e.,* a subject below 20 years of age.

[0141] As used herein, the terms "treating" or "treatment" refer to a beneficial or desired result including, but not limited to, alle*via*tion or amelioration of one or more signs or symptoms associated with HTT gene expression or HTT protein production, *e.g.,* HTT-associated diseases, such as Huntington's disease. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

[0142] The term "lower" in the context of the level of HTT in a subject or a disease marker or symptom refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, 15%, 20%, 25%, 30%, %, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In certain embodiments, a decrease is at least 20%. In certain embodiments, the decrease is at least 50% in a disease marker, *e.g.*, protein or gene expression level. "Lower" in the context of the level of HTT in a subject is preferably down to a level accepted as within the range of normal for an individual without such disorder. In certain embodiments, "lower" is the decrease in the difference between the level of a marker or symptom for a subject suffering from a disease and a level accepted within the range of normal for an individual, *e.g.*, the level of decrease in bodyweight between an obese individual and an individual having a weight accepted within the range of normal.

[0143] As used herein, "prevention" or "preventing," when used in reference to a disease, disorder, or condition thereof, that would benefit from a reduction in expression of an HTT gene or production of an HTT protein, refers to a reduction in the likelihood that a subject will develop a symptom associated with such a disease, disorder, or condition, *e.g.,* a symptom of an HTT-associated disease. The failure to develop a disease, disorder, or condition, or the reduction in the development of a symptom associated with such a disease, disorder, or condition (*e.g.*, by at least about 10% on a clinically accepted scale for that disease or disorder), or the exhibition of delayed symptoms delayed (*e.g.*, by days, weeks, months or years) is considered effective prevention.

[0144] As used herein, the term "HTT-associated disease" or "HTT-associated disorder" is understood as any disease or disorder that would benefit from reduction in the expression and/or activity of HTT. Exemplary HTT-associated diseases include Huntington's disease.

[0145] "Huntington's disease," also known as HD, Huntington's Chorea, Chorea Maior, Chronic Progressive Chorea, and Hereditary Chorea, is an autosomal dominant genetic disorder characterized by choreiform movements and progressive intellectual deterioration, usually beginning in middle age (35 to 50 yr). The disease affects both sexes equally. The caudate nucleus atrophies, the small-cell population degenerates, and levels of the neurotransmitters gamma-aminobutyric acid (GABA) and substance P decrease. This degeneration results in characteristic "boxcar ventricles" seen on CT scans.

[0146] Symptoms and signs of HD develop insidiously. HD's most obvious symptoms are abnormal body movements called chorea and lack of coordination, but it also affects a number of mental abilities and some aspects of personality. These physical symptoms commonly become noticable in a person`s forties, but can occur at any age. If the age of onset is below 20 years then it is known as Juvenile HD.

[0147] Dementia or psychiatric disturbances, ranging from apathy and irritability to full-blown bipolar or schizophreniform disorder, may precede the movement disorder or develop during its course. Anhedonia or asocial behavior may be the first behavioral manifestation. Motor manifestations include flicking movements of the extremities, a lilting gait, motor impersistence (inability to sustain a motor act, such as tongue protrusion), facial grimacing, ataxia, and dystonia.

[0148] HD is caused by a trinucleotide repeat expansion in the Huntingtin (HTT) gene, and is one of several polyglutamine expansion (or PolyQ expansion) diseases. This produces an extended form of the mutant Huntingtin protein (mHtt), which causes cell death in selective areas of the brain.

[0149] "Therapeutically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having an HTT-associated disease, is sufficient to effect treatment of the disease (*e.g.*, by diminishing, ameliorating, or maintaining the existing disease or one or more symptoms of disease). The "therapeutically effective amount" may vary depending on the RNAi agent, how the agent is administered, the disease and its severity and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the subject to be treated.

[0150] "Prophylactically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having an HTT-associated disorder, is sufficient to prevent or ameliorate the disease or one or more symptoms of the disease. Ameliorating the disease includes slowing the course of the disease or reducing the severity of later-developing disease. The "prophylactically effective amount" may vary depending on the RNAi agent, how the agent is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

[0151] A "therapeutically-effective amount" or "prophylacticaly effective amount" also includes an amount of an RNAi agent that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. An RNAi agent employed in the methods of the present disclosure may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment.

[0152] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds (including salts), materials, compositions, or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human subjects and animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0153] The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium state, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

[0154] The term “sample,” as used herein, includes a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Examples of biological fluids include blood, serum and serosal fluids, plasma, cerebrospinal fluid, ocular fluids, lymph, urine, saliva, and the like. Tissue samples may include samples from tissues, organs or localized regions. For example, samples may be derived from particular organs, parts of organs, or fluids or cells within those organs. In certain embodiments, samples may be derived from the brain (*e.g.*, whole brain or certain segments of brain, *e.g.,* striatum, or certain types of cells in the brain, such as, *e.g.*, neurons and glial cells (astrocytes, oligodendrocytes, microglial cells)). In some embodiments, a “sample derived from a subject” refers to blood drawn from the subject or plasma or serum derived therefrom. In further embodiments, a “sample derived from a subject” refers to brain tissue (or subcomponents thereof) or retinal tissue (or subcomponents thereof) derived from the subject.

II. RNAi Agents of the Disclosure

[0155] Described herein are RNAi agents which inhibit the expression of an HTT gene. In one embodiment, the RNAi agent includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of an HTT gene in a cell, such as a cell within a subject, *e.g.,* a mammal, such as a human having an HTT-associated disease, *e.g.,* Huntington's disease. The dsRNA includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of an HTT gene. The region of complementarity is about 15-30 nucleotides or less in length. Upon contact with a cell expressing the HTT gene, the RNAi agent inhibits the expression of the HTT gene (*e.g.,* a human gene, a primate gene, a non-primate gene) by at least 50% as assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by immunofluorescence analysis, using, for example, western blotting or flow cytometric techniques. In one, the level of knockdown is assayed in Cos7 cells using a Dual-Luciferase assay method.

[0156] A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence. The target sequence can be derived from the sequence of an mRNA formed during the expression of an HTT gene. The other strand (the sense strand) includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. As described elsewhere herein and as known in the art, the complementary sequences of a dsRNA can also be contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides.

[0157] Generally, the duplex structure is 15 to 30 base pairs in length, *e.g.,* 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain preferred embodiments, the duplex structure is 18 to 25 base pairs in length, *e.g.*, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-25, 20-24,20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 base pairs in length, for example, 19-21 basepairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

[0158] Similarly, the region of complementarity to the target sequence is 15 to 30 nucleotides in length, *e.g.,* 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides

in length, for example 19-23 nucleotides in length or 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

[0159] In some embodiments, the duplex structure is 19 to 30 base pairs in length. Similarly, the region of complementarity to the target sequence is 19 to 30 nucleotides in length.

[0160] In some embodiments, the dsRNA is 15 to 23 nucleotides in length, 19 to 23 nucleotides in length, or 25 to 30 nucleotides in length. In general, the dsRNA is long enough to serve as a substrate for the Dicer enzyme. For example, it is well known in the art that dsRNAs longer than about 21-23 nucleotides can serve as substrates for Dicer. As the ordinarily skilled person will also recognize, the region of an RNA targeted for cleavage will most often be part of a larger RNA molecule, often an mRNA molecule. Where relevant, a "part" of an mRNA target is a contiguous sequence of an mRNA target of sufficient length to allow it to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway).

[0161] One of skill in the art will also recognize that the duplex region is a primary functional portion of a dsRNA, *e.g.*, a duplex region of about 15 to 36 base pairs, *e.g.*, 15-36, 15-35, 15-34, 15-33, 15-32, 15-31, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs, for example, 19-21 base pairs. Thus, in one embodiment, to the extent that it becomes processed to a functional duplex, of *e.g.*, 15-30 base pairs, that targets a desired RNA for cleavage, an RNA molecule or complex of RNA molecules having a duplex region greater than 30 base pairs is a dsRNA. Thus, an ordinarily skilled artisan will recognize that in one embodiment, a miRNA is a dsRNA. In another embodiment, a dsRNA is not a naturally occurring miRNA. In another embodiment, an RNAi agent useful to target HTT expression is not generated in the target cell by cleavage of a larger dsRNA.

[0162] A dsRNA as described herein can further include one or more single-stranded nucleotide overhangs *e.g.,* 1, 2, 3, or 4 nucleotides. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a dsRNA.

[0163] A dsRNA can be synthesized by standard methods known in the art. Double stranded RNAi compounds of the invention may be prepared using a two-step procedure. First, the individual strands of the double stranded RNA molecule are prepared separately. Then, the component strands are annealed. The individual strands of the siRNA compound can be prepared using solution-phase or solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide strands comprising unnatural or modified nucleotides can be easily prepared. Similarly, single-stranded oligonucleotides of the invention can be prepared using solution-phase or solid-phase organic synthesis or both.

[0164] In one aspect, a dsRNA of the disclosure includes at least two nucleotide sequences, a sense sequence and an antisense sequence. The sense strand sequence for HTT may be selected from the group of sequences provided in any one of Tables 2-3 and 5-6, and the corresponding nucleotide sequence of the antisense strand of the sense strand may be selected from the group of sequences of any one of Tables 2-3 and 5-6. In this aspect, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a sequence of an mRNA generated in the expression of an HTT gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand (passenger strand) in any one of Tables 2-3 and 5-6, and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 2 -3 and 5-6.

[0165] In certain embodiments, the sense or antisense strand is selected from the sense or antisense strand of any one of duplexes AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

[0166] In one embodiment, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In another embodiment, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

[0167] It will be understood that, although some of the sequences in Tables 2-3 and 5-6 are described as modified or conjugated sequences, the RNA of the RNAi agent of the disclosure *e.g.*, a dsRNA of the disclosure, may comprise any one of the sequences set forth in any one of Tables 2-3 and 5-6 that is un-modified, un-conjugated, or modified or conjugated differently than described therein. For example, although the sense strands of the agents of the invention shown in Table 3 are conjugated to a C16 and L96 ligand, these agents may be conjugated to either a C6 moiety or an L96 ligand that directs delivery to the liver, *e.g.,* a GalNAc ligand, as described herein, and not both. A lipophilic ligand can be included in any of the positions provided in the instant application.

[0168] The skilled person is well aware that dsRNAs having a duplex structure of about 20 to 23 base pairs, *e.g.,* 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, (2001) *EMBO J.*, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can also be effective (Chu and Rana (2007) *RNA* 14:1714-1719; Kim *et al.* (2005) *Nat Biotech* 23:222-226) . In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided herein, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides derived from one of the sequences provided herein, and differing in their ability to inhibit the expression of an HTT gene by not more than 10, 15, 20, 25, or 30 % inhibition from a dsRNA comprising the full sequence using the *in vitro* assay with Cos7 and a 10 nM

concentration of the RNA agent and the PCR assay as provided in the examples herein, are contemplated to be within the scope of the present disclosure.

[0169] In addition, the RNAs described herein identify a site(s) in an HTT transcript that is susceptible to RISC-mediated cleavage. As such, the present disclosure further features RNAi agents that target within this site(s). As used herein, an RNAi agent is said to target within a particular site of an RNA transcript if the RNAi agent promotes cleavage of the transcript anywhere within that particular site. Such an RNAi agent will generally include at least about 15 contiguous nucleotides, preferably at least 19 nucleotides, from one of the sequences provided herein coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in an HTT gene.

III. Modified RNAi Agents of the Disclosure

[0170] In one embodiment, the RNA of the RNAi agent of the disclosure *e.g.*, a dsRNA, is un-modified, and does not comprise, *e.g.,* chemical modifications or conjugations known in the art and described herein. In preferred embodiments, the RNA of an RNAi agent of the disclosure, *e.g.*, a dsRNA, is chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the disclosure, substantially all of the nucleotides of an RNAi agent of the disclosure are modified. In other embodiments of the disclosure, all of the nucleotides of an RNAi agent of the disclosure are modified. RNAi agents of the disclosure in which "substantially all of the nucleotides are modified" are largely but not wholly modified and can include not more than 5, 4, 3, 2, or unmodified nucleotides. In still other embodiments of the disclosure, RNAi agents of the disclosure can include not more than 5, 4, 3, 2 or 1 modified nucleotides.

[0171] The nucleic acids featured in the disclosure can be synthesized or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. *et al*. (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, end modifications, *e.g.*, 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleotides, inverted linkages, *etc*.); base modifications, *e.g.*, replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases; sugar modifications (*e.g.*, at the 2'-position or 4'-position) or replacement of the sugar; or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNAi agents useful in the embodiments described herein include, but are not limited to, RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified RNAi agent will have a phosphorus atom in its internucleoside backbone.

[0172] Modified RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and

other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included. In some embodiments of the invention, the dsRNA agents of the invention are in a free acid form. In other embodiments of the invention, the dsRNA agents of the invention are in a salt form. In one embodiment, the dsRNA agents of the invention are in a sodium salt form. In certain embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for substantially all of the phosphodiester and/or phosphorothiotate groups present in the agent. Agents in which substantially all of the phosphodiester and/or phosphorothioate linkages have a sodium counterion include not more than 5, 4, 3, 2, or 1 phosphodiester and/or phosphorothioate linkages without a sodium counterion. In some embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for all of the phosphodiester and/or phosphorothiotate groups present in the agent.

[0173] Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6, 239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and US Pat RE39464, the entire contents of each of which are hereby incorporated herein by reference.

[0174] Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH2 component parts.

[0175] Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and, 5,677,439, the entire contents of each of which are hereby incorporated herein by reference.

[0176] In other embodiments, suitable RNA mimetics are contemplated for use in RNAi agents, in which both the sugar and the internucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, a RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, the entire contents of each of which are hereby incorporated herein by reference. Additional PNA compounds suitable for use in the RNAi agents of the disclosure are described in, for example, in Nielsen *et al.*, *Science*, 1991, 254, 1497-1500.

[0177] Some embodiments featured in the disclosure include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH_2--NH--CH_2-, --CH_2--N(CH_3)--O--CH_2--[known as a methylene (methylimino) or MMI backbone], --CH_2--O--N(CH_3)--CH_2--, --CH_2--N(CH_3)--N(CH_3)--CH_2-- and --N(CH_3)--CH_2--CH_2--[wherein the native phosphodiester backbone is represented as --O--P--O--CH_2--] of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced US5,034,506.

[0178] Modified RNAs can also contain one or more substituted sugar moieties. The RNAi agents, *e.g.*, dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include O[$(CH_2)_n$O] $_m$$CH_3$, O$(CH_2)._nOCH_3$, O$(CH_2)_n$$NH_2$, O$(CH_2)$ $_n$$CH_3$, O$(CH_2)_nONH_2$, and O$(CH_2)_n$ON[$(CH_2)_n$$CH_3$)]$_2$, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an RNAi agent, or a group for improving the pharmacodynamic properties of an RNAi agent, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a O$(CH_2)_2$O$N(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--N$(CH_2)_2$. Further exemplary modifications include : 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-

deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

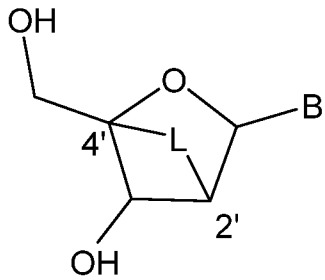
[0179] Other modifications include 2'-methoxy (2'-OCH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$), 2'-*O*-hexadecyl, and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of an RNAi agent, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. RNAi agents can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application. The entire contents of each of the foregoing are hereby incorporated herein by reference.

[0180] An RNAi agent of the disclosure can also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl anal other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, these disclosed by Englisch *et al*., (1991) *Angewandte Chemie, International Edition*, 30:613, and those disclosed by Sanghvi, Y S., Chapter 15, dsRNA Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the disclosure. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2 °C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., dsRNA Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

[0181] Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Patent Nos. 3,687,808, 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the entire contents of each of which are hereby incorporated herein by reference.

[0182] In some embodiments, an RNAi agent of the disclosure can also be modified to include one or more bicyclic sugar moieties. A "bicyclic sugar" is a furanosyl ring modified by a ring formed by the bridging of two carbons, whether adjacent or non-adjacent. A "bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a ring formed by bridging two carbons, whether adjacent or non-adjacent, of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4′-carbon and the 2′-carbon of the sugar ring, optionally, via the 2'-acyclic oxygen atom. Thus, in some embodiments an agent of the invention may include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. In other words, an LNA is a nucleotide comprising a bicyclic sugar moiety comprising a 4'-CH_2-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193). Examples of bicyclic nucleosides for use in the polynucleotides of the invention include without limitation nucleosides comprising a bridge between the 4′ and the 2′ ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the invention include one or more bicyclic nucleosides comprising a 4′ to 2′ bridge.

[0183] A locked nucleoside can be represented by the structure (omitting stereochemistry),



wherein B is a nucleobase or modified nucleobase and L is the linking group that joins the 2'-carbon to the 4'-carbon of the ribose ring. Examples of such 4′ to 2′ bridged bicyclic nucleosides, include but are not limited to 4′-(CH_2)—O-2′ (LNA); 4′-(CH_2)—S-2′; 4′-(CH_2)$_2$—O-2′ (ENA); 4′-$CH(CH_3)$—O-2′ (also referred to as "constrained ethyl" or "cEt") and 4′-$CH(CH_2OCH_3)$—O-2′ (and analogs thereof; see, *e.g.*, U.S. Patent No. 7,399,845); 4′-$C(CH_3)(CH_3)$—O-2′ (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,283); 4′-CH_2—$N(OCH_3)$-2′ (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,425); 4′-CH_2—O—$N(CH_3)$-2′ (see, *e.g.*, U.S. Patent Publication No. 2004/0171570); 4′-CH_2—

N(R)—O-2′, wherein R is H, C1-C12 alkyl, or a nitrogen protecting group (see, *e.g.*, U.S. Patent No. 7,427,672); 4′-CH_2—C(H)(CH_3)-2′ (see, *e.g.*, Chattopadhyaya *et al., J. Org. Chem.*, 2009, 74, 118-134); and 4′-CH_2—C(=CH_2)-2′ (and analogs thereof; see, *e.g.*, U.S. Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

[0184] Additional representative U.S. Patents and U.S. Patent Publications that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: U.S. Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 6,998,484; 7,053,207; 7,034,133;7,084,125; 7,399,845; 7,427,672; 7,569,686; 7,741,457; 8,022,193; 8,030,467; 8,278,425; 8,278,426; 8,278,283; US 2008/0039618; and US 2009/0012281, the entire contents of each of which are hereby incorporated herein by reference.

[0185] Any of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see WO 99/14226).

[0186] The RNA of an iRNA can also be modified to include one or more constrained ethyl nucleotides. As used herein, a "constrained ethyl nucleotide" or "cEt" is a locked nucleic acid comprising a bicyclic sugar moiety comprising a 4'-CH(CH3)-O-2' bridge (*i.e.*, L in the preceding structure). In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as “S-cEt.”

[0187] An iRNA of the invention may also include one or more “conformationally restricted nucleotides” (“CRN”). CRN are nucleotide analogs with a linker connecting the C2’and C4’ carbons of ribose or the C3 and -C5′ carbons of ribose. CRN lock the ribose ring into a stable conformation and increase the hybridization affinity to mRNA. The linker is of sufficient length to place the oxygen in an optimal position for stability and affinity resulting in less ribose ring puckering.

[0188] Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, U.S. Patent Publication No. 2013/0190383; and PCT publication WO 2013/036868, the entire contents of each of which are hereby incorporated herein by reference.

[0189] In some embodiments, an iRNA of the invention comprises one or more monomers that are UNA (unlocked nucleic acid) nucleotides. UNA is unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomer with bonds between C1'-C4' have been removed (*i.e.* the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (*i.e.* the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar has been removed (see *Nuc. Acids Symp. Series,* 52, 133-134 (2008) and Fluiter *et al.*, *Mol. Biosyst.,* 2009, 10, 1039 hereby incorporated by reference).

[0190] Representative U.S. publications that teach the preparation of UNA include, but are not limited to, U.S. Patent No. 8,314,227; and U.S. Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

[0191] Potentially stabilizing modifications to the ends of RNA molecules can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3'- phosphate, inverted 2'-deoxy-modified ribonucleotide, such as inverted dT(idT), inverted dA (idA), and inverted abasic 2'-deoxyribonucleotide (iAb) and others. Disclosure of this modification can be found in WO 2011/005861.

[0192] In one example, the 3' or 5' terminal end of a oligonucleotide is linked to an inverted 2'-deoxy-modified ribonucleotide, such as inverted dT(idT), inverted dA (idA), or a inverted abasic 2'-deoxyribonucleotide (iAb). In one particular example, the inverted 2'-deoxy-modified ribonucleotide is linked to the 3'end of an oligonucleotide, such as the 3'-end of a sense strand described herein, where the linking is via a 3'-3' phosphodiester linkage or a 3'-3'-phosphorothioate linkage.

[0193] In another example, the 3'-end of a sense strand is linked via a 3'-3'-phosphorothioate linkage to an inverted abasic ribonucleotide (iAb). In another example, the 3'-end of a sense strand is linked via a 3'-3'-phosphorothioate linkage to an inverted dA (idA).

[0194] In one particular example, the inverted 2'-deoxy-modified ribonucleotide is linked to the 3'end of an oligonucleotide, such as the 3'-end of a sense strand described herein, where the linking is via a 3'-3' phosphodiester linkage or a 3'-3'-phosphorothioate linkage.

[0195] In another example, the 3'-terminal nucleotides of a sense strand is an inverted dA (idA) and is linked to the preceding nucleotide via a 3'-3'- linkage (e.g., 3'-3'-phosphorothioate linkage).

[0196] Other modifications of the nucleotides of an iRNA of the invention include a 5' phosphate or 5' phosphate mimic, *e.g.,* a 5'-terminal phosphate or phosphate mimic on the antisense strand of an iRNA. Suitable phosphate mimics are disclosed in, for example U.S. Patent Publication No. 2012/0157511, the entire contents of which are incorporated herein by reference.

A. Modified RNAi agents Comprising Motifs of the Disclosure

[0197] In certain aspects of the disclosure, the double-stranded RNAi agents of the disclosure include agents with chemical modifications as disclosed, for example, in WO 2013/075035, the entire contents of which are incorporated herein by reference. As shown herein and in WO 2013/075035, a superior result may be obtained by introducing one or more motifs of three identical modifications on three consecutive nucleotides into a sense strand or antisense strand of an RNAi agent, particularly at or near the cleavage site. In some embodiments, the sense strand and antisense strand of the RNAi agent may otherwise be completely modified. The introduction of these motifs interrupts the modification pattern, if present, of the sense or antisense strand. The RNAi agent may be optionally conjugated with a lipophilic ligand, *e.g.*, a C16 ligand, for instance on the sense strand. The RNAi agent may be optionally modified with a (*S*)-glycol nucleic acid (GNA) modification, for instance on one or more residues of the antisense strand. The resulting RNAi agents present superior gene silencing activity.

[0198] Accordingly, the disclosure provides double stranded RNAi agents capable of inhibiting the expression of a target gene (*i.e.*, an HTT gene) *in vivo*. The RNAi agent comprises a sense strand and an antisense strand. Each strand of the RNAi agent may be 15-30 nucleotides in length. For example, each strand may be 16-30 nucleotides in length, 17-30 nucleotides in length, 25-30 nucleotides in length, 27-30 nucleotides in length, 17-23 nucleotides in length, 17-21 nucleotides in length, 17-19 nucleotides in length, 19-25 nucleotides in length, 19-23 nucleotides in length, 19-21 nucleotides in length, 21-25 nucleotides in length, or 21-23 nucleotides in length. In certain embodiments, each strand is 19-23 nucleotides in length.

[0199] The sense strand and antisense strand typically form a duplex double stranded RNA ("dsRNA"), also referred to herein as an "RNAi agent." The duplex region of an RNAi agent may be 15-30 nucleotide pairs in length. For example, the duplex region can be 16-30 nucleotide pairs in length, 17-30 nucleotide pairs in length, 27-30 nucleotide pairs in length, 17 - 23 nucleotide pairs in length, 17-21 nucleotide pairs in length, 17-19 nucleotide pairs in length, 19-25 nucleotide pairs in length, 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-25 nucleotide pairs in length, or 21-23 nucleotide pairs in length. In another example, the duplex region is selected from 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length. In preferred embodiments, the duplex region is 19-21 nucleotide pairs in length.

[0200] In one embodiment, the RNAi agent may contain one or more overhang regions or capping groups at the 3'-end, 5'-end, or both ends of one or both strands. The overhang can be 1-6 nucleotides in length, for instance 2-6 nucleotides in length, 1-5 nucleotides in length, 2-5 nucleotides in length, 1-4 nucleotides in length, 2-4 nucleotides in length, 1-3 nucleotides in length, 2-3 nucleotides in length, or 1-2 nucleotides in length. In preferred embodiments, the nucleotide overhang region is 2 nucleotides in length. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence. The first and second strands can also be joined, *e.g.*, by additional bases to form a hairpin, or by other non-base linkers.

[0201] In one embodiment, the nucleotides in the overhang region of the RNAi agent can each independently be a modified or unmodified nucleotide including, but no limited to 2'-sugar modified, such as, 2-F, 2'-O-methyl, thymidine (T), and any combinations thereof.

[0202] For example, TT can be an overhang sequence for either end on either strand. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence.

[0203] The 5'- or 3'- overhangs at the sense strand, antisense strand or both strands of the RNAi agent may be phosphorylated. In some embodiments, the overhang region(s) contains two nucleotides having a phosphorothioate between the two nucleotides, where the two nucleotides can be the same or different. In one embodiment, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In one embodiment, this 3'-overhang is present in the antisense strand. In one embodiment, this 3'-overhang is present in the sense strand.

[0204] The RNAi agent may contain only a single overhang, which can strengthen the interference activity of the RNAi, without affecting its overall stability. For example, the single-stranded overhang may be located at the 3'-terminal end of the sense strand or, alternatively, at the 3'-terminal end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (or the 3'-end of the sense strand) or *vice versa*. Generally, the antisense strand of the RNAi has a nucleotide overhang at the 3'-end, and the 5'-end is blunt. While not wishing to be bound by theory, the asymmetric blunt end at the 5'-end of the antisense strand and 3'-end overhang of the antisense strand favor the guide strand loading into RISC process.

[0205] In one embodiment, the RNAi agent is a double ended bluntmer of 19 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 7, 8, 9 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end.

[0206] In another embodiment, the RNAi agent is a double ended bluntmer of 20 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 8, 9, 10 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end.

[0207] In yet another embodiment, the RNAi agent is a double ended bluntmer of 21 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, 11 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end.

[0208] In one embodiment, the RNAi agent comprises a 21 nucleotide sense strand and a 23 nucleotide antisense strand, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, 11 from the 5'end; the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end, wherein one end of the RNAi agent is blunt, while the other end comprises a 2 nucleotide overhang. Preferably, the 2 nucleotide overhang is at the 3'-end of the antisense strand. When the 2 nucleotide overhang is at the 3'-end of the antisense strand, there may be two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. In one embodiment, the RNAi agent additionally has two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the sense strand and at the 5'-end of the antisense strand. In one embodiment, every nucleotide in the sense strand and the antisense strand of the RNAi agent, including the nucleotides that are part of the motifs are modified nucleotides. In one embodiment each residue is independently modified with a 2'-O-methyl or 3'-fluoro, *e.g.,* in an alternating motif. Optionally, the RNAi agent further comprises a ligand (*e.g.*, a lipophilic ligand, optionally a C16 ligand).

[0209] In one embodiment, the RNAi agent comprises a sense and an antisense strand, wherein the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1) positions 1 to 23 of the first strand comprise at least 8 ribonucleotides; the antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, comprises at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least the 3 ' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when the double stranded nucleic acid is introduced into a mammalian cell; and wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

[0210] In one embodiment, the RNAi agent comprises sense and antisense strands, wherein the RNAi agent comprises a first strand having a length which is at least 25 and at most 29 nucleotides and a second strand having a length which is at most 30 nucleotides with at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at position 11, 12, 13 from the 5' end; wherein the 3' end of the first strand and the 5' end of the second strand form a blunt end and the second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region region which is at least 25 nucleotides in length, and the second strand is sufficiently complemenatary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein dicer cleavage of the RNAi agent preferentially results in an siRNA comprising the 3' end of the second strand, thereby reducing expression of the target gene in the mammal. Optionally, the RNAi agent further comprises a ligand.

[0211] In one embodiment, the sense strand of the RNAi agent contains at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at the cleavage site in the sense strand.

[0212] In one embodiment, the antisense strand of the RNAi agent can also contain at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at or near the cleavage site in the antisense strand.

[0213] For an RNAi agent having a duplex region of 17-23 nucleotide in length, the cleavage site of the antisense strand is typically around the 10, 11 and 12 positions from the 5'-end. Thus the motifs of three identical modifications may occur at the 9, 10, 11 positions; 10, 11, 12 positions; 11, 12, 13

positions; 12, 13, 14 positions; or 13, 14, 15 positions of the antisense strand, the count starting from the 1st nucleotide from the 5'-end of the antisense strand, or, the count starting from the 1st paired nucleotide within the duplex region from the 5'- end of the antisense strand. The cleavage site in the antisense strand may also change according to the length of the duplex region of the RNAi from the 5'-end.

[0214] The sense strand of the RNAi agent may contain at least one motif of three identical modifications on three consecutive nucleotides at the cleavage site of the strand; and the antisense strand may have at least one motif of three identical modifications on three consecutive nucleotides at or near the cleavage site of the strand. When the sense strand and the antisense strand form a dsRNA duplex, the sense strand and the antisense strand can be so aligned that one motif of the three nucleotides on the sense strand and one motif of the three nucleotides on the antisense strand have at least one nucleotide overlap, *i.e.*, at least one of the three nucleotides of the motif in the sense strand forms a base pair with at least one of the three nucleotides of the motif in the antisense strand. Alternatively, at least two nucleotides may overlap, or all three nucleotides may overlap.

[0215] In one embodiment, the sense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides. The first motif may occur at or near the cleavage site of the strand and the other motifs may be a wing modification. The term "wing modification" herein refers to a motif occurring at another portion of the strand that is separated from the motif at or near the cleavage site of the same strand. The wing modification is either adajacent to the first motif or is separated by at least one or more nucleotides. When the motifs are immediately adjacent to each other then the chemistry of the motifs are distinct from each other and when the motifs are separated by one or more nucleotide than the chemistries can be the same or different. Two or more wing modifications may be present. For instance, when two wing modifications are present, each wing modification may occur at one end relative to the first motif which is at or near cleavage site or on either side of the lead motif.

[0216] Like the sense strand, the antisense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides, with at least one of the motifs occurring at or near the cleavage site of the strand. This antisense strand may also contain one or more wing modifications in an alignment similar to the wing modifications that may be present on the sense strand.

[0217] In one embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two terminal nucleotides at the 3'-end, 5'-end or both ends of the strand.

[0218] In another embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two paired nucleotides within the duplex region at the 3'-end, 5'-end or both ends of the strand.

[0219] When the sense strand and the antisense strand of the RNAi agent each contain at least one wing modification, the wing modifications may fall on the same end of the duplex region, and have an overlap of one, two or three nucleotides.

[0220] When the sense strand and the antisense strand of the RNAi agent each contain at least two wing modifications, the sense strand and the antisense strand can be so aligned that two modifications each from one strand fall on one end of the duplex region, having an overlap of one, two or three nucleotides; two modifications each from one strand fall on the other end of the duplex region, having an overlap of one, two or three nucleotides; two modifications one strand fall on each side of the lead motif, having an overlap of one, two, or three nucleotides in the duplex region.

[0221] In one embodiment, the RNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mistmatch may occur in the overhang region or the duplex region. The base pair may be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

[0222] In one embodiment, the RNAi agent comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'- end of the antisense strand independently selected from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

[0223] In one embodiment, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2 or 3 base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair.

[0224] In another embodiment, the nucleotide at the 3'-end of the sense strand is deoxy-thymine (dT). In another embodiment, the nucleotide at the 3'-end of the antisense strand is deoxy-thymine (dT). In one embodiment, there is a short sequence of deoxy-thymine nucleotides, for example, two dT nucleotides on the 3'-end of the sense or antisense strand.

[0225] In one embodiment, the sense strand sequence may be represented by formula (I):

[0226] $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\ \text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$ (I)

[0227] wherein:

[0228] i and j are each independently 0 or 1;

[0229] p and q are each independently 0-6;

[0230] each N_a independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

[0231] each N_b independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

[0232] each n_p and n_q independently represent an overhang nucleotide;

[0233] wherein Nb and Y do not have the same modification; and

[0234] XXX, YYY and ZZZ each independently represent one motif of three identical modifications on three consecutive nucleotides. Preferably YYY is all 2'-F modified nucleotides.

[0235] In one embodiment, the N_a or N_b comprise modifications of alternating pattern.

[0236] In one embodiment, the YYY motif occurs at or near the cleavage site of the sense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotides in length, the YYY motif can occur at or the vicinity of the cleavage site (*e.g.*: can occur at positions 6, 7, 8, 7, 8, 9, 8, 9, 10, 9, 10, 11, 10, 11,12 or 11, 12, 13) of - the sense strand, the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end.

[0237] In one embodiment, i is 1 and j is 0, or i is 0 and j is 1, or both i and j are 1. The sense strand can therefore be represented by the following formulas:

[0238] 5' n_p-N_a-YYY-N_b-ZZZ-N_a-n_q 3' (Ib);

[0239] 5' n_p-N_a-XXX-N_b-YYY-N_a-n_q 3' (Ic); or

[0240] 5' n_p-N_a-XXX-N_b-YYY-N_b-ZZZ-N_a-n_q 3' (Id).

[0241] When the sense strand is represented by formula (Ib), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides.

[0242] Each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0243] When the sense strand is represented as formula (Ic), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0244] When the sense strand is represented as formula (Id), each N_b independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Preferably, N_b is 0, 1, 2, 3, 4, 5 or 6. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0245] Each of X, Y and Z may be the same or different from each other.

[0246] In other embodiments, i is 0 and j is 0, and the sense strand may be represented by the formula:

[0247] 5' n_p-N_a-YYY- N_a-n_q 3' (Ia).

[0248] When the sense strand is represented by formula (Ia), each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0249] In one embodiment, the antisense strand sequence of the RNAi may be represented by formula (II):

[0250] 5' $n_{q'}$-N_a'-$(Z'Z'Z')_k$-N_b'-$Y'Y'Y'$-N_b'-$(X'X'X')_l$-N'_a-n_p' 3' (II)

[0251] wherein:

[0252] k and l are each independently 0 or 1;

[0253] p' and q' are each independently 0-6;

[0254] each N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

[0255] each N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

[0256] each n_p' and n_q' independently represent an overhang nucleotide;

[0257] wherein N_b' and Y' do not have the same modification;

[0258] and

[0259] X'X'X', Y'Y'Y' and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides.

[0260] In one embodiment, the N_a' or N_b' comprise modifications of alternating pattern.

[0261] The Y'Y'Y' motif occurs at or near the cleavage site of the antisense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotide in length, the Y'Y'Y' motif can occur at positions 9, 10, 11;10, 11, 12; 11, 12, 13; 12, 13, 14 ; or 13, 14, 15 of the antisense strand, with the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end. Preferably, the Y'Y'Y' motif occurs at positions 11, 12, 13.

[0262] In one embodiment, Y'Y'Y' motif is all 2'-OMe modified nucleotides.

[0263] In one embodiment, k is 1 and l is 0, or k is 0 and l is 1, or both k and l are 1.

[0264] The antisense strand can therefore be represented by the following formulas:

[0265] 5' $n_{q'}$-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_a'-$n_{p'}$ 3' (IIb);

[0266] 5' $n_{q'}$-N_a'-Y'Y'Y'-N_b'-X'X'X'-$n_{p'}$ 3' (IIc); or

[0267] 5' $n_{q'}$-N_a'- Z'Z'Z'-N_b'-Y'Y'Y'-N_b'- X'X'X'-N_a'-$n_{p'}$ 3' (IId).

[0268] When the antisense strand is represented by formula (IIb), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0269] When the antisense strand is represented as formula (IIc), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0270] When the antisense strand is represented as formula (IId), each N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Preferably, N_b is 0, 1, 2, 3, 4, 5 or 6.

[0271] In other embodiments, k is 0 and l is 0 and the antisense strand may be represented by the formula:

[0272] 5' np'-Na'-Y'Y'Y'- Na'-nq' 3' (Ia).

[0273] When the antisense strand is represented as formula (IIa), each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0274] Each of X′, Y′ and Z′ may be the same or different from each other.

[0275] Each nucleotide of the sense strand and antisense strand may be independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-C- allyl, 2'-hydroxyl, or 2'-fluoro. For example, each nucleotide of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. Each X, Y, Z, X′, Y′ and Z′, in particular, may represent a 2'-O-methyl modification or a 2'-fluoro modification.

[0276] In one embodiment, the sense strand of the RNAi agent may contain YYY motif occurring at 9, 10 and 11 positions of the strand when the duplex region is 21 nt, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end; and Y represents 2'-F modification. The sense strand may additionally contain XXX motif or ZZZ motifs as wing modifications at the opposite end of the duplex region; and XXX and ZZZ each independently represents a 2'-OMe modification or 2'-F modification.

[0277] In one embodiment the antisense strand may contain Y′Y′Y′ motif occurring at positions 11, 12, 13 of the strand, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end; and Y′ represents 2'-O-methyl modification. The antisense strand may additionally contain X′X′X′ motif or Z′Z′Z′ motifs as wing modifications at the opposite end of the duplex region; and X′X′X′ and Z′Z′Z′ each independently represents a 2'-OMe modification or 2'-F modification.

[0278] The sense strand represented by any one of the above formulas (Ia), (Ib), (Ic), and (Id) forms a duplex with a antisense strand being represented by any one of formulas (IIa), (IIb), (IIc), and (IId), respectively.

[0279] Accordingly, the RNAi agents for use in the methods of the disclosure may comprise a sense strand and an antisense strand, each strand having 14 to 30 nucleotides, the RNAi duplex represented by formula (III):

[0280] sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}\ Y\ Y\ Y\ \text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

[0281] antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$

(III)

[0282] wherein:

[0283] i, j, k, and l are each independently 0 or 1;

[0284] p, p′, q, and q′ are each independently 0-6;

[0285] each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

[0286] each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

[0287] wherein

[0288] each n_p', n_p, n_q', and n_q, each of which may or may not be present, independently represents an overhang nucleotide; and

[0289] XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides.

[0290] In one embodiment, i is 0 and j is 0; or i is 1 and j is 0; or i is 0 and j is 1; or both i and j are 0; or both i and j are 1. In another embodiment, k is 0 and l is 0; or k is 1 and l is 0; k is 0 and l is 1; or both k and l are 0; or both k and l are 1.

[0291] Exemplary combinations of the sense strand and antisense strand forming an RNAi duplex include the formulas below:

[0292] 5' n_p - N_a -Y Y Y -N_a-n_q 3'

[0293] 3' n_p'-N_a'-Y′Y′Y′ -N_a'n_q' 5'

(IIIa)

[0294] 5' n_p -N_a -Y Y Y -N_b -Z Z Z -N_a-n_q 3'

[0295] 3' n_p'-N_a'-Y′Y′Y′-N_b'-Z′Z′Z′-N_a'n_q' 5'

(IIIb)

[0296] 5' n_p-N_a- X X X -N_b -Y Y Y - N_a-n_q 3'

[0297] 3' n_p'-N_a'-X′X′X′-N_b'-Y′Y′Y′-N_a'-n_q' 5'

(IIIc)

[0298] 5' n_p -N_a -X X X -N_b-Y Y Y -N_b- Z Z Z -N_a-n_q 3'

[0299] 3' n_p'-N_a'-X′X′X′-N_b'-Y′Y′Y′-N_b'-Z′Z′Z′-N_a-n_q' 5'

(IIId)

[0300] When the RNAi agent is represented by formula (IIIa), each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0301] When the RNAi agent is represented by formula (IIIb), each N_b independently represents an oligonucleotide sequence comprising 1-10, 1-7, 1-5 or 1-4 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0302] When the RNAi agent is represented as formula (IIIc), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0303] When the RNAi agent is represented as formula (IIId), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a, N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of N_a, N_a', N_b and N_b' independently comprises modifications of alternating pattern.

[0304] In one embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications. In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications and n_p′ >0 and at least one n_p′ is linked to a neighboring nucleotide a *via* phosphorothioate linkage. In yet another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications

are 2′-O-methyl or 2′-fluoro modifications , n_p' >0 and at least one n_p' is linked to a neighboring nucleotide *via* phosphorothioate linkage, and the sense strand is conjugated to one or more C16 (or related) moieties attached through a bivalent or trivalent branched linker (described below). In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications , n_p' >0 and at least one n_p' is linked to a neighboring nucleotide *via* phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more lipophilic, *e.g.*, C16 (or related) moieties, optionally attached through a bivalent or trivalent branched linker.

[0305] In one embodiment, when the RNAi agent is represented by formula (IIIa), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications , n_p' >0 and at least one n_p' is linked to a neighboring nucleotide *via* phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more lipophilic, *e.g.*, C16 (or related) moieties attached through a bivalent or trivalent branched linker.

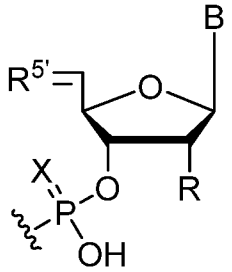
[0306] In one embodiment, the RNAi agent is a multimer containing at least two duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

[0307] In one embodiment, the RNAi agent is a multimer containing three, four, five, six or more duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

[0308] In one embodiment, two RNAi agents represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends and are optionally conjugated to to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

[0309] Various publications describe multimeric RNAi agents that can be used in the methods of the disclosure. Such publications include WO2007/091269, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520; and US 7858769, the entire contents of each of which are hereby incorporated herein by reference.

[0310] In certain embodiments, the compositions and methods of the disclosure include a vinyl phosphonate (VP) modification of an RNAi agent as described herein. In exemplary embodiments, a 5' vinyl phosphonate modified nucleotide of the disclosure has the structure:



wherein X is O or S;

[0311] R is hydrogen, hydroxy, fluoro, or C_{1-20}alkoxy (*e.g.*, methoxy or n-hexadecyloxy);

[0312] $R^{5'}$ is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and $R^{5'}$ is in the *E* or *Z* orientation (*e.g.*, *E* orientation); and

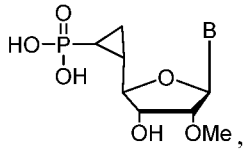
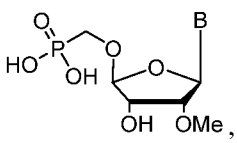
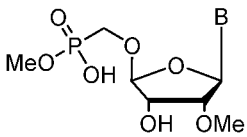
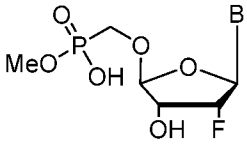
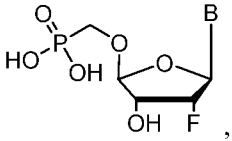
[0313] B is a nucleobase or a modified nucleobase, optionally where B is adenine, guanine, cytosine, thymine, or uracil.

[0314] In one embodiment, $R^{5'}$ is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and $R^{5'}$ is in the E orientation. In another embodiment, R is methoxy and $R^{5'}$ is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and $R^{5'}$ is in the E orientation. In another embodiment, X is S, R is methoxy, and $R^{5'}$ is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and $R^{5'}$ is in the E orientation.

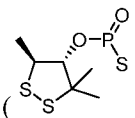
[0315] The 5'-end phosphorus-containing group also includes a 5'-phosphate prodrug or 5'-phosphonate prodrug.

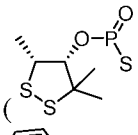
[0316] A vinyl phosphonate of the instant disclosure may be attached to either the antisense or the sense strand of a dsRNA of the disclosure. In certain embodiments, a vinyl phosphonate of the instant disclosure is attached to the antisense strand of a dsRNA, optionally at the 5' end of the antisense strand of the dsRNA.

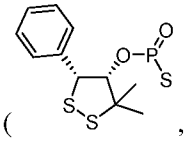
[0317] Vinyl phosphate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphate structure includes the preceding structure, where $R^{5'}$ is $=C(H)-OP(O)(OH)2$ and the double bond between the C5' carbon and $R^{5'}$ is in the E or Z orientation (*e.g.*, E orientation).

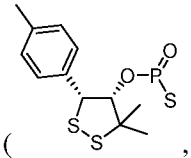
[0318] In other examples, the 5'-end phosphorus-containing group is  ,  ,  ,  , or  , or a salt (e.g., sodium salt) thereof, wherein B is an optionally modified nucleobase (e.g., U).

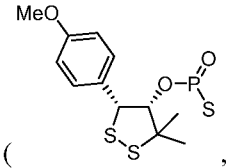
In other examples, the 5'-phosphate prodrug or 5'-phosphonate prodrug has a structure disclosed in WO2022/147214, which is incorporated herein by reference.

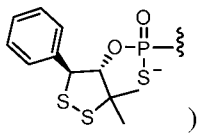
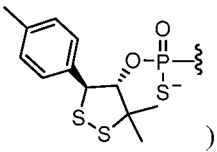
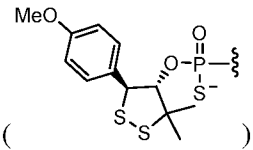
Pmmds ( , ((4SR,5SR)-3,3,5-trimethyl-1,2-dithiolan-4-ol) phosphodiester);

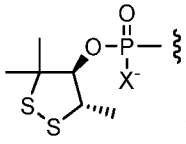
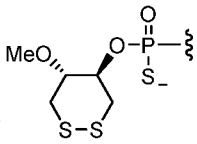
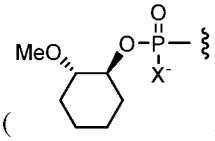
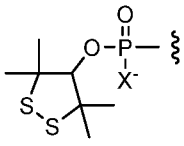
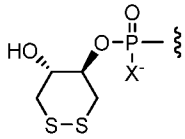
cPmmds ( , ((4SR,5RS)-3,3,5-trimethyl-1,2-dithiolan-4-ol) phosphodiester (Cis Pmmds));

PdAr1s ( , ((4SR,5RS)-5-phenyl-3,3-dimethyl-1,2-dithiolan-4-ol) phosphodiester);

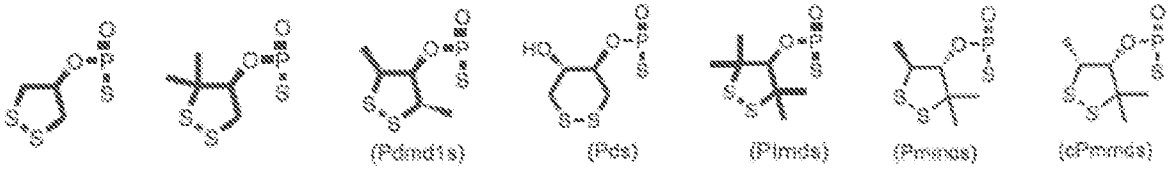
PdAr3s ( , ((4SR,5RS)-5-(4-methylphenyl)-3,3-dimethyl-1,2-dithiolan-4-ol) phosphodiester);

PdAr5s ( , ((4SR,5RS)-5-(4-methoxyphenyl)-3,3-dimethyl-1,2-dithiolan-4-ol) phosphodiester);

PdAr2s (); PdAr4s (); PdAr6s ();

Pmmd/Pmmds (); Pmds (); Cymd/Cymds ( , X is O/S); Ptmd/Ptmds ( , X is O/S), Pd/Pds ( , X is O/S),.

[0319] For instance, the activity of the siRNAs containing the following list of 5' modified phosphate prodrugs,



,

were generally comparable to the activity of siRNAs containing 5'-VP. The siRNAs containing the following list of 5' modified phosphate

prodrugs,

,

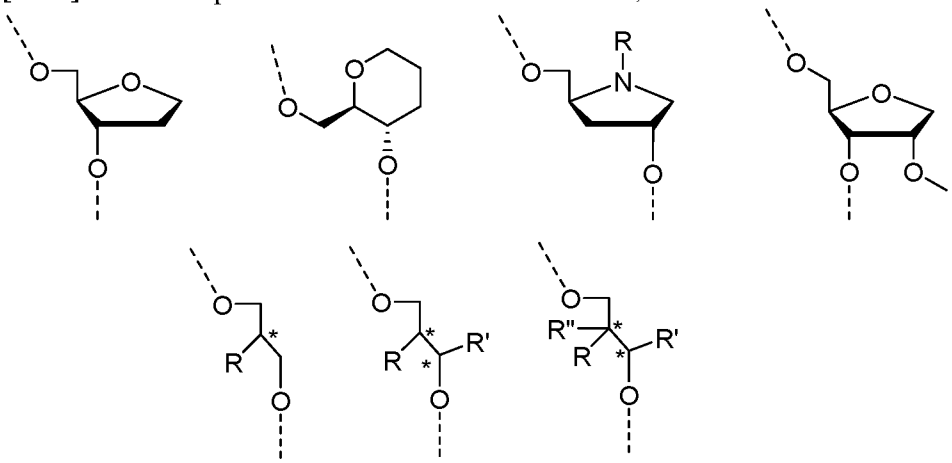
generally have an improved stability than that of siRNAs containing 5'-VP and have a better or comparable activity than that of siRNAs containing 5'-VP.

i. Thermally Destabilizing Modifications

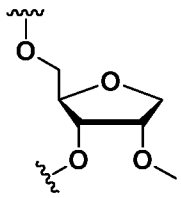
[0320] In certain embodiments, a dsRNA molecule can be optimized for RNA interference by incorporating thermally destabilizing modifications in the seed region of the antisense strand (*i.e.*, at positions 2-9 of the 5'-end of the antisense strand or at positions 2-8 of the 5'-end of the antisense strand) to reduce or inhibit off-target gene silencing. It has been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, the antisense strand comprises at least one (*e.g.*, one, two, three, four, five or more) thermally destabilizing modification of the duplex within the first 9 nucleotide positions of the 5' region of the antisense strand. In some embodiments, one or more thermally destabilizing modification(s) of the duplex is/are located in positions 2-9, or preferably positions 4-8, from the 5'-end of the antisense strand. In some further embodiments, the thermally destabilizing modification(s) of the duplex is/are located at position 6, 7 or 8 from the 5'-end of the antisense strand. In still some further embodiments, the thermally destabilizing modification of the duplex is located at position 7 from the 5'-end of the antisense strand. The term "thermally destabilizing modification(s)" includes modification(s) that would result with a dsRNA with a lower overall melting temperature (Tm) (preferably a Tm with one, two, three or four degrees lower than the Tm of the dsRNA without having such modification(s). In some embodiments, the thermally destabilizing modification of the duplex is located at position 2, 3, 4, 5 or 9 from the 5'-end of the antisense strand.

[0321] The thermally destabilizing modifications can include, but are not limited to, abasic modification; mismatch with the opposing nucleotide in the opposing strand; and sugar modification such as 2'-deoxy modification or acyclic nucleotide, *e.g.*, unlocked nucleic acids (UNA), glycol nucleic acid (GNA) and 2'-5'-linked ribonucleotides ("3'-RNA").

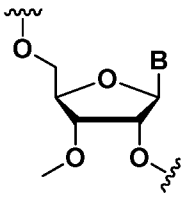
[0322] Exemplified abasic modifications include, but are not limited to the following:



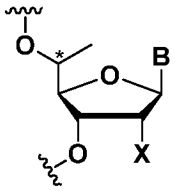
[0323] Wherein R = H, Me, Et or OMe; R' = H, Me, Et or OMe; R" = H, Me, Et or OMe



Mod2
(2'-OMe Abasic Spacer)

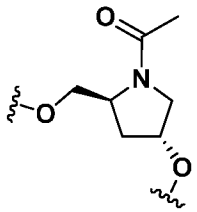


Mod3
(3'-OMe)

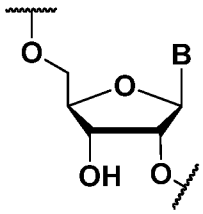


Mod4
(5'-Me)

X = OMe, F



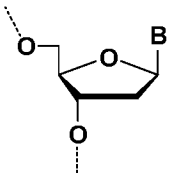
Mod5
(Hyp-spacer)



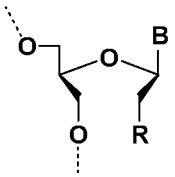
(3'-RNA)

wherein B is a modified or unmodified nucleobase.

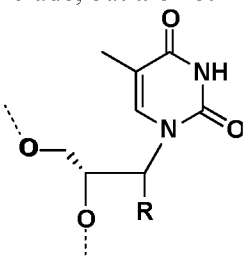
[0324] Exemplified sugar modifications include, but are not limited to the following:



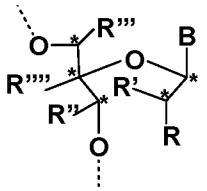
2'-deoxy

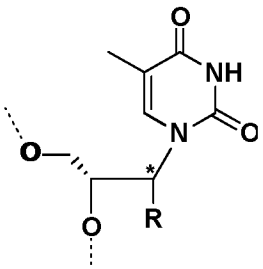


unlocked nucleic acid
R = H, OH, O-alkyl



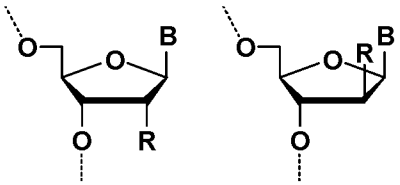
Glycol nucleic acid
R = H, OH, O-alkyl





Glycol nucleic acid
R = H, OH, O-alkyl

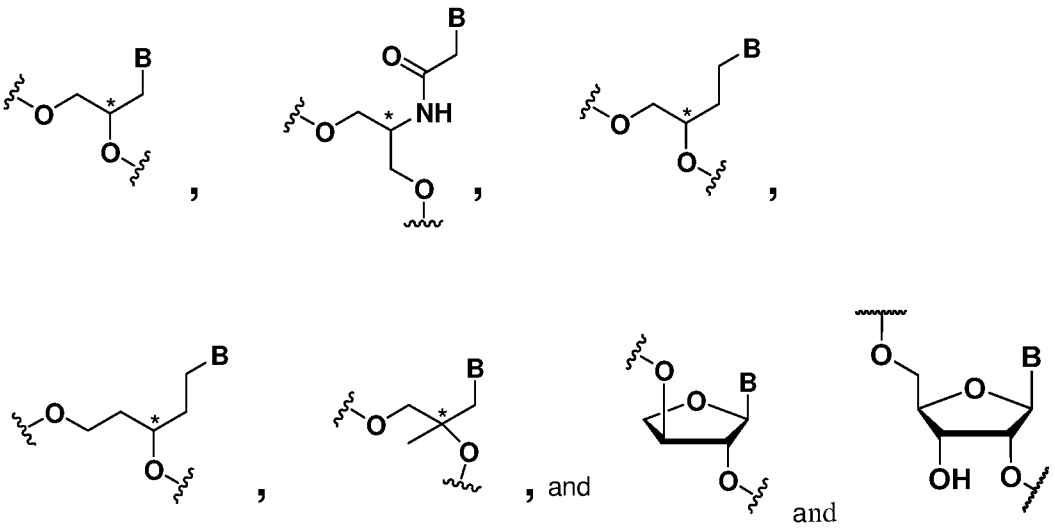
unlocked nucleic acid
R = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R" = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R"' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R"" = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2



R = H, methyl, ethyl

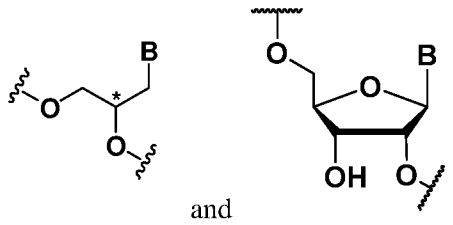
wherein B is a modified or unmodified nucleobase.

[0325] In some embodiments the thermally destabilizing modification of the duplex is selected from the group consisting of:



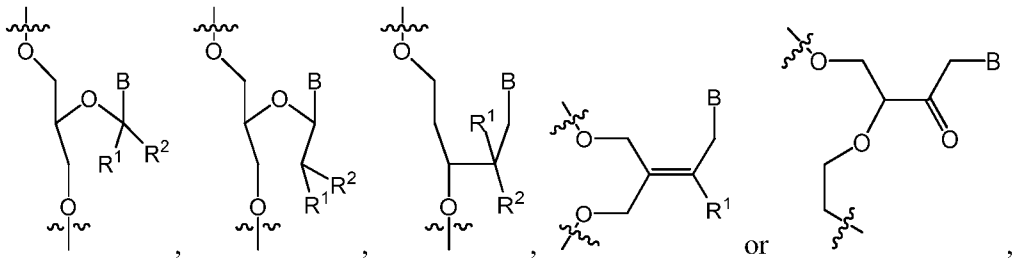
wherein B is a modified or unmodified nucleobase and the asterisk on each structure represents either *R*, *S* or *racemic*.

[0326] In some embodiments the thermally destabilizing modification of the duplex is selected from the group consisting of:



wherein B is a modified or unmodified nucleobase and the asterisk represents either R, S or racemic (*e.g.* S).

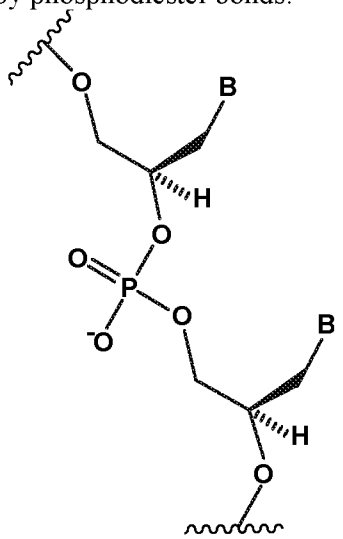
[0327] The term "acyclic nucleotide" refers to any nucleotide having an acyclic ribose sugar, for example, where any of bonds between the ribose carbons (*e.g.*, C1'-C2', C2'-C3', C3'-C4', C4'-O4', or C1'-O4') is absent or at least one of ribose carbons or oxygen (*e.g.*, C1', C2', C3', C4' or O4') are independently or in combination absent from the nucleotide. In some embodiments, acyclic nucleotide is



wherein B is a modified or unmodified nucleobase, R^1 and R^2 independently are H, halogen, OR_3, or alkyl; and R_3 is H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar). The term "UNA" refers to unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomers with bonds between C1'-C4' being removed (*i.e.* the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (*i.e.* the covalent carbon-carbon bond between the C2'

and C3' carbons) of the sugar is removed (see Mikhailov et. al., Tetrahedron Letters, 26 (17): 2059 (1985); and Fluiter *et al.*, Mol. Biosyst., 10: 1039 (2009), which are hereby incorporated by reference in their entirety). The acyclic derivative provides greater backbone flexibility without affecting the Watson-Crick pairings. The acyclic nucleotide can be linked *via* 2'-5' or 3'-5' linkage.

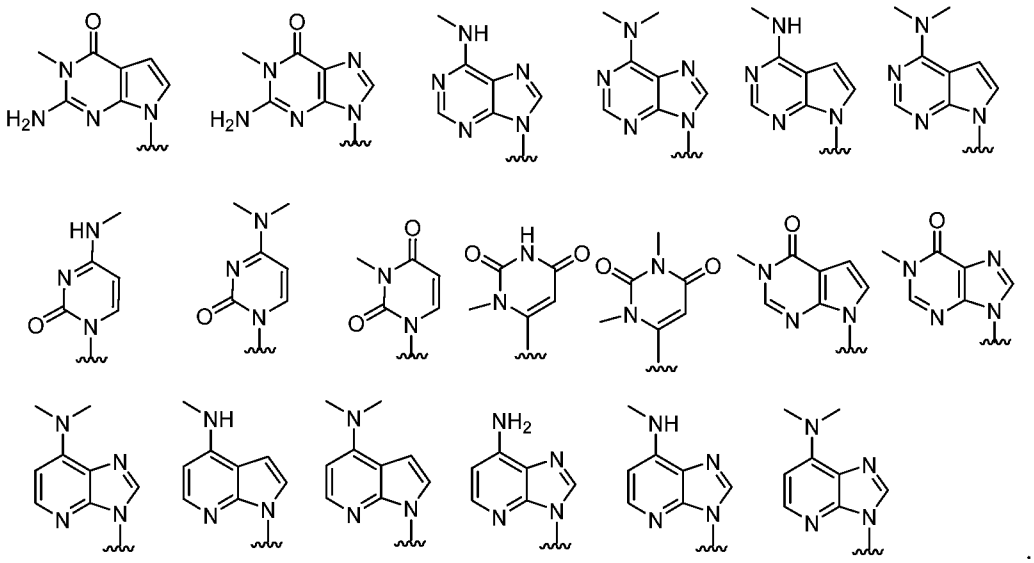
[0328] The term 'GNA' refers to glycol nucleic acid which is a polymer similar to DNA or RNA but differing in the composition of its "backbone" in that is composed of repeating glycerol units linked by phosphodiester bonds:



(R)-GNA

[0329] The thermally destabilizing modification of the duplex can be mismatches (*i.e.*, noncomplementary base pairs) between the thermally destabilizing nucleotide and the opposing nucleotide in the opposite strand within the dsRNA duplex. Exemplary mismatch base pairs include G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, U:U, T:T, U:T, or a combination thereof. Other mismatch base pairings known in the art are also amenable to the present invention. A mismatch can occur between nucleotides that are either naturally occurring nucleotides or modified nucleotides, *i.e.*, the mismatch base pairing can occur between the nucleobases from respective nucleotides independent of the modifications on the ribose sugars of the nucleotides. In certain embodiments, the dsRNA molecule contains at least one nucleobase in the mismatch pairing that is a 2'-deoxy nucleobase; *e.g.*, the 2'-deoxy nucleobase is in the sense strand.

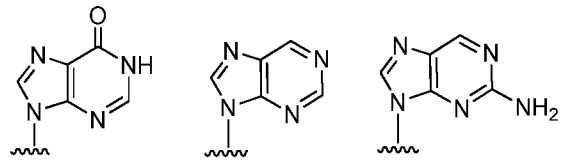
[0330] In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes nucleotides with impaired W-C H-bonding to complementary base on the target mRNA, such as:



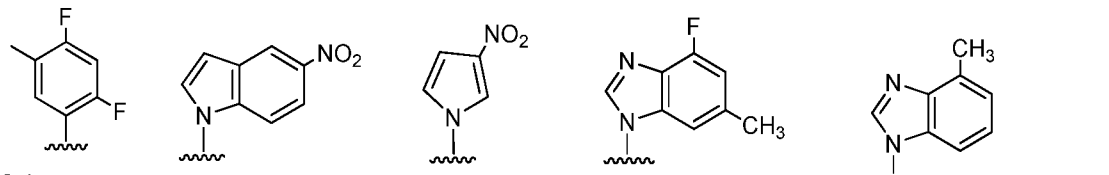
[0331] More examples of abasic nucleotide, acyclic nucleotide modifications (including UNA and GNA), and mismatch modifications have been described in detail in WO 2011/133876, which is herein incorporated by reference in its entirety.

The thermally destabilizing modifications may also include universal base with reduced or abolished capability to form hydrogen bonds with the opposing bases, and phosphate modifications.

[0332] In some embodiments, the thermally destabilizing modification of the duplex includes nucleotides with non-canonical bases such as, but not limited to, nucleobase modifications with impaired or completely abolished capability to form hydrogen bonds with bases in the opposite strand. These nucleobase modifications have been evaluated for destabilization of the central region of the dsRNA duplex as described in WO 2010/0011895, which is herein incorporated by reference in its entirety. Exemplary nucleobase modifications are:

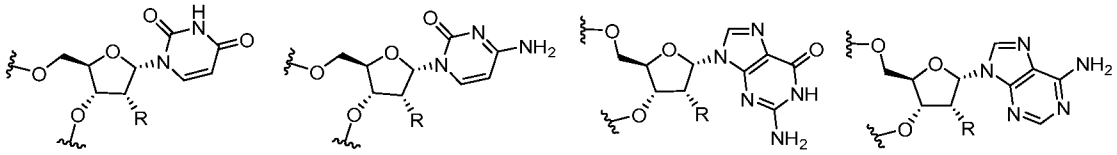


inosine nebularine 2-aminopurine



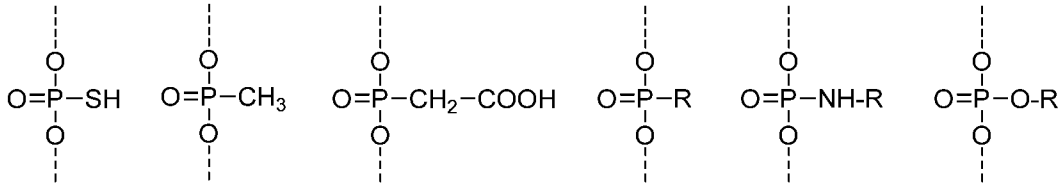
2,4-difluorotoluene 5-nitroindole 3-nitropyrrole 4-Fluoro-6-methylbenzimidazole 4-Methylbenzimidazole

[0333] In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes one or more α-nucleotide complementary to the base on the target mRNA, such as:



wherein R is H, OH, OCH_3, F, NH_2, NHMe, NMe_2 or O-alkyl.

[0334] Exemplary phosphate modifications known to decrease the thermal stability of dsRNA duplexes compared to natural phosphodiester linkages are:



[0335] The alkyl for the R group can be a C_1-C_6alkyl. Specific alkyls for the R group include, but are not limited to methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl.

As the skilled artisan will recognize, in view of the functional role of nucleobases is defining specificity of an RNAi agent of the disclosure, while nucleobase modifications can be performed in the various manners as described herein, *e.g.*, to introduce destabilizing modifications into an RNAi agent of the disclosure, *e.g.*, for purpose of enhancing on-target effect relative to off-target effect, the range of modifications available and, in general, present upon RNAi agents of the disclosure tends to be much greater for non-nucleobase modifications, *e.g.*, modifications to sugar groups or phosphate backbones of polyribonucleotides. Such modifications are described in greater detail in other sections of the instant disclosure and are expressly contemplated for RNAi agents of the disclosure, either possessing native nucleobases or modified nucleobases as described above or elsewhere herein.

[0336] In addition to the antisense strand comprising a thermally destabilizing modification, the dsRNA can also comprise one or more stabilizing modifications. For example, the dsRNA can comprise at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, the stabilizing modifications all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two stabilizing modifications. The stabilizing modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the stabilizing modification can occur on every nucleotide on the sense strand or antisense strand; each stabilizing modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both stabilizing modification in an alternating pattern. The alternating pattern of the stabilizing modifications on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the stabilizing modifications on the sense strand can have a shift relative to the alternating pattern of the stabilizing modifications on the antisense strand.

[0337] In some embodiments, the antisense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, a stabilizing modification in the antisense strand can be present at any positions. In some embodiments, the antisense comprises stabilizing modifications at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In

some other embodiments, the antisense comprises stabilizing modifications at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense comprises stabilizing modifications at positions 2, 14, and 16 from the 5'-end.

[0338] In some embodiments, the antisense strand comprises at least one stabilizing modification adjacent to the destabilizing modification. For example, the stabilizing modification can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand comprises a stabilizing modification at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*, positions -1 and +1 from the position of the destabilizing modification.

[0339] In some embodiments, the antisense strand comprises at least two stabilizing modifications at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

[0340] In some embodiments, the sense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, a stabilizing modification in the sense strand can be present at any positions. In some embodiments, the sense strand comprises stabilizing modifications at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises stabilizing modifications at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises stabilizing modifications at positions opposite or complimentary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises stabilizing modifications at positions opposite or complimentary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three, or four stabilizing modifications.

[0341] In some embodiments, the sense strand does not comprise a stabilizing modification in position opposite or complimentary to the thermally destabilizing modification of the duplex in the antisense strand.

[0342] Exemplary thermally stabilizing modifications include, but are not limited to, 2'-fluoro modifications. Other thermally stabilizing modifications include, but are not limited to, LNA.

[0343] In some embodiments, the dsRNA of the disclosure comprises at least four (*e.g.*, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, the 2'-fluoro nucleotides all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two 2'-fluoro nucleotides. The 2'-fluoro modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the 2'-fluoro modification can occur on every nucleotide on the sense strand or antisense strand; each 2'-fluoro modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both 2'-fluoro modifications in an alternating pattern. The alternating pattern of the 2'-fluoro modifications on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the 2'-fluoro modifications on the sense strand can have a shift relative to the alternating pattern of the 2'-fluoro modifications on the antisense strand.

[0344] In some embodiments, the antisense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the antisense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 14, and 16 from the 5'-end.

[0345] In some embodiments, the antisense strand comprises at least one 2'-fluoro nucleotide adjacent to the destabilizing modification. For example, the 2'-fluoro nucleotide can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand comprises a 2'-fluoro nucleotide at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*, positions -1 and +1 from the position of the destabilizing modification.

[0346] In some embodiments, the antisense strand comprises at least two 2'-fluoro nucleotides at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

[0347] In some embodiments, the sense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the sense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complimentary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complimentary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three or four 2'-fluoro nucleotides.

[0348] In some embodiments, the sense strand does not comprise a 2'-fluoro nucleotide in position opposite or complimentary to the thermally destabilizing modification of the duplex in the antisense strand.

[0349] In some embodiments, the dsRNA molecule of the disclosure comprises a 21 nucleotides (nt) sense strand and a 23 nucleotides (nt) antisense, wherein the antisense strand contains at least one thermally destabilizing nucleotide, where the at least one thermally destabilizing nucleotide occurs in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand or at positions 2-8 of the 5'-end of the antisense strand), wherein one end of the dsRNA is blunt, while the other end is comprises a 2 nt overhang, and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the

sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA comprises a blunt end at 5'-end of the antisense strand. Preferably, the 2 nt overhang is at the 3'-end of the antisense.

[0350] In some embodiments, the dsRNA molecule of the disclosure comprise a sense and antisense strands, wherein: the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1), positions 1 to 23 of said sense strand comprise at least 8 ribonucleotides; antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least the 3 ' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when said double stranded nucleic acid is introduced into a mammalian cell; and wherein the antisense strand contains at least one thermally destabilizing nucleotide, where at least one thermally destabilizing nucleotide is in the seed region of the antisense strand (*i.e.* at position 2-9 of the 5'-end of the antisense strand or at positions 2-8 of the 5'-end of the antisense strand). For example, the thermally destabilizing nucleotide occurs between positions opposite or complimentary to positions 14-17 of the 5'-end of the sense strand, and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5, or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4, or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; and (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA comprises a duplex region of 12-30 nucleotide pairs in length.

[0351] In some embodiments, the dsRNA molecule of the disclosure comprises a sense and antisense strands, wherein said dsRNA molecule comprises a sense strand having a length which is at least 25 and at most 29 nucleotides and an antisense strand having a length which is at most 30 nucleotides with the sense strand comprises a modified nucleotide that is susceptible to enzymatic degradation at position 11 from the 5'end, wherein the 3' end of said sense strand and the 5' end of said antisense strand form a blunt end and said antisense strand is 1-4 nucleotides longer at its 3' end than the sense strand, wherein the duplex region which is at least 25 nucleotides in length, and said antisense strand is sufficiently complementary to a target mRNA along at least 19 nt of said antisense

strand length to reduce target gene expression when said dsRNA molecule is introduced into a mammalian cell, and wherein dicer cleavage of said dsRNA preferentially results in an siRNA comprising said 3' end of said antisense strand, thereby reducing expression of the target gene in the mammal, wherein the antisense strand contains at least one thermally destabilizing nucleotide, where the at least one thermally destabilizing nucleotide is in the seed region of the antisense strand (*i.e.* at position 2-9 of the 5'-end of the antisense strand or at positions 2-8 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5, or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4, or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; and (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA has a duplex region of 12-29 nucleotide pairs in length.

[0352] In some embodiments, every nucleotide in the sense strand and antisense strand of the dsRNA molecule may be modified. Each nucleotide may be modified with the same or different modification which can include one or more alteration of one or both of the non-linking phosphate oxygens or of one or more of the linking phosphate oxygens; alteration of a constituent of the ribose sugar, *e.g.*, of the 2′ hydroxyl on the ribose sugar; wholesale replacement of the phosphate moiety with "dephospho" linkers; modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

[0353] As nucleic acids are polymers of subunits, many of the modifications occur at a position which is repeated within a nucleic acid, *e.g.*, a modification of a base, or a phosphate moiety, or a non-linking O of a phosphate moiety. In some cases, the modification will occur at all of the subject positions in the nucleic acid but in many cases it will not. By way of example, a modification may only occur at a 3' or 5' terminal position, may only occur in a terminal region, *e.g.,* at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand. A modification may occur in a double strand region, a single strand region, or in both. A modification may occur only in the double strand region of an RNA or may only occur in a single strand region of an RNA. *E.g.*, a phosphorothioate modification at a non-linking O position may only occur at one or both termini, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand, or may occur in double strand and single strand regions, particularly at termini. The 5' end or ends can be phosphorylated.

[0354] It may be possible, *e.g.*, to enhance stability, to include particular bases in overhangs, or to include modified nucleotides or nucleotide surrogates, in single strand overhangs, *e.g.*, in a 5' or 3' overhang, or in both. *E.g.*, it can be desirable to include purine nucleotides in overhangs. In some embodiments all or some of the bases in a 3' or 5' overhang may be modified, *e.g.*, with a modification described herein. Modifications can include, *e.g.*, the use of modifications at the 2' position of the ribose sugar with modifications that are known in the art, *e.g.*, the use of deoxyribonucleotides, 2'-deoxy-2'-fluoro (2'-F) or 2'-O-methyl modified instead of the ribosugar of

the nucleobase, and modifications in the phosphate group, *e.g.*, phosphorothioate modifications. Overhangs need not be homologous with the target sequence.

[0355] In some embodiments, each residue of the sense strand and antisense strand is independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-allyl, 2'-C-allyl, 2'-deoxy, or 2'-fluoro. The strands can contain more than one modification. In some embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. It is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

[0356] At least two different modifications are typically present on the sense strand and antisense strand. Those two modifications may be the 2'-deoxy, 2'- O-methyl or 2'-fluoro modifications, acyclic nucleotides or others. In some embodiments, the sense strand and antisense strand each comprises two differently modified nucleotides selected from 2'-O-methyl or 2'-deoxy. In some embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl nucleotide, 2'-deoxy nucleotide, 2´-deoxy-2'-fluoro nucleotide, 2'-O-N-methylacetamido (2'-O-NMA) nucleotide, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleotide, 2'-O-aminopropyl (2'-O-AP) nucleotide, or 2'-ara-F nucleotide. Again, it is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

[0357] In some embodiments, the dsRNA molecule of the disclosure comprises modifications of an alternating pattern, particular in the B1, B2, B3, B1', B2', B3', B4' regions. The term "alternating motif" or "alternative pattern" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar pattern. For example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be "ABABABABABAB…," "AABBAABBAABB…," "AABAABAABAAB…," "AAABAAABAAAB…," "AAABBBAAABBB…," or "ABCABCABCABC…," etc.

[0358] The type of modifications contained in the alternating motif may be the same or different. For example, if A, B, C, D each represent one type of modification on the nucleotide, the alternating pattern, *i.e.*, modifications on every other nucleotide, may be the same, but each of the sense strand or antisense strand can be selected from several possibilities of modifications within the alternating motif such as "ABABAB…", "ACACAC…" "BDBDBD…" or "CDCDCD…," etc.

[0359] In some embodiments, the dsRNA molecule of the disclosure comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the antisense strand and vice versa. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with "ABABAB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 3'-5'of the strand within the duplex region. As another example, the alternating motif in the sense strand may

start with "AABBAABB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BBAABBAA" from 3'-5'of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

[0360] In one particular example, the alternating motif in the sense strand is "ABABAB" sfrom 5'-3' of the strand, where each A is an unmodified ribonucleotide and each B is a 2'-Omethyl modified nucleotide.

[0361] In one particular example, the alternating motif in the sense strand is "ABABAB" sfrom 5'-3' of the strand, where each A is an 2'-deoxy-2'-fluoro modified nucleotide and each B is a 2'-Omethyl modified nucleotide.

[0362] In another particular example, the alternating motif in the antisense strand is "BABABA" from 3'-5'of the strand, where each A is a 2'-deoxy-2'-fluoro modified nucleotide and each B is a 2'-Omethyl modified nucleotide.

[0363] In one particular example, the alternating motif in the sense strand is "ABABAB" sfrom 5'-3' of the strand and the alternating motif in the antisense strand is "BABABA" from 3'-5'of the strand, where each A is an unmodified ribonucleotide and each B is a 2'-Omethyl modified nucleotide.

[0364] In one particular example, the alternating motif in the sense strand is "ABABAB" sfrom 5'-3' of the strand and the alternating motif in the antisense strand is "BABABA" from 3'-5'of the strand, where each A is a 2'-deoxy-2'-fluoro modified nucleotide and each B is a 2'-Omethyl modified nucleotide.

[0365] The dsRNA molecule of the disclosure may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand or antisense strand or both in any position of the strand. For instance, the internucleotide linkage modification may occur on every nucleotide on the sense strand or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand.

[0366] In some embodiments, the dsRNA molecule comprises the phosphorothioate or methylphosphonate internucleotide linkage modification in the overhang region. For example, the overhang region comprises two nucleotides having a phosphorothioate or methylphosphonate internucleotide linkage between the two nucleotides. Internucleotide linkage modifications also may be made to link the overhang nucleotides with the terminal paired nucleotides within duplex region. For example, at least 2, 3, 4, or all the overhang nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage, and optionally, there may be additional

phosphorothioate or methylphosphonate internucleotide linkages linking the overhang nucleotide with a paired nucleotide that is next to the overhang nucleotide. For instance, there may be at least two phosphorothioate internucleotide linkages between the terminal three nucleotides, in which two of the three nucleotides are overhang nucleotides, and the third is a paired nucleotide next to the overhang nucleotide. Preferably, these terminal three nucleotides may be at the 3'-end of the antisense strand.

[0367] In some embodiments, the sense strand of the dsRNA molecule comprises 1-10 blocks of two to ten phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said sense strand is paired with an antisense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

[0368] In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

[0369] In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of three phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

[0370] In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of four phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

[0371] In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of five phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of

phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

[0372] In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of six phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

[0373] In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of seven phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, or 8 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

[0374] In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of eight phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, or 6 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

[0375] In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of nine phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, or 4 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

[0376] In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within 1-10 of the termini position(s) of the sense or antisense strand. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage at one end or both ends of the sense or antisense strand.

[0377] In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within 1-10 of the internal region of the duplex of each of the sense or antisense strand. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate methylphosphonate

internucleotide linkage at position 8-16 of the duplex region counting from the 5'-end of the sense strand; the dsRNA molecule can optionally further comprise one or more phosphorothioate or methylphosphonate internucleotide linkage modification within 1-10 of the termini position(s).

[0378] In some embodiments, the dsRNA molecule of the disclosure further comprises one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within position 1-5 and one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within position 18-23 of the sense strand (counting from the 5'-end), and one to five phosphorothioate or methylphosphonate internucleotide linkage modification at positions 1 and 2 and one to five within positions 18-23 of the antisense strand (counting from the 5'-end).

[0379] In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate or methylphosphonate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate or methylphosphonate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

[0380] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

[0381] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

[0382] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

[0383] In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

[0384] In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modification at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

[0385] In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 (counting from the 5'-end) of the sense strand, and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

[0386] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 (counting from the 5'-end) of the sense strand, and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

[0387] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

[0388] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

[0389] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

[0390] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 20 and 21 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one at position 21 of the antisense strand (counting from the 5'-end).

[0391] In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate

internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 20 and 21 of the antisense strand (counting from the 5'-end).

[0392] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 21 and 22 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

[0393] In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 21 and 22 of the antisense strand (counting from the 5'-end).

[0394] In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 22 and 23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

[0395] In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 23 and 23 of the antisense strand (counting from the 5'-end).

[0396] In some embodiments, compound of the disclosure comprises a pattern of backbone chiral centers. In some embodiments, a common pattern of backbone chiral centers comprises at least 5 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 6 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 7 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 8 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 9 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 11 internucleotidic linkages in the Sp configuration. In

some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 15 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 16 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 17 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 18 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 19 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 7 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 5 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages which are not chiral (as a non-limiting example, a phosphodiester). In some embodiments, a common pattern of backbone chiral centers comprises no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration, and no more than 8 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 11

internucleotidic linkages in the Sp configuration, and no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration, and no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 15 internucleotidic linkages in the Sp configuration, and no more than 4 internucleotidic linkages which are not chiral. In some embodiments, the internucleotidic linkages in the Sp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages in the Rp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages which are not chiral are optionally contiguous or not contiguous.

[0397] In some embodiments, compound of the disclosure comprises a block is a stereochemistry block. In some embodiments, a block is an Rp block in that each internucleotidic linkage of the block is Rp. In some embodiments, a 5'-block is an Rp block. In some embodiments, a 3'-block is an Rp block. In some embodiments, a block is an Sp block in that each internucleotidic linkage of the block is Sp. In some embodiments, a 5'-block is an Sp block. In some embodiments, a 3'-block is an Sp block. In some embodiments, provided oligonucleotides comprise both Rp and Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Rp but no Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Sp but no Rp blocks. In some embodiments, provided oligonucleotides comprise one or more PO blocks wherein each internucleotidic linkage in a natural phosphate linkage.

[0398] In some embodiments, compound of the disclosure comprises a 5'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block comprises 4 or more nucleoside units. In some embodiments, a 5'-block comprises 5 or more nucleoside units. In some embodiments, a 5'-block comprises 6 or more nucleoside units. In some embodiments, a 5'-block comprises 7 or more nucleoside units. In some embodiments, a 3'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block comprises 4 or more nucleoside units. In some embodiments, a 3'-block

comprises 5 or more nucleoside units. In some embodiments, a 3'-block comprises 6 or more nucleoside units. In some embodiments, a 3'-block comprises 7 or more nucleoside units.

[0399] In some embodiments, compound of the disclosure comprises a type of nucleoside in a region or an oligonucleotide is followed by a specific type of internucleotidic linkage, *e.g.*, natural phosphate linkage, modified internucleotidic linkage, Rp chiral internucleotidic linkage, Sp chiral internucleotidic linkage, etc. In some embodiments, A is followed by Sp. In some embodiments, A is followed by Rp. In some embodiments, A is followed by natural phosphate linkage (PO). In some embodiments, U is followed by Sp. In some embodiments, U is followed by Rp. In some embodiments, U is followed by natural phosphate linkage (PO). In some embodiments, C is followed by Sp. In some embodiments, C is followed by Rp. In some embodiments, C is followed by natural phosphate linkage (PO). In some embodiments, G is followed by Sp. In some embodiments, G is followed by Rp. In some embodiments, G is followed by natural phosphate linkage (PO). In some embodiments, C and U are followed by Sp. In some embodiments, C and U are followed by Rp. In some embodiments, C and U are followed by natural phosphate linkage (PO). In some embodiments, A and G are followed by Sp. In some embodiments, A and G are followed by Rp.

[0400] In some embodiments, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand or at positions 2-8 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the antisense comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

[0401] In some embodiments, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand or at positions 2-8 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the sense strand is conjugated with a ligand; (iii) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (iv) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (v) the dsRNA comprises at least four 2'-fluoro modifications; (vi) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in

length; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

[0402] In some embodiments, the sense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand or at positions 2-8 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (v) the sense strand comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

[0403] In some embodiments, the sense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand or at positions 2-8 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the sense strand is conjugated with a ligand; (iii) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (iv) the sense strand comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (v) the dsRNA comprises at least four 2'-fluoro modifications; (vi) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (vii) the dsRNA has a blunt end at 5'-end of the antisense strand.

[0404] In some embodiments, the dsRNA molecule of the disclosure comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch can occur in the overhang region or the duplex region. The base pair can be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

[0405] In some embodiments, the dsRNA molecule of the disclosure comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'- end of the antisense strand

can be chosen independently from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

[0406] In some embodiments, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2 or 3 base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair.

[0407] It was found that introducing 4'-modified or 5'-modified nucleotide to the 3'-end of a phosphodiester (PO), phosphorothioate (PS), or phosphorodithioate (PS2) linkage of a dinucleotide at any position of single stranded or double stranded oligonucleotide can exert steric effect to the internucleotide linkage and, hence, protecting or stabilizing it against nucleases.

[0408] In some embodiments, 5'-modified nucleoside is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 5'-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The alkyl group at the 5' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleoside is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

[0409] In some embodiments, 4'-modified nucleoside is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 4'-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The alkyl group at the 4' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleoside is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer. Alternatively, a 4'-*O*-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The 4'-*O*-alkyl of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleoside is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

[0410] In some embodiments, 5'-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleoside is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

[0411] In some embodiments, 4'-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 4'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleoside is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer.

[0412] In some embodiments, 4'-*O*-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleoside is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

[0413] In some embodiments, the dsRNA molecule of the disclosure can comprise 2'-5' linkages (with 2'-H, 2'-OH and 2'-OMe and with P=O or P=S). For example, the 2'-5' linkages modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

[0414] In another embodiment, the dsRNA molecule of the disclosure can comprise L sugars (*e.g.*, L ribose, L-arabinose with 2'-H, 2'-OH and 2'-OMe). For example, these L sugars modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

[0415] Various publications describe multimeric siRNA which can all be used with the dsRNA of the disclosure. Such publications include WO2007/091269, US 7858769, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520 which are hereby incorporated by their entirely.

[0416] As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to an RNAi agent can optimize one or more properties of the RNAi agent. In many cases, the carbohydrate moiety will be attached to a modified subunit of the RNAi agent. For example, the ribose sugar of one or more ribonucleotide subunits of a dsRNA agent can be replaced with another moiety, *e.g.*, a non-carbohydrate (preferably cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). A cyclic carrier may be a carbocyclic ring system, *i.e.*, all ring atoms are carbon atoms, or a heterocyclic ring system, *i.e.*, one or more ring atoms may be a heteroatom, *e.g.*, nitrogen, oxygen, sulfur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, *e.g.* fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

[0417] The ligand may be attached to the polynucleotide *via* a carrier. The carriers include (i) at least one "backbone attachment point," preferably two "backbone attachment points" and (ii) at least one "tethering attachment point." A "backbone attachment point" as used herein refers to a functional group, *e.g.* a hydroxyl group, or generally, a bond available for, and that is suitable for incorporation of the carrier into the backbone, *e.g.*, the phosphate, or modified phosphate, *e.g.*, sulfur containing, backbone, of a ribonucleic acid. A "tethering attachment point" (TAP) in some embodiments refers to a constituent ring atom of the cyclic carrier, *e.g.*, a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a selected moiety. The moiety can be, *e.g.*, a carbohydrate, *e.g.* monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide and polysaccharide. Optionally, the selected moiety is connected by an intervening tether to the cyclic

carrier. Thus, the cyclic carrier will often include a functional group, *e.g.*, an amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, *e.g.*, a ligand to the constituent ring.

[0418] The RNAi agents may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group; preferably, the cyclic group is selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and and decalin; preferably, the acyclic group is selected from serinol backbone or diethanolamine backbone.

[0419] In certain specific embodiments, the RNAi agent for use in the methods of the disclosure is an agent selected from the group of agents listed in any one of Tables 2-5. These agents may further comprise a ligand.

IV. iRNAs Conjugated to Ligands

[0420] Another modification of the RNA of an iRNA of the invention involves chemically linking to the iRNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the iRNA, *e.g.*, into a cell. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger *et al.*, *Proc. Natl. Acid. Sci. USA*, 1989, 86: 6553-6556), cholic acid (Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1994, 4:1053-1060), a thioether, *e.g.*, beryl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306-309; Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1993, 3:2765-2770), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533-538), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J*, 1991, 10:1111-1118; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327-330; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49-54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14:969-973), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229-237), or an octadecylamine or hexylamino-carbonyloxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277:923-937).

[0421] In certain embodiments, a ligand alters the distribution, targeting or lifetime of an iRNA agent into which it is incorporated. In some embodiments, a ligand provides an enhanced affinity for a selected target, *e.g.*, molecule, cell or cell type, compartment, *e.g.*, a cellular or organ compartment, tissue, organ or region of the body, as, *e.g.*, compared to a species absent such a ligand. Typical ligands will not take part in duplex pairing in a duplexed nucleic acid.

[0422] Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic polyamino acid.

Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an α helical peptide.

[0423] Ligands can also include targeting groups, *e.g.*, a cell or tissue targeting agent, *e.g.*, a lectin, glycoprotein, lipid or protein, *e.g.*, an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, or an RGD peptide or RGD peptide mimetic. In certain embodiments, the ligand is a multivalent galactose, *e.g.*, an N-acetyl-galactosamine.

[0424] Other examples of ligands include dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), lipophilic molecules, *e.g.*, cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid,O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine)and peptide conjugates (*e.g.*, antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), MPEG, $[MPEG]_2$, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic acid), synthetic ribonucleases (*e.g.*, imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu3+ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

[0425] Ligands can be proteins, *e.g.*, glycoproteins, or peptides, *e.g.*, molecules having a specific affinity for a co-ligand, or antibodies *e.g.*, an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell. Ligands may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF-κB.

[0426] The ligand can be a substance, *e.g.*, a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, or intermediate filaments. The drug can be, for example, taxon,

vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

[0427] In some embodiments, a ligand attached to an iRNA as described herein acts as a pharmacokinetic modulator (PK modulator). PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, PEG, vitamins *etc*. Exemplary PK modulators include, but are not limited to, cholesterol, fatty acids, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, phospholipids, sphingolipids, naproxen, ibuprofen, vitamin E, biotin *etc*. Oligonucleotides that comprise a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, *e.g.*, oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone are also amenable to the present invention as ligands (*e.g.* as PK modulating ligands). In addition, aptamers that bind serum components (*e.g.* serum proteins) are also suitable for use as PK modulating ligands in the embodiments described herein.

[0428] Ligand-conjugated iRNAs of the invention may be synthesized by the use of an oligonucleotide that bears a pendant reactive functionality, such as that derived from the attachment of a linking molecule onto the oligonucleotide (described below). This reactive oligonucleotide may be reacted directly with commercially-available ligands, ligands that are synthesized bearing any of a variety of protecting groups, or ligands that have a linking moiety attached thereto.

[0429] The oligonucleotides used in the conjugates of the present invention may be conveniently and routinely made through the well-known technique of solid-phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems® (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is also known to use similar techniques to prepare other oligonucleotides, such as the phosphorothioates and alkylated derivatives.

[0430] In the ligand-conjugated oligonucleotides and ligand-molecule bearing sequence-specific linked nucleosides of the present invention, the oligonucleotides and oligonucleosides may be assembled on a suitable DNA synthesizer utilizing standard nucleotide or nucleoside precursors, or nucleotide or nucleoside conjugate precursors that already bear the linking moiety, ligand-nucleotide or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

[0431] When using nucleotide-conjugate precursors that already bear a linking moiety, the synthesis of the sequence-specific linked nucleosides is typically completed, and the ligand molecule is then reacted with the linking moiety to form the ligand-conjugated oligonucleotide. In some embodiments, the oligonucleotides or linked nucleosides of the present invention are synthesized by an automated synthesizer using phosphoramidites derived from ligand-nucleoside conjugates in addition to the standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

A. Lipid Conjugates

[0432] In certain embodiments, the ligand or conjugate is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule can typically bind a serum protein, such as human serum albumin (HSA). An HSA binding ligand allows for distribution of the conjugate to a target tissue, *e.g.*, a non-kidney target tissue of the body. For example, the target tissue can be the liver, including parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, naproxen or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, or (c) can be used to adjust binding to a serum protein, *e.g.*, HSA.

[0433] A lipid-based ligand can be used to modulate, *e.g.*, control (*e.g.*, inhibit) the binding of the conjugate to a target tissue. For example, a lipid or lipid-based ligand that binds to HSA more strongly will be less likely to be targeted to the kidney and therefore less likely to be cleared from the body. A lipid or lipid-based ligand that binds to HSA less strongly can be used to target the conjugate to the kidney.

[0434] In certain embodiments, the lipid-based ligand binds HSA. For example, the ligand can bind HSA with a sufficient affinity such that distribution of the conjugate to a non-kidney tissue is enhanced. However, the affinity is typically not so strong that the HSA-ligand binding cannot be reversed.

[0435] In certain embodiments, the lipid-based ligand binds HSA weakly or not at all, such that distribution of the conjugate to the kidney is enhanced. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid-based ligand.

[0436] In another aspect, the ligand is a moiety, *e.g.*, a vitamin, which is taken up by a target cell, *e.g.*, a proliferating cell. These are particularly useful for treating disorders characterized by unwanted cell proliferation, *e.g.*, of the malignant or non-malignant type, *e.g.*, cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include are B vitamin, *e.g.*, folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by cancer cells. Also included are HSA and low density lipoprotein (LDL).

B. Cell Permeation Agents

[0437] In another aspect, the ligand is a cell-permeation agent, such as a helical cell-permeation agent. In certain embodiments, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopedia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is typically an α-helical agent and can have a lipophilic and a lipophobic phase.

[0438] The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The attachment of peptide and peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, *e.g.*, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[0439] A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.*, consisting primarily of Tyr, Trp, or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 11). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 12)) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a "delivery" peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO: 13)) and the *Drosophila Antennapedia* protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 14)) have been found to be capable of functioning as delivery peptides. A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam *et al.*, *Nature*, 354:82-84, 1991). Typically, the peptide or peptidomimetic tethered to a dsRNA agent *via* an incorporated monomer unit is a cell targeting peptide such as an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

[0440] An RGD peptide for use in the compositions and methods of the invention may be linear or cyclic, and may be modified, *e.g.,* glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidiomimemtics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand. Preferred conjugates of this ligand target PECAM-1 or VEGF.

[0441] An RGD peptide moiety can be used to target a particular cell type, *e.g.*, a tumor cell, such as an endothelial tumor cell or a breast cancer tumor cell (Zitzmann *et al.*, *Cancer Res.*, 62:5139-43, 2002). An RGD peptide can facilitate targeting of an dsRNA agent to tumors of a variety of other tissues, including the lung, kidney, spleen, or liver (Aoki *et al.*, *Cancer Gene Therapy* 8:783-787, 2001). Typically, the RGD peptide will facilitate targeting of an iRNA agent to the kidney. The RGD peptide can be linear or cyclic, and can be modified, *e.g.,* glycosylated or methylated to facilitate targeting to specific tissues. For example, a glycosylated RGD peptide can deliver an iRNA agent to a tumor cell expressing $\alpha_V\beta_3$ (Haubner *et al.*, *Jour. Nucl. Med.*, 42:326-336, 2001).

[0442] A "cell permeation peptide" is capable of permeating a cell, *e.g.,* a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α-helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α -defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite

amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, *Nucl. Acids Res.* 31:2717-2724, 2003).

C. Carbohydrate Conjugates

[0443] In some embodiments of the compositions and methods of the invention, an iRNA further comprises a carbohydrate. The carbohydrate conjugated iRNA are advantageous for the *in vivo* delivery of nucleic acids, as well as compositions suitable for *in vivo* therapeutic use, as described herein. As used herein, "carbohydrate" refers to a compound which is either a carbohydrate *per se* made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which can be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri- and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (*e.g.,* C5, C6, C7, or C8) sugars; di- and tri-saccharides include sugars having two or three monosaccharide units (*e.g.,* C5, C6, C7, or C8).

[0444] In certain embodiments, a carbohydrate conjugate comprises a monosaccharide.

[0445] In certain embodiments, the monosaccharide is an N-acetylgalactosamine (GalNAc). GalNAc conjugates, which comprise one or more N-acetylgalactosamine (GalNAc) derivatives, are described, for example, in US 8,106,022, the entire content of which is hereby incorporated herein by reference. In some embodiments, the GalNAc conjugate serves as a ligand that targets the iRNA to particular cells. In some embodiments, the GalNAc conjugate targets the iRNA to liver cells, *e.g.*, by serving as a ligand for the asialoglycoprotein receptor of liver cells (*e.g.*, hepatocytes).

[0446] In some embodiments, the carbohydrate conjugate comprises one or more GalNAc derivatives. The GalNAc derivatives may be attached *via* a linker, *e.g.*, a bivalent or trivalent branched linker. In some embodiments the GalNAc conjugate is conjugated to the 3' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 3' end of the sense strand) *via* a linker, *e.g.*, a linker as described herein. In some embodiments the GalNAc conjugate is conjugated to the 5' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 5' end of the sense strand) *via* a linker, *e.g.*, a linker as described herein.

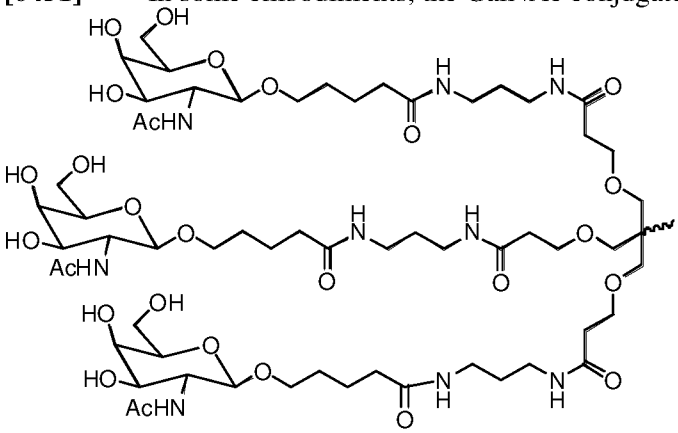
[0447] In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a trivalent linker. In other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a tetravalent linker.

[0448] In certain embodiments, the double stranded RNAi agents of the invention comprise one GalNAc or GalNAc derivative attached to the iRNA agent. In certain embodiments, the double stranded RNAi agents of the invention comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of monovalent linkers.

[0449] In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

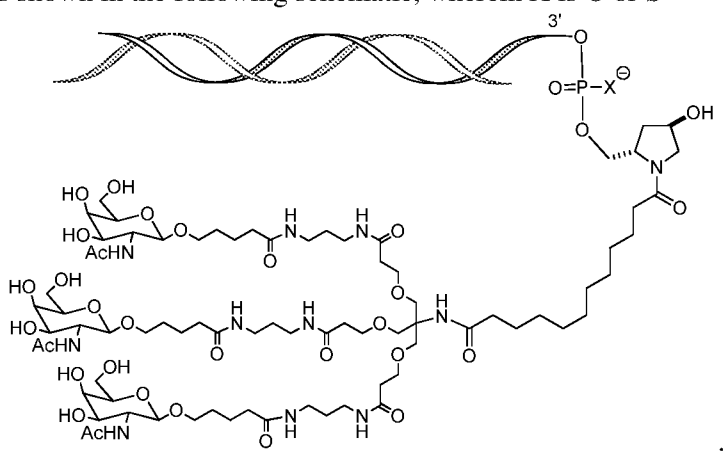
[0450] In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

[0451] In some embodiments, the GalNAc conjugate is



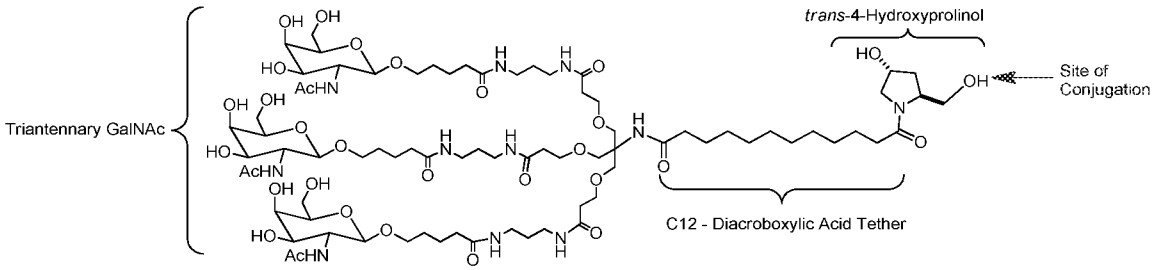
Formula II.

[0452] In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S

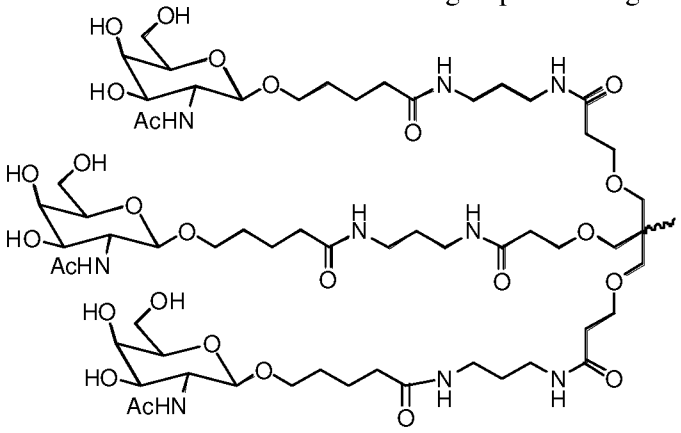


.

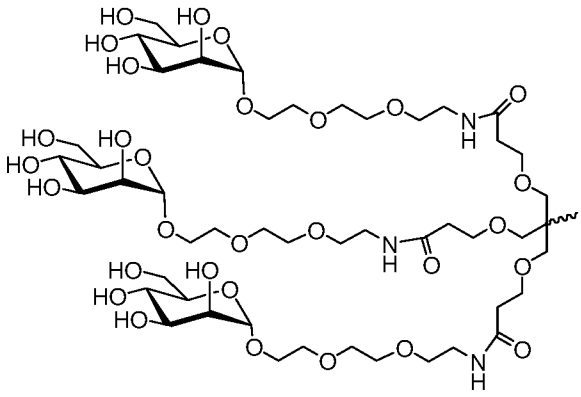
[0453] In some embodiments, the RNAi agent is conjugated to L96 as defined in Table 1 and shown below:



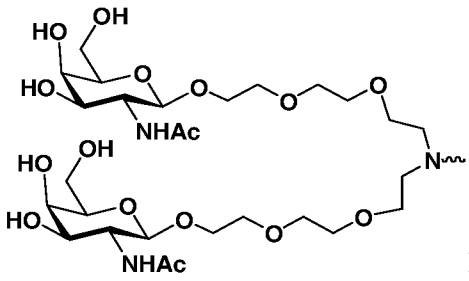
[0454] In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



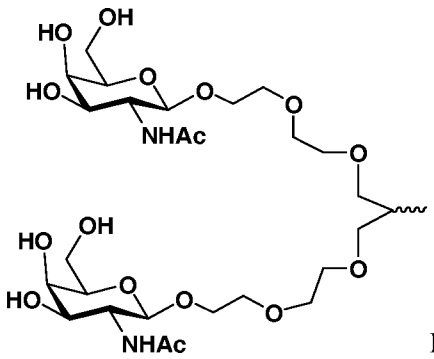
Formula II,



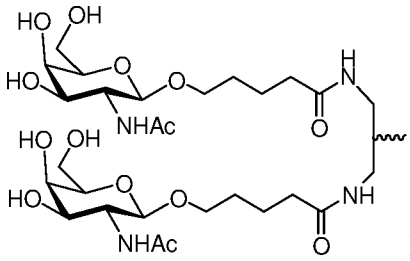
Formula III,



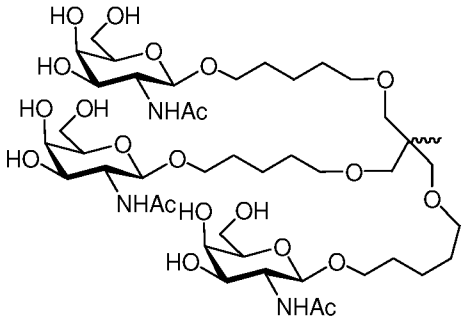
Formula IV,



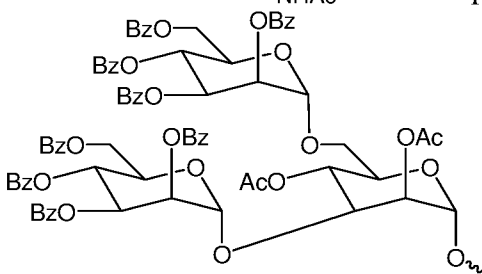
Formula V,



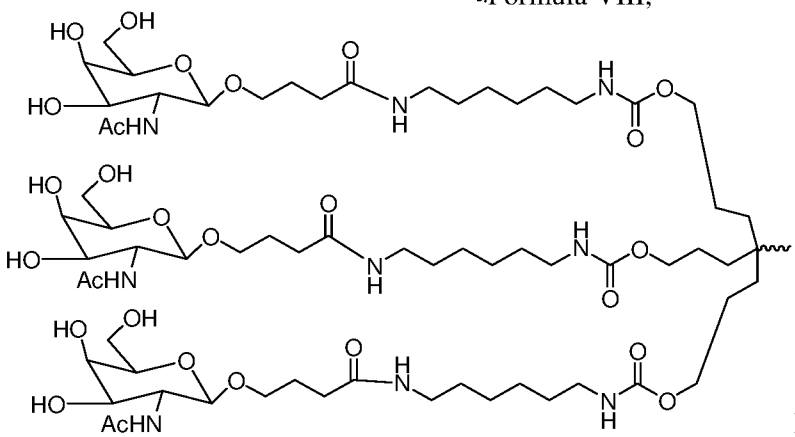
Formula VI,



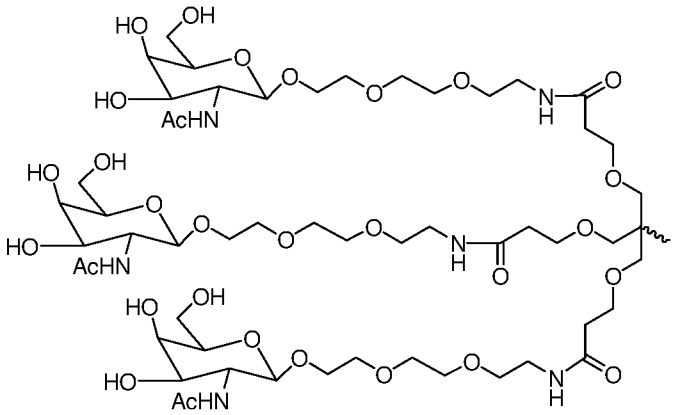
Formula VII,



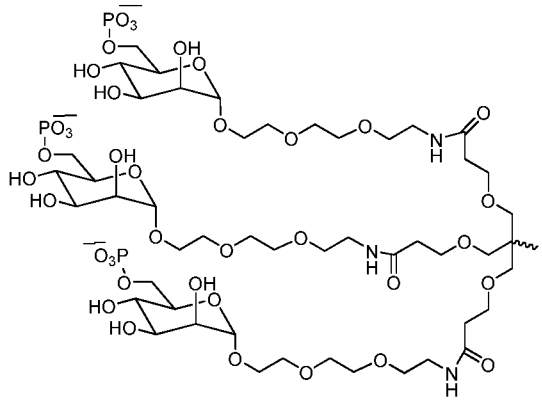
Formula VIII,



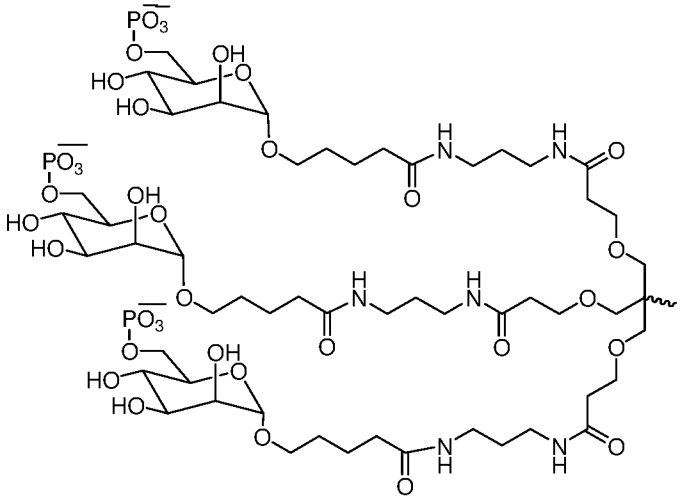
Formula IX,



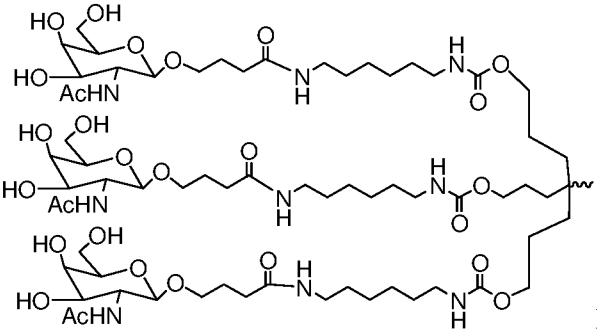
Formula X,



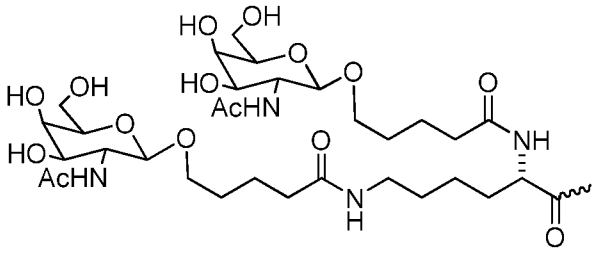
Formula XI,

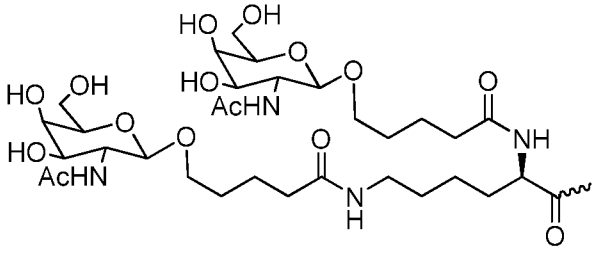


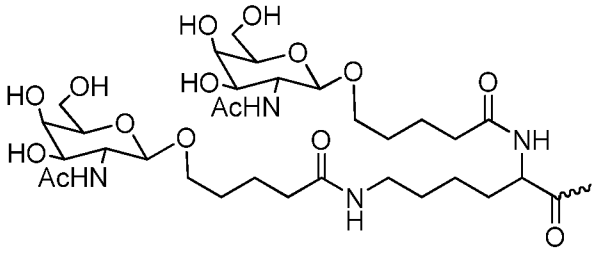
Formula XII,

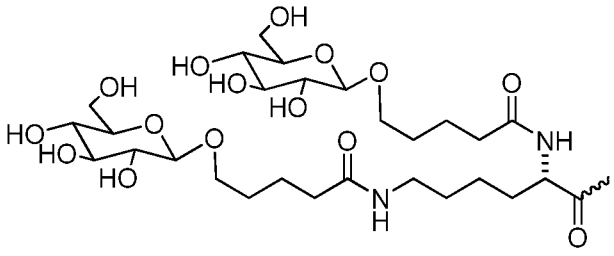


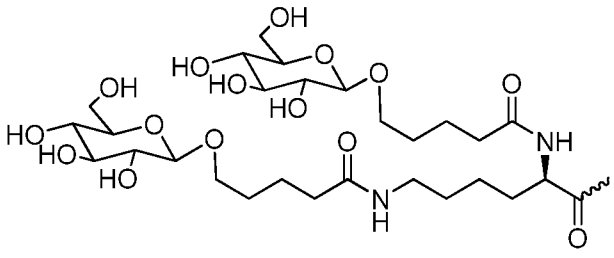
Formula XIII,

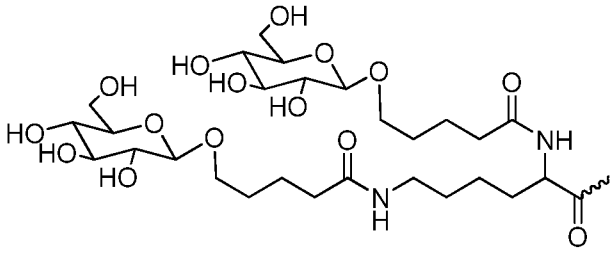

Formula XIV,

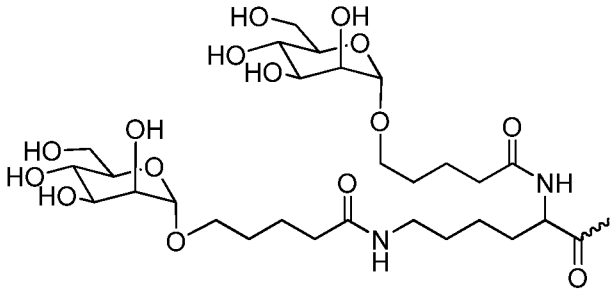

Formula XV,

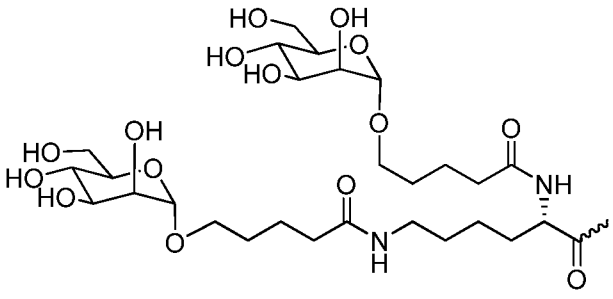

Formula XVI,


Formula XVII,

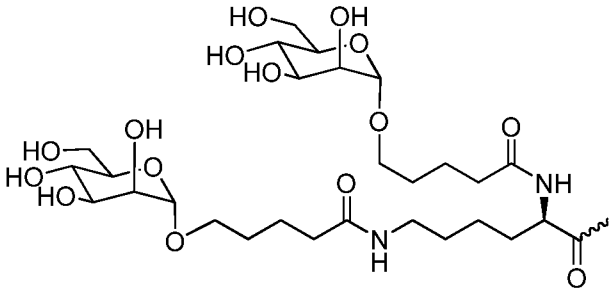

Formula XVIII,


Formula XIX,

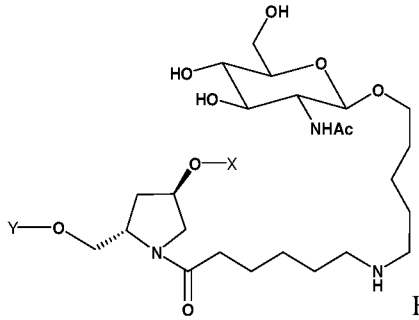

Formula XX,



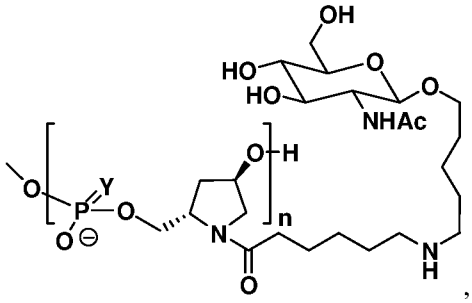
Formula XXI,



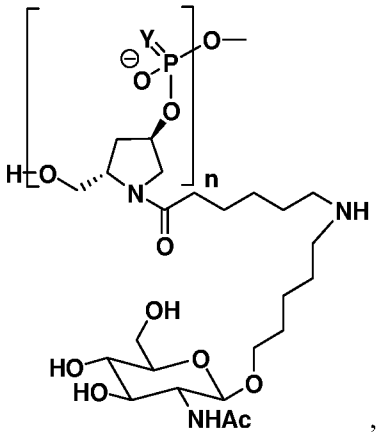
Formula XXII,



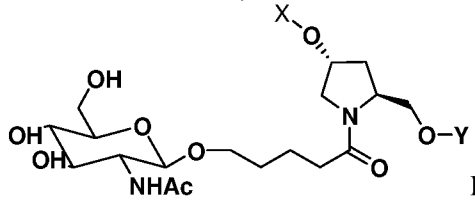
Formula XXIII;



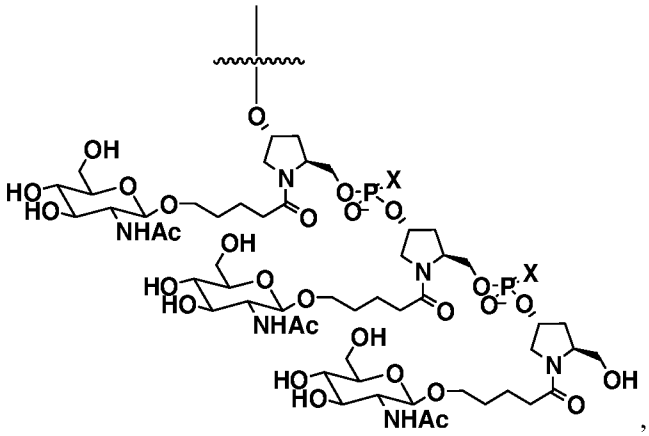
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



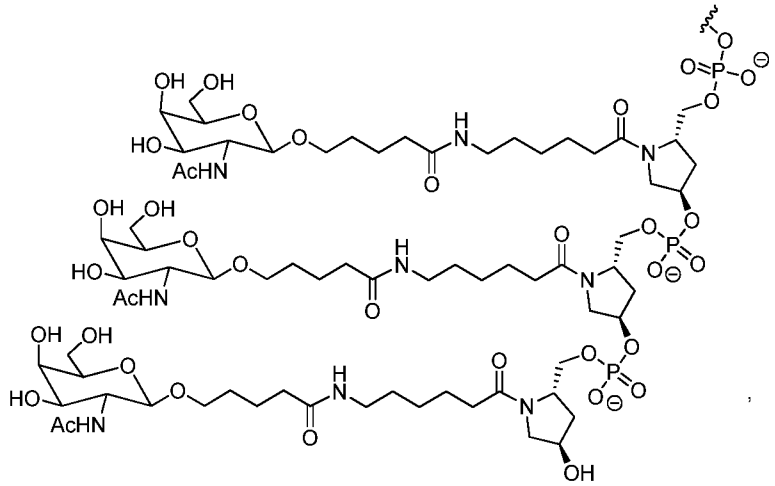
, wherein Y is O or S and n is 3-6 (Formula XXV);



Formula XXVI;



, wherein X is O or S (Formula XXVII);



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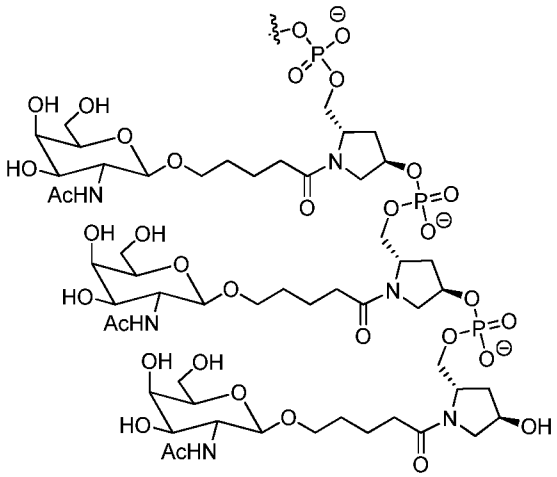
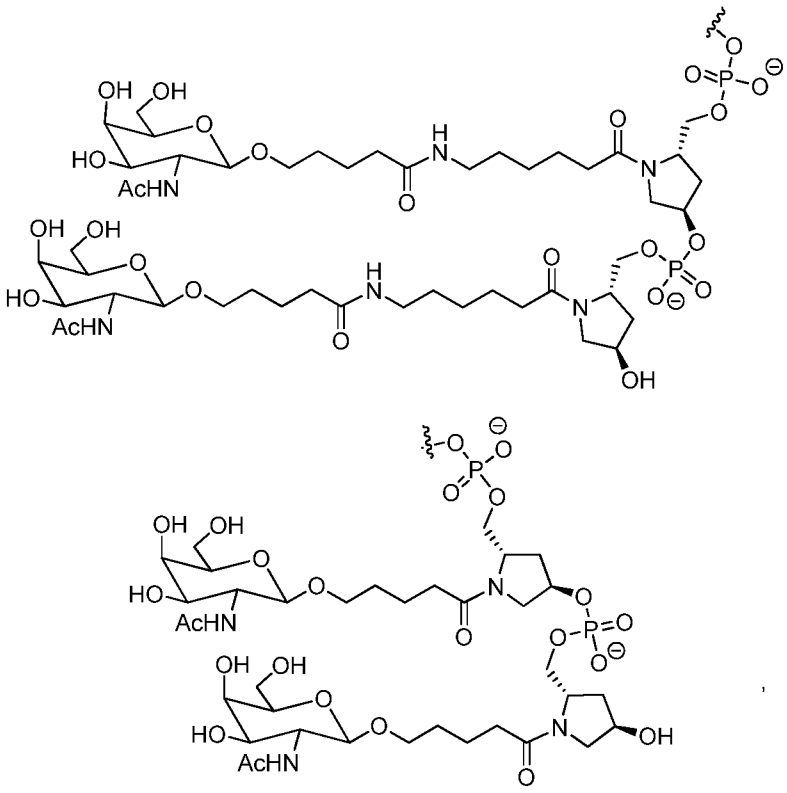
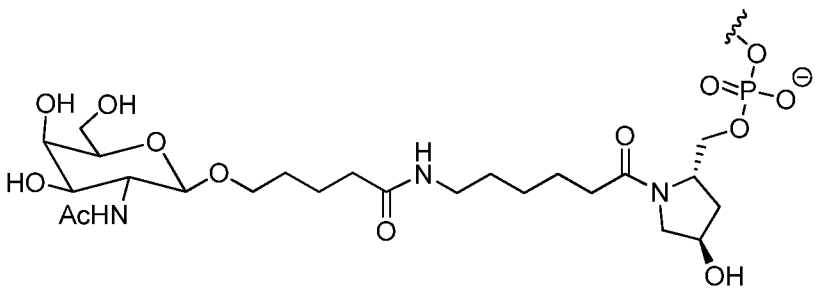


Formula XXVII; Formula XXIX;

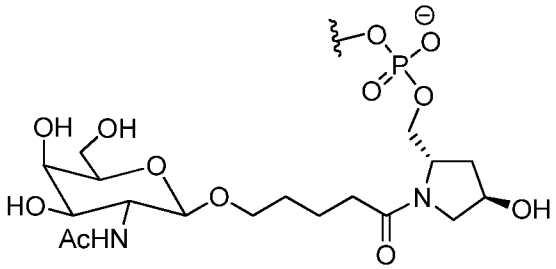


Formula XXX;

Formula XXXI;

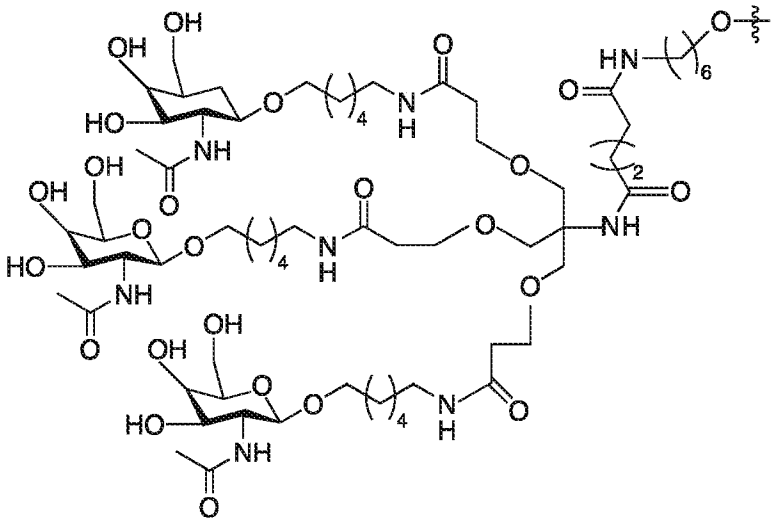


, and



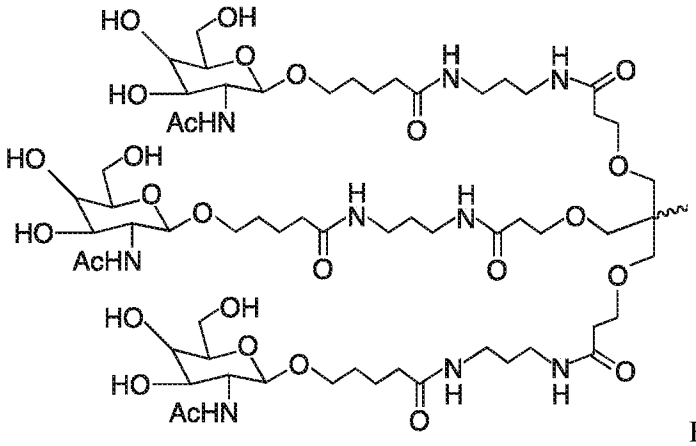
Formula XXXII;

Formula XXXIII.



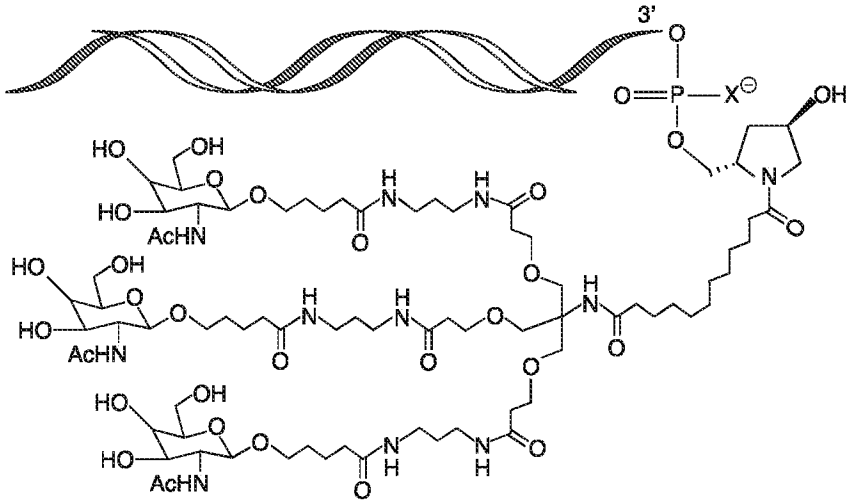
Formula XXXIV.

[0455] In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the invention is a monosaccharide. In certain embodiments, the monosaccharide is an N-acetylgalactosamine, such as

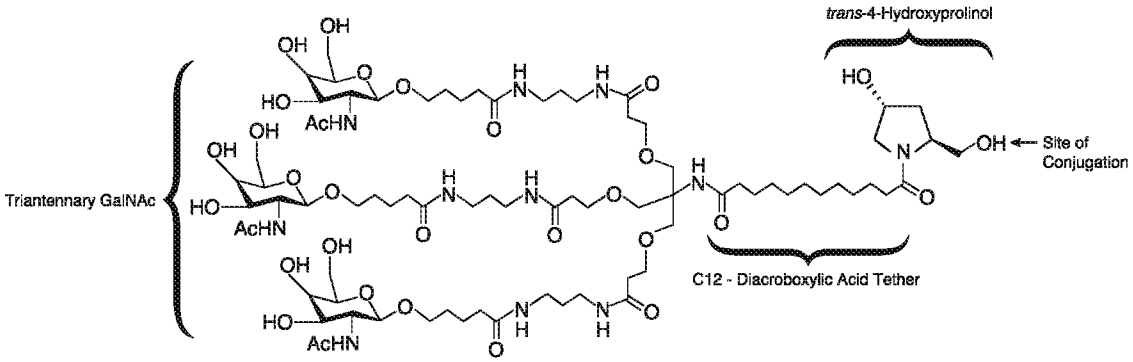


Formula II.

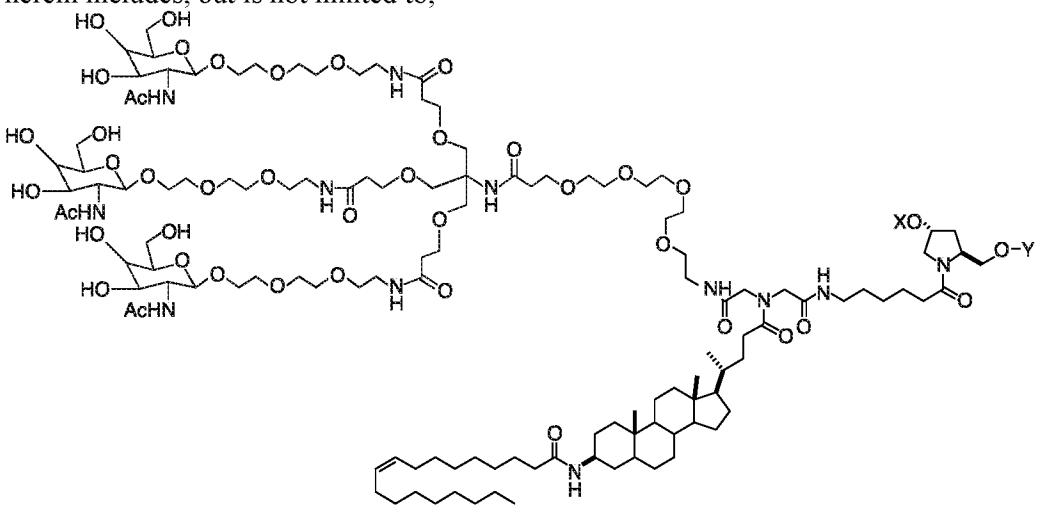
[0456] In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S



[0457] In some embodiments, the RNAi agent is conjugated to L96 as defined in Table 1 and shown below:



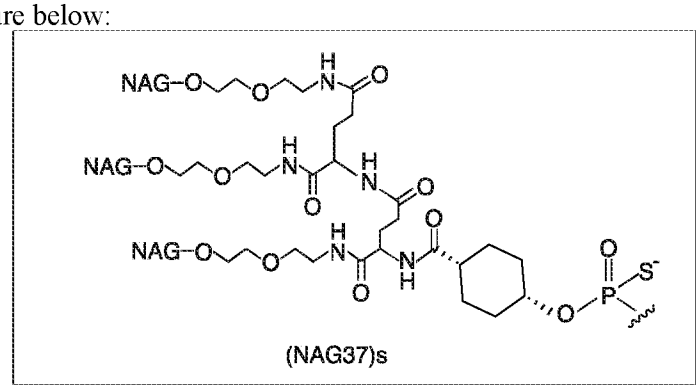
[0458] Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



(Formula XXXVI),

[0459] when one of X or Y is an oligonucleotide, the other is a hydrogen.

[0460] In some embodiments, a suitable ligand is a ligand disclosed in WO 2019/055633, the entire contents of which are incorporated herein by reference. In one embodiment the ligand comprises the structure below:



[0461] In certain embodiments, the RNAi agents of the disclosure may include GalNAc ligands, even if such GalNAc ligands are currently projected to be of limited value for the preferred intrathecal/CNS delivery route(s) of the instant disclosure.

[0462] In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a trivalent linker.

[0463] In one embodiment, the double stranded RNAi agents of the invention comprise one or more GalNAc or GalNAc derivative attached to the iRNA agent. The GalNAc may be attached to any nucleotide *via* a linker on the sense strand or antsisense strand. The GalNac may be attached to the 5'-end of the sense strand, the 3' end of the sense strand, the 5'-end of the antisense strand, or the 3' – end of the antisense strand. In one embodiment, the GalNAc is attached to the 3' end of the sense strand, *e.g., via* a trivalent linker.

[0464] In other embodiments, the double stranded RNAi agents of the invention comprise a plurality (*e.g.,* 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of linkers, *e.g.,* monovalent linkers.

[0465] In some embodiments, for example, when the two strands of an iRNA agent of the invention is part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker.

[0466] In some embodiments, the carbohydrate conjugate further comprises one or more additional ligands as described above, such as, but not limited to, a PK modulator or a cell permeation peptide.

[0467] Additional carbohydrate conjugates and linkers suitable for use in the present invention include those described in WO 2014/179620 and WO 2014/179627, the entire contents of each of which are incorporated herein by reference.

D. Linkers

[0468] In some embodiments, the conjugate or ligand described herein can be attached to an iRNA oligonucleotide with various linkers that can be cleavable or non-cleavable.

[0469] The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, *e.g.,* covalently attaches two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR8, C(O), C(O)NH, SO, SO_2, SO_2NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl,

alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylhereroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO_2, N(R8), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R8 is hydrogen, acyl, aliphatic or substituted aliphatic. In certain embodiments, the linker is between about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18 atoms, 7-17, 8-17, 6-16, 7-16, or 8-16 atoms.

[0470] A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In a preferred embodiment, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times or more, or at least about 100 times faster in a target cell or under a first reference condition (which can, *e.g.*, be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.*, be selected to mimic or represent conditions found in the blood or serum).

[0471] Cleavable linking groups are susceptible to cleavage agents, *e.g.*, pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, *e.g.*, oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, *e.g.*, those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

[0472] A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at a preferred pH, thereby releasing a cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

[0473] A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted. For example, a liver-targeting ligand can be linked to a cationic lipid through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

[0474] Linkers that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

[0475] In general, the suitability of a candidate cleavable linking group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linking group. It will also be desirable to also test the candidate cleavable linking group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, *e.g.*, blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It can be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In preferred embodiments, useful candidate compounds are cleaved at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

i. Redox cleavable linking groups

[0476] In certain embodiments, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable "reductively cleavable linking group," or for example is suitable for use with a particular iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents know in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.*, a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In other embodiments, useful candidate compounds are degraded at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

ii. Phosphate-based cleavable linking groups

[0477] In certain embodiments, a cleavable linker comprises a phosphate-based cleavable linking group. A phosphate-based cleavable linking group is cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-

P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-. Preferred embodiments are -O-P(O)(OH)-O-, -O-P(S)(OH)-O-, -O-P(S)(SH)-O-, -S-P(O)(OH)-O-, -O-P(O)(OH)-S-, -S-P(O)(OH)-S-, -O-P(S)(OH)-S-, -S-P(S)(OH)-O-, -O-P(O)(H)-O-, -O-P(S)(H)-O-, -S-P(O)(H)-O, -S-P(S)(H)-O-, -S-P(O)(H)-S-, -O-P(S)(H)-S-. A preferred embodiment is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

iii. Acid cleavable linking groups

[0478] In certain embodiments, a cleavable linker comprises an acid cleavable linking group. An *a*cid cleavable linking group is a linking group that is cleaved under acidic conditions. In preferred embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of about 6.5 or lower (*e.g.*, about 6.0, 5.75, 5.5, 5.25, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula -C=NN-, C(O)O, or -OC(O). A preferred embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

iv. Ester-based cleavable linking groups

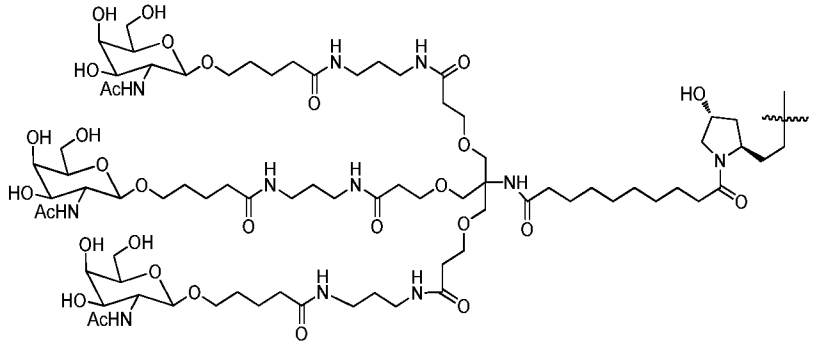
[0479] In certain embodiments, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula -C(O)O-, or -OC(O)-. These candidates can be evaluated using methods analogous to those described above.

v. Peptide-based cleavable linking groups

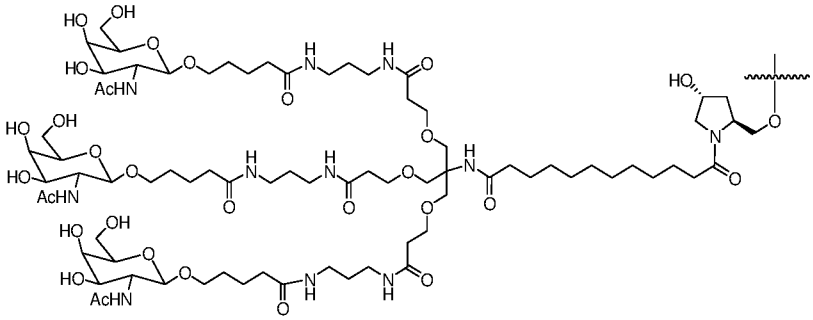
[0480] In yet another embodiment, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.*, dipeptides, tripeptides *etc.*) and polypeptides. Peptide-based cleavable groups do not include the amide group (-C(O)NH-). The amide group can be formed between any alkylene, alkenylene or alkynelene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula – NHCHRAC(O)NHCHRBC(O)-, where RA and RB are the

R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

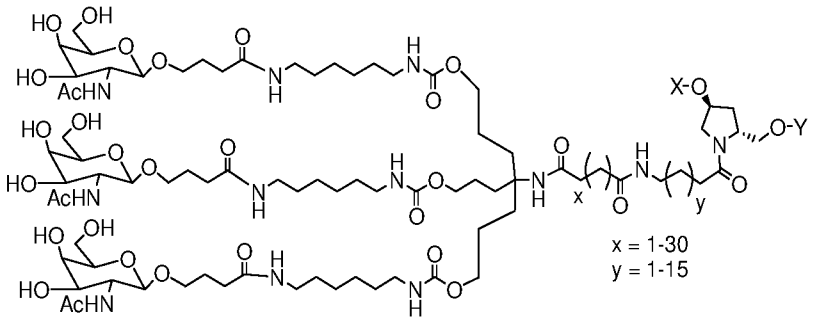
[0481] In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



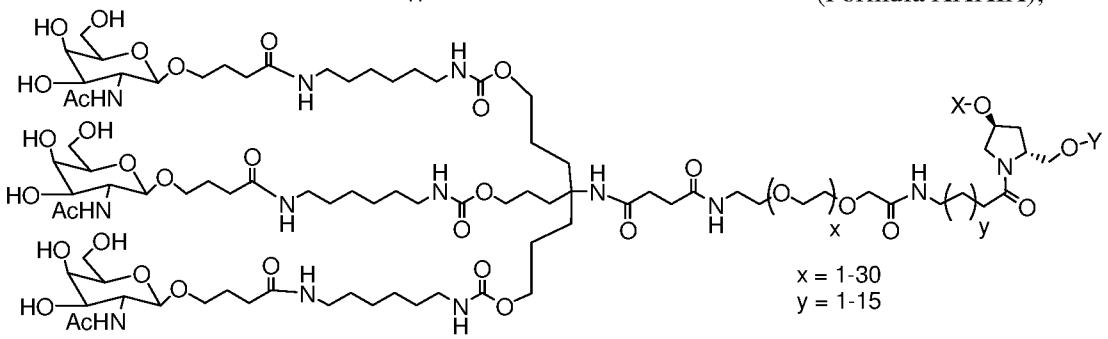
(Formula XXXVII),



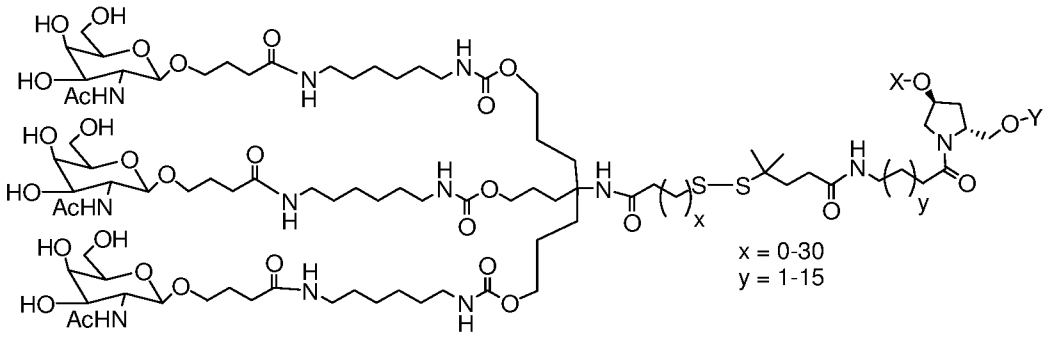
(Formula XXXVIII),



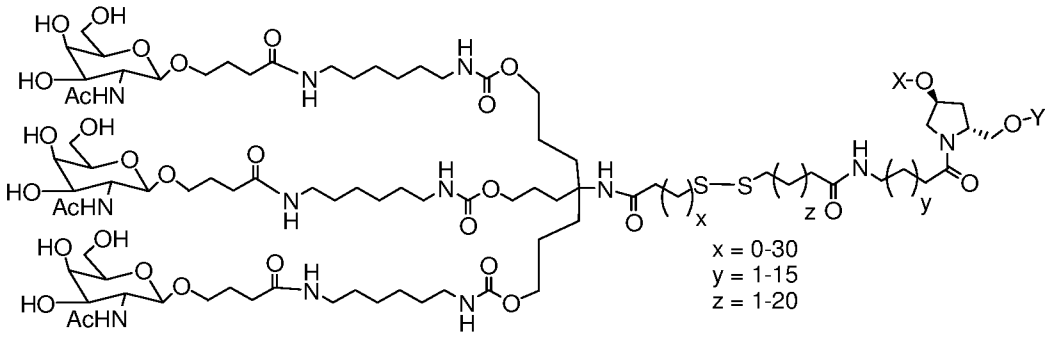
(Formula XXXIX),



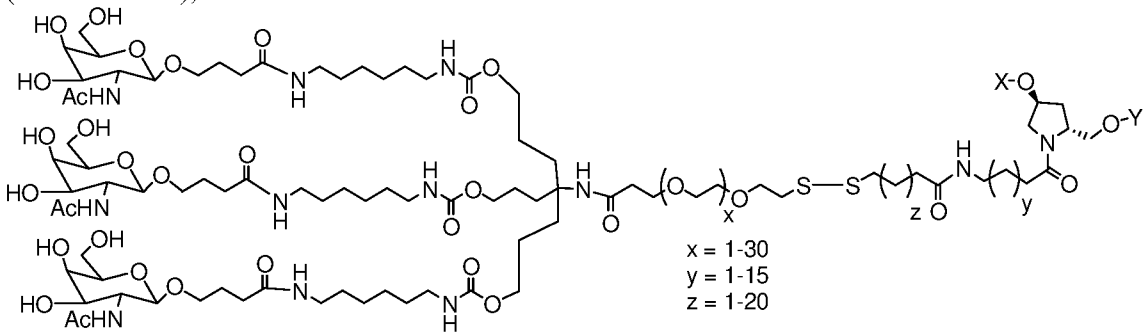
(Formula XL),



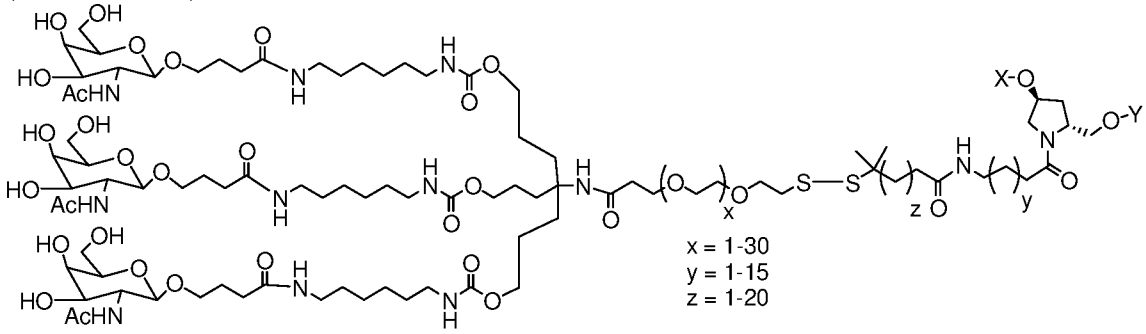
(Formula XLI),



(Formula XLII),



(Formula XLIII), and

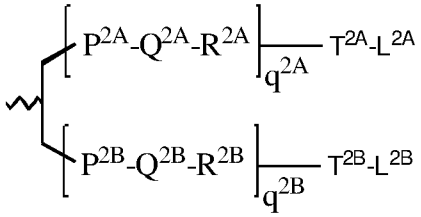


(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

[0482] In certain embodiments of the compositions and methods of the invention, a ligand is one or more "GalNAc" (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

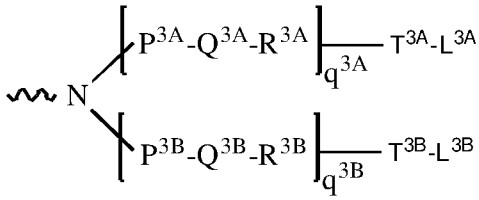
[0483] In certain embodiments, a dsRNA of the invention is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XLV) – (XLVI):

Formula XXXXV

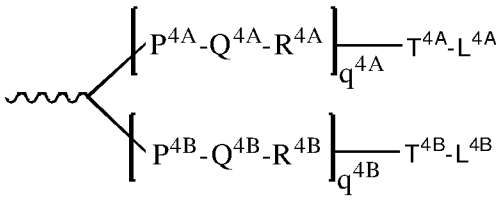


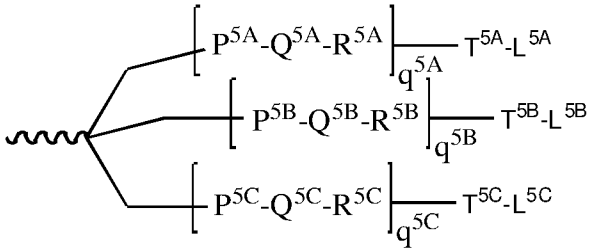
(IV)

Formula XLVI



V)





;

Formula XLVII

Formula XLVIII

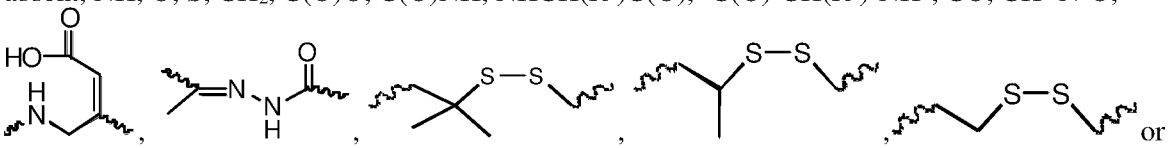
[0484] wherein:

[0485] q2A, q2B, q3A, q3B, q4A, q4B, q5A, q5B and q5C represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

[0486] P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

[0487] Q^{2A}, Q^{2B}, Q^{3A}, Q^{3B}, Q^{4A}, Q^{4B}, Q^{5A}, Q^{5B}, Q^{5C} are independently for each occurrence absent, alkylene, substituted alkylene wherin one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO_2, $N(R^N)$, C(R')=C(R''), C≡C or C(O);

[0488] R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C} are each independently for each occurrence absent, NH, O, S, CH_2, C(O)O, C(O)NH, $NHCH(R^a)C(O)$, -C(O)-$CH(R^a)$-NH-, CO, CH=N-O,

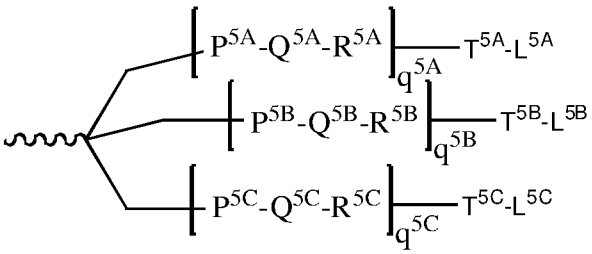


heterocyclyl;

[0489] L^{2A}, L^{2B}, L^{3A}, L^{3B}, L^{4A}, L^{4B}, L^{5A}, L^{5B} and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; andR^a is H or amino acid side chain.Trivalent conjugating

GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (XLIX):

Formula XLIX



Form

,

[0490] wherein L^{5A}, L^{5B} and L^{5C} represent a monosaccharide, such as GalNAc derivative.

[0491] Examples of suitable bivalent and trivalent branched linker groups conjugating GalNAc derivatives include, but are not limited to, the structures recited above as formulas II, VII, XI, X, and XIII.

[0492] Representative U.S. Patents that teach the preparation of RNA conjugates include, but are not limited to, U.S. Patent Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928;5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; and 8,106,022, the entire contents of each of which are hereby incorporated herein by reference.

[0493] It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications can be incorporated in a single compound or even at a single nucleoside within an iRNA. The present invention also includes iRNA compounds that are chimeric compounds.

[0494] "Chimeric" iRNA compounds or "chimeras," in the context of this invention, are iRNA compounds, preferably dsRNA agents, that contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of a dsRNA compound. These iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, or increased binding affinity for the target nucleic acid. An additional region of the iRNA can serve as a substrate for

enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to the same target region. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

[0495] In certain instances, the RNA of an iRNA can be modified by a non-ligand group. A number of non-ligand molecules have been conjugated to iRNAs in order to enhance the activity, cellular distribution or cellular uptake of the iRNA, and procedures for performing such conjugations are available in the scientific literature. Such non-ligand moieties have included lipid moieties, such as cholesterol (Kubo, T. *et al., Biochem. Biophys. Res. Comm.*, 2007, 365(1):54-61; Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 1989, 86:6553), cholic acid (Manoharan *et al.*, *Bioorg. Med. Chem. Lett.*, 1994, 4:1053), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306; Manoharan *et al.*, *Bioorg. Med. Chem. Let.*, 1993, 3:2765), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J.*, 1991, 10:111; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14:969), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277:923). Representative United States patents that teach the preparation of such RNA conjugates have been listed above. Typical conjugation protocols involve the synthesis of RNAs bearing an aminolinker at one or more positions of the sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction can be performed either with the RNA still bound to the solid support or following cleavage of the RNA, in solution phase. Purification of the RNA conjugate by HPLC typically affords the pure conjugate.

V. Delivery of an RNAi Agent of the Disclosure

[0496] The delivery of an RNAi agent of the disclosure to a cell *e.g.,* a cell within a subject, such as a human subject (*e.g.,* a subject in need thereof, such as a subject having an HTT-associated disorder, *e.g.,* Huntington's disease, can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with an RNAi agent of the disclosure either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising an RNAi agent, *e.g.,* a dsRNA, to a subject. Alternatively, *in vivo* delivery may be performed

indirectly by administering one or more vectors that encode and direct the expression of the RNAi agent. These alternatives are discussed further below.

[0497] In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with an RNAi agent of the disclosure (see *e.g.*, Akhtar S. and Julian RL., (1992) *Trends Cell. Biol.* 2(5):139-144 and WO94/02595, which are incorporated herein by reference in their entireties). For *in vivo* delivery, factors to consider in order to deliver an RNAi agent include, for example, biological stability of the delivered agent, prevention of non-specific effects, and accumulation of the delivered agent in the target tissue. The non-specific effects of an RNAi agent can be minimized by local administration, for example, by direct injection or implantation into a tissue or topically administering the preparation. Local administration to a treatment site maximizes local concentration of the agent, limits the exposure of the agent to systemic tissues that can otherwise be harmed by the agent or that can degrade the agent, and permits a lower total dose of the RNAi agent to be administered. Several studies have shown successful knockdown of gene products when an RNAi agent is administered locally. For example, intraocular delivery of a VEGF dsRNA by intravitreal injection in cynomolgus monkeys (Tolentino, MJ. *et al.*, (2004) *Retina* 24:132-138) and subretinal injections in mice (Reich, SJ. *et al.* (2003) *Mol. Vis.* 9:210-216) were both shown to prevent neovascularization in an experimental model of age-related macular degeneration. In addition, direct intratumoral injection of a dsRNA in mice reduces tumor volume (Pille, J. *et al.* (2005) *Mol. Ther.* 11:267-274) and can prolong survival of tumor-bearing mice (Kim, WJ. *et al.*, (2006) *Mol. Ther.* 14:343-350; Li, S. *et al.*, (2007) *Mol. Ther.* 15:515-523). RNA interference has also shown success with local delivery to the CNS by direct injection (Dorn, G. *et al.,* (2004) *Nucleic Acids* 32:e49; Tan, PH. *et al.* (2005) *Gene Ther.* 12:59-66; Makimura, H. *et a.l* (2002) *BMC Neurosci.* 3:18; Shishkina, GT., *et al.* (2004) *Neuroscience* 129:521-528; Thakker, ER., *et al.* (2004) *Proc. Natl. Acad. Sci. U.S.A.* 101:17270-17275; Akaneya,Y., *et al.* (2005) *J. Neurophysiol.* 93:594-602) and to the lungs by intranasal administration (Howard, KA. *et al.*, (2006) *Mol. Ther.* 14:476-484; Zhang, X. *et al.*, (2004) *J. Biol. Chem.* 279:10677-10684; Bitko, V. *et al.*, (2005) *Nat. Med.* 11:50-55). For administering an RNAi agent systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the dsRNA by endo- and exo-nucleases *in vivo*. Modification of the RNA or the pharmaceutical carrier can also permit targeting of the RNAi agent to the target tissue and avoid undesirable off-target effects (*e.g.*, without wishing to be bound by theory, use of GNAs as described herein has been identified to destabilize the seed region of a dsRNA, resulting in enhanced preference of such dsRNAs for on-target effectiveness, relative to off-target effects, as such off-target effects are significantly weakened by such seed region destabilization). RNAi agents can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an RNAi agent directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the liver and jejunum (Soutschek, J. *et al.*, (2004) *Nature* 432:173-178). Conjugation of an RNAi agent to an aptamer has been shown to inhibit tumor growth and mediate tumor regression in a mouse model

of prostate cancer (McNamara, JO. *et al.*, (2006) *Nat. Biotechnol.* 24:1005-1015). In an alternative embodiment, the RNAi agent can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of molecule RNAi agent (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an RNAi agent by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an RNAi agent, or induced to form a vesicle or micelle (see *e.g.*, Kim SH. *et al.*, (2008) *Journal of Controlled Release* 129(2):107-116) that encases an RNAi agent. The formation of vesicles or micelles further prevents degradation of the RNAi agent when administered systemically. Methods for making and administering cationic- RNAi agent complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, DR., *et al.* (2003) *J. Mol. Biol* 327:761-766; Verma, UN. *et al.*, (2003) *Clin. Cancer Res.* 9:1291-1300; Arnold, AS *et al.* (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of RNAi agents include DOTAP (Sorensen, DR., *et al* (2003), supra; Verma, UN. *et al.*, (2003), supra), Oligofectamine, "solid nucleic acid lipid particles" (Zimmermann, TS. *et al.,* (2006) *Nature* 441:111-114), cardiolipin (Chien, PY. *et al.*, (2005) *Cancer Gene Ther.* 12:321-328; Pal, A. *et al.*, (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet ME. *et al.*, (2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3:472-487), and polyamidoamines (Tomalia, DA. *et al.*, (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H. *et al.*, (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an RNAi agent forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of RNAi agents and cyclodextrins can be found in U.S. Patent No. 7, 427, 605, which is herein incorporated by reference in its entirety.

[0498] Certain aspects of the instant disclosure relate to a method of reducing the expression of an HTT target gene in a cell, comprising contacting said cell with the double-stranded RNAi agent of the disclosure. In one embodiment, the cell is an extraheptic cell, optionally a CNS cell.

[0499] Another aspect of the disclosure relates to a method of reducing the expression of an HTT target gene in a subject, comprising administering to the subject the double-stranded RNAi agent of the disclosure.

[0500] Another aspect of the disclosure relates to a method of treating a subject having a CNS disorder, comprising administering to the subject a therapeutically effective amount of the double-stranded HTT-targeting RNAi agent of the disclosure, thereby treating the subject. Exemplary CNS disorders that can be treated by the method of the disclosure include Huntington's disease.

[0501] In one embodiment, the double-stranded RNAi agent is administered intrathecally. By intrathecal administration of the double-stranded RNAi agent, the method can reduce the expression of an HTT target gene in a brain (*e.g.,* striatum) or spine tissue, for instance, cortex, cerebellum, cervical spine, lumbar spine, and thoracic spine.

[0502] For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to modified siRNA compounds. It may be understood, however, that

these formulations, compositions and methods can be practiced with other siRNA compounds, *e.g.*, unmodified siRNA compounds, and such practice is within the disclosure. A composition that includes an RNAi agent can be delivered to a subject by a variety of routes. Exemplary routes include: intrathecal, intravenous, topical, rectal, anal, vaginal, nasal, pulmonary, and ocular.

[0503] The RNAi agents of the disclosure can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically include one or more species of RNAi agent and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0504] The pharmaceutical compositions of the present disclosure may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic, vaginal, rectal, intranasal, transdermal), oral, or parenteral. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, or intrathecal or intraventricular administration.

[0505] The route and site of administration may be chosen to enhance targeting. For example, to target muscle cells, intramuscular injection into the muscles of interest would be a logical choice. Lung cells might be targeted by administering the RNAi agent in aerosol form. The vascular endothelial cells could be targeted by coating a balloon catheter with the RNAi agent and mechanically introducing the RNA.

[0506] Formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids, and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

[0507] Compositions for oral administration include powders or granules, suspensions or solutions in water, syrups, elixirs or non-aqueous media, tablets, capsules, lozenges, or troches. In the case of tablets, carriers that can be used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the nucleic acid compositions can be combined with emulsifying and suspending agents. If desired, certain sweetening or flavoring agents can be added.

[0508] Compositions for intrathecal or intraventricular administration may include sterile aqueous solutions which may also contain buffers, diluents, and other suitable additives.

[0509] Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents, and other suitable additives. Intraventricular injection may be

facilitated by an intraventricular catheter, for example, attached to a reservoir. For intravenous use, the total concentration of solutes may be controlled to render the preparation isotonic.

[0510] In one embodiment, the administration of the siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, composition is parenteral, *e.g.,* intravenous (*e.g.*, as a bolus or as a diffusible infusion), intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular, intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary, intranasal, urethral, or ocular. Administration can be provided by the subject or by another person, *e.g.*, a health care provider. The medication can be provided in measured doses or in a dispenser which delivers a metered dose. Selected modes of delivery are discussed in more detail below.

A. Intrathecal Administration.

[0511] In one embodiment, the double-stranded RNAi agent is delivered by intrathecal injection (*i.e.*, injection into the spinal fluid which bathes the brain and spinal cord tissue). Intrathecal injection of RNAi agents into the spinal fluid can be performed as a bolus injection or *via* minipumps which can be implanted beneath the skin, providing a regular and constant delivery of siRNA into the spinal fluid. The circulation of the spinal fluid from the choroid plexus, where it is produced, down around the spinal chord and dorsal root ganglia and subsequently up past the cerebellum and over the cortex to the arachnoid granulations, where the fluid can exit the CNS, that, depending upon size, stability, and solubility of the compounds injected, molecules delivered intrathecally could hit targets throughout the entire CNS.

[0512] In some embodiments, the intrathecal administration is *via* a pump. The pump may be a surgically implanted osmotic pump. In one embodiment, the osmotic pump is implanted into the subarachnoid space of the spinal canal to facilitate intrathecal administration.

[0513] In some embodiments, the intrathecal administration is *via* an intrathecal delivery system for a pharmaceutical including a reservoir containing a volume of the pharmaceutical agent, and a pump configured to deliver a portion of the pharmaceutical agent contained in the reservoir. More details about this intrathecal delivery system may be found in WO 2015/116658, which is incorporated by reference in its entirety.

[0514] The amount of intrathecally injected RNAi agents may vary from one target gene to another target gene and the appropriate amount that has to be applied may have to be determined individually for each target gene. Typically, this amount ranges from 10 μg to 2 mg, preferably 50 μg to 1500 μg, more preferably 100 μg to 1000 μg.

B. Vector encoded RNAi agents of the Disclosure

[0515] RNAi agents targeting the HTT gene can be expressed from transcription units inserted into DNA or RNA vectors (see, *e.g.*, Couture, A, *et al.*, *TIG.* (1996), 12:5-10; WO 00/22113, WO 00/22114, and US 6,054,299). Expression is preferablysustained (months or longer), depending upon the specific construct used and the target tissue or cell type. These transgenes can be introduced as a

linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, *et al.*, (1995) *Proc. Natl. Acad. Sci. USA* 92:1292).

[0516] The individual strand or strands of an RNAi agent can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced (*e.g.*, by transfection or infection) into a target cell. Alternatively, each individual strand of a dsRNA can be transcribed by promoters both of which are located on the same expression plasmid. In one embodiment, a dsRNA is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

[0517] RNAi agent expression vectors are generally DNA plasmids or viral vectors. Expression vectors compatible with eukaryotic cells, preferably those compatible with vertebrate cells, can be used to produce recombinant constructs for the expression of an RNAi agent as described herein. Delivery of RNAi agent expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

[0518] Viral vector systems which can be utilized with the methods and compositions described herein include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, *etc.*; (c) adeno- associated virus vectors; (d) herpes simplex virus vectors; (e) SV 40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, *e.g.*, vaccinia virus vectors or avipox, *e.g.* canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Replication-defective viruses can also be advantageous. Different vectors will or will not become incorporated into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct can be incorporated into vectors capable of episomal replication, *e.g.* EPV and EBV vectors. Constructs for the recombinant expression of an RNAi agent will generally require regulatory elements, *e.g.*, promoters, enhancers, *etc.*, to ensure the expression of the RNAi agent in target cells. Other aspects to consider for vectors and constructs are known in the art.

VI. Compositions of the Invention

[0519] The present disclosure also includes compositions, including pharmaceutical compositions and formulations which include the RNAi agents of the disclosure.

[0520] In another embodiment, provided herein are pharmaceutical compositions containing an RNAi agent, or a composition, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the RNAi agent or the composition are useful for treating a disease or disorder associated with the expression or activity of HTT, *e.g.*, Huntington's disease.

[0521] In some embodiments, the pharmaceutical compositions of the invention are sterile. In another embodiment, the pharmaceutical compositions of the invention are pyrogen free or non-pyrogenic.

[0522] Such pharmaceutical compositions are formulated based on the mode of delivery. One example is compositions that are formulated for systemic administration *via* parenteral delivery, *e.g.*, by intravenous (IV), intramuscular (IM), or for subcutaneous (subQ) delivery. Another example is compositions that are formulated for direct delivery into the CNS, *e.g.*, by intrathecal or intravitreal routes of injection, optionally by infusion into the brain (*e.g.,* striatum), such as by continuous pump infusion.

[0523] The pharmaceutical compositions of the disclosure may be administered in dosages sufficient to inhibit expression of an HTT gene. In general, a suitable dose of an RNAi agent of the disclosure will be in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day.

[0524] A repeat-dose regimen may include administration of a therapeutic amount of an RNAi agent on a regular basis, such as monthly to once every six months. In certain embodiments, the RNAi agent is administered about once per quarter (*i.e.*, about once every three months) to about twice per year.

[0525] After an initial treatment regimen (*e.g.*, loading dose), the treatments can be administered on a less frequent basis.

[0526] In other embodiments, a single dose of the pharmaceutical compositions can be long lasting, such that subsequent doses are administered at not more than 1, 2, 3, or 4 or more month intervals. In some embodiments of the disclosure, a single dose of the pharmaceutical compositions of the disclosure is administered once per month. In other embodiments of the disclosure, a single dose of the pharmaceutical compositions of the disclosure is administered once per quarter to twice per year.

[0527] The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments.

[0528] Advances in mouse genetics have generated a number of mouse models for the study of various human diseases, such as HD that would benefit from reduction in the expression of HTT. Such models can be used for *in vivo* testing of RNAi agents, as well as for determining a therapeutically effective dose. Suitable rodent models are known in the art and include, for example, those described in, for example, Cepeda, *et al.* (*ASN Neuro* (2010) 2(2):e00033) and Pouladi, *et al.* (*Nat Reviews* (2013) 14:708).

[0529] The pharmaceutical compositions of the present disclosure can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (*e.g.*, by a transdermal patch), pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial,

subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, *e.g.*, *via* an implanted device; or intracranial, *e.g.*, by intraparenchymal, intrathecal or intraventricular, administration.

[0530] The RNAi agents can be delivered in a manner to target a particular tissue, such as the CNS (*e.g.*, neuronal, glial or vascular tissue of the brain).

[0531] Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like can be necessary or desirable. Coated condoms, gloves and the like can also be useful. Suitable topical formulations include those in which the RNAi agents featured in the disclosure are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (*e.g.,* dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearolyphosphatidyl choline) negative (*e.g.,* dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.,* dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). RNAi agents featured in the disclosure can be encapsulated within liposomes or can form complexes thereto, in particular to cationic liposomes. Alternatively, RNAi agents can be complexed to lipids, in particular to cationic lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C_{1-20} alkyl ester (*e.g.,* isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in US 6,747,014, which is incorporated herein by reference.

A. RNAi Agent Formulations Comprising Membranous Molecular Assemblies

[0532] An RNAi agent for use in the compositions and methods of the disclosure can be formulated for delivery in a membranous molecular assembly, *e.g.*, a liposome or a micelle. As used herein, the term "liposome" refers to a vesicle composed of amphiphilic lipids arranged in at least one bilayer, *e.g.*, one bilayer or a plurality of bilayers. Liposomes include unilamellar and multilamellar vesicles that have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the RNAi agent composition. The lipophilic material isolates the aqueous interior from an aqueous exterior, which typically does not include the RNAi agent composition, although in some examples, it may. Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomal bilayer fuses with bilayer of the cellular membranes. As the merging of the liposome and cell progresses, the internal aqueous contents that include the RNAi agent are delivered into the cell where the RNAi agent can specifically bind to a target RNA and can mediate RNAi. In some cases the liposomes are also specifically targeted, *e.g.*, to direct the RNAi agent to particular cell types.

[0533] A liposome containing an RNAi agent can be prepared by a variety of methods. In one example, the lipid component of a liposome is dissolved in a detergent so that micelles are formed with the lipid component. For example, the lipid component can be an amphipathic cationic lipid or lipid conjugate. The detergent can have a high critical micelle concentration and may be nonionic. Exemplary detergents include cholate, CHAPS, octylglucoside, deoxycholate, and lauroyl sarcosine. The RNAi agent preparation is then added to the micelles that include the lipid component. The cationic groups on the lipid interact with the RNAi agent and condense around the RNAi agent to form a liposome. After condensation, the detergent is removed, *e.g.*, by dialysis, to yield a liposomal preparation of RNAi agent.

[0534] If necessary a carrier compound that assists in condensation can be added during the condensation reaction, *e.g.*, by controlled addition. For example, the carrier compound can be a polymer other than a nucleic acid (*e.g.*, spermine or spermidine). pH can also adjusted to favor condensation.

[0535] Methods for producing stable polynucleotide delivery vehicles, which incorporate a polynucleotide/cationic lipid complex as structural components of the delivery vehicle, are further described in, *e.g.*, WO 96/37194, the entire contents of which are incorporated herein by reference. Liposome formation can also include one or more aspects of exemplary methods described in Felgner, P. L. *et al.*, (1987) *Proc. Natl. Acad. Sci. USA* 8:7413-7417; United States Patent No. 4,897,355; United States Patent No. 5,171,678; Bangham *et al.,* (1965) *M. Mol. Biol.* 23:238; Olson *et al.*, (1979) *Biochim. Biophys. Acta* 557:9; Szoka *et al.*, (1978) *Proc. Natl. Acad. Sci.* 75: 4194; Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775:169; Kim *et al.*, (1983) *Biochim. Biophys. Acta* 728:339; and Fukunaga *et al.*, (1984) *Endocrinol.* 115:757. Commonly used techniques for preparing lipid aggregates of appropriate size for use as delivery vehicles include sonication and freeze-thaw plus extrusion (see, *e.g.*, Mayer *et al.*, (1986) *Biochim. Biophys. Acta* 858:161. Microfluidization can be used when consistently small (50 to 200 nm) and relatively uniform aggregates are desired (Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775:169. These methods are readily adapted to packaging RNAi agent preparations into liposomes.

[0536] Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged nucleic acid molecules to form a stable complex. The positively charged nucleic acid/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang *et al.* (1987) *Biochem. Biophys. Res. Commun.*, 147:980-985).

[0537] Liposomes, which are pH-sensitive or negatively charged, entrap nucleic acids rather than complex with them. Since both the nucleic acid and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some nucleic acid is entrapped within the aqueous interior of these liposomes. pH sensitive liposomes have been used to deliver nucleic acids encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou *et al.* (1992) *Journal of Controlled Release*, 19:269-274).

[0538] One major type of liposomal composition includes phospholipids other than naturally-derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid or phosphatidylcholine or cholesterol.

[0539] Examples of other methods to introduce liposomes into cells *in vitro* and *in vivo* include United States Patent No. 5,283,185; United States Patent No. 5,171,678; WO 94/00569; WO 93/24640; WO 91/16024; Felgner, (1994) *J. Biol. Chem.* 269:2550; Nabel, (1993) *Proc. Natl. Acad. Sci.* 90:11307; Nabel, (1992) *Human Gene Ther.* 3:649; Gershon, (1993) *Biochem.* 32:7143; and Strauss, (1992) *EMBO J.* 11:417.

[0540] Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome™ II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results indicated that such non-ionic liposomal systems were effective in facilitating the deposition of cyclosporine A into different layers of the skin (Hu *et al.*, (1994) *S.T.P.Pharma. Sci.*, 4(6):466).

[0541] Liposomes also include "sterically stabilized" liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside G_{M1}, or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen *et al.*, (1987) *FEBS Letters,* 223:42; Wu *et al.*, (1993) *Cancer Research*, 53:3765).

[0542] Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos *et al.* (*Ann. N.Y. Acad. Sci.*, (1987), 507:64) reported the ability of monosialoganglioside G_{M1}, galactocerebroside sulfate and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon *et al.* (*Proc. Natl. Acad. Sci. U.S.A.,* (1988), 85,:6949). United States Patent No. 4,837,028 and WO 88/04924, both to Allen *et al.*, disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside G_{M1} or a galactocerebroside sulfate ester. United States Patent No. 5,543,152 (Webb *et al.*) discloses liposomes comprising

sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim *et al*).

[0543] In one embodiment, cationic liposomes are used. Cationic liposomes possess the advantage of being able to fuse to the cell membrane. Non-cationic liposomes, although not able to fuse as efficiently with the plasma membrane, are taken up by macrophages *in vivo* and can be used to deliver RNAi agents to macrophages.

[0544] Further advantages of liposomes include: liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated RNAi agents in their internal compartments from metabolism and degradation (Rosoff, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 245). Important considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

[0545] A positively charged synthetic cationic lipid, N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) can be used to form small liposomes that interact spontaneously with nucleic acid to form lipid-nucleic acid complexes which are capable of fusing with the negatively charged lipids of the cell membranes of tissue culture cells, resulting in delivery of RNAi agent (see, *e.g.*, Felgner, P. L. *et al.*, (1987) *Proc. Natl. Acad. Sci. USA* 8:7413-7417, and United States Patent No.4,897,355 for a description of DOTMA and its use with DNA).

[0546] A DOTMA analogue, 1,2-bis(oleoyloxy)-3-(trimethylammonia)propane (DOTAP) can be used in combination with a phospholipid to form DNA-complexing vesicles. Lipofectin™ Bethesda Research Laboratories, Gaithersburg, Md.) is an effective agent for the delivery of highly anionic nucleic acids into living tissue culture cells that comprise positively charged DOTMA liposomes which interact spontaneously with negatively charged polynucleotides to form complexes. When enough positively charged liposomes are used, the net charge on the resulting complexes is also positive. Positively charged complexes prepared in this way spontaneously attach to negatively charged cell surfaces, fuse with the plasma membrane, and efficiently deliver functional nucleic acids into, for example, tissue culture cells. Another commercially available cationic lipid, 1,2-bis(oleoyloxy)-3,3-(trimethylammonia)propane ("DOTAP") (Boehringer Mannheim, Indianapolis, Indiana) differs from DOTMA in that the oleoyl moieties are linked by ester, rather than ether linkages.

[0547] Other reported cationic lipid compounds include those that have been conjugated to a variety of moieties including, for example, carboxyspermine which has been conjugated to one of two types of lipids and includes compounds such as 5-carboxyspermylglycine dioctaoleoylamide ("DOGS") (Transfectam™, Promega, Madison, Wisconsin) and dipalmitoylphosphatidylethanolamine 5-carboxyspermyl-amide ("DPPES") (see, *e.g.*, United States Patent No. 5,171,678).

[0548] Another cationic lipid conjugate includes derivatization of the lipid with cholesterol ("DC-Chol") which has been formulated into liposomes in combination with DOPE (See, Gao, X. and Huang, L., (1991) *Biochim. Biophys. Res. Commun.* 179:280). Lipopolylysine, made by conjugating

polylysine to DOPE, has been reported to be effective for transfection in the presence of serum (Zhou, X. *et al.*, (1991) *Biochim. Biophys. Acta* 1065:8). For certain cell lines, these liposomes containing conjugated cationic lipids, are said to exhibit lower toxicity and provide more efficient transfection than the DOTMA-containing compositions. Other commercially available cationic lipid products include DMRIE and DMRIE-HP (Vical, La Jolla, California) and Lipofectamine (DOSPA) (Life Technology, Inc., Gaithersburg, Maryland). Other cationic lipids suitable for the delivery of oligonucleotides are described in WO 98/39359 and WO 96/37194.

[0549] Liposomal formulations are particularly suited for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer RNAi agent into the skin. In some implementations, liposomes are used for delivering RNAi agent to epidermal cells and also to enhance the penetration of RNAi agent into dermal tissues, *e.g.*, into skin. For example, the liposomes can be applied topically. Topical delivery of drugs formulated as liposomes to the skin has been documented (see, *e.g.*, Weiner *et al.*, (1992) *Journal of Drug Targeting*, vol. 2,405-410 and du Plessis *et al.*, (1992) *Antiviral Research*, 18:259-265; Mannino, R. J. and Fould-Fogerite, S., (1998) *Biotechniques* 6:682-690; Itani, T. *et al.*, (1987) *Gene* 56:267-276; Nicolau, C. *et al.* (1987) *Meth. Enzymol.* 149:157-176; Straubinger, R. M. and Papahadjopoulos, D. (1983) *Meth. Enzymol.* 101:512-527; Wang, C. Y. and Huang, L., (1987) *Proc. Natl. Acad. Sci. USA* 84:7851-7855).

[0550] Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome II (glyceryl distearate/ cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver a drug into the dermis of mouse skin. Such formulations with RNAi agent are useful for treating a dermatological disorder.

[0551] Liposomes that include RNAi agents can be made highly deformable. Such deformability can enable the liposomes to penetrate through pore that are smaller than the average radius of the liposome. For example, transfersomes are a type of deformable liposomes. Transferosomes can be made by adding surface edge activators, usually surfactants, to a standard liposomal composition. Transfersomes that include RNAi agent can be delivered, for example, subcutaneously by infection in order to deliver RNAi agent to keratinocytes in the skin. In order to cross intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. In addition, due to the lipid properties, these transferosomes can be self-optimizing (adaptive to the shape of pores, *e.g.*, in the skin), self-repairing, and can frequently reach their targets without fragmenting, and often self-loading.

[0552] Other formulations amenable to the present disclosure are described in United States provisional application serial Nos. 61/018,616, filed January 2, 2008; 61/018,611, filed January 2, 2008; 61/039,748, filed March 26, 2008; 61/047,087, filed April 22, 2008 and 61/051,528, filed May

8, 2008. PCT application number PCT/US2007/080331, filed October 3, 2007, also describes formulations that are amenable to the present disclosure.

[0553] Transfersomes, yet another type of liposomes, are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes can be described as lipid droplets which are so highly deformable that they are easily able to penetrate through pores which are smaller than the droplet. Transfersomes are adaptable to the environment in which they are used, *e.g.*, they are self-optimizing (adaptive to the shape of pores in the skin), self-repairing, frequently reach their targets without fragmenting, and often self-loading. To make transfersomes it is possible to add surface edge-activators, usually surfactants, to a standard liposomal composition. Transfersomes have been used to deliver serum albumin to the skin. The transfersome-mediated delivery of serum albumin has been shown to be as effective as subcutaneous injection of a solution containing serum albumin.

[0554] Surfactants find wide application in formulations such as those described herein, particularlay in emulsions (including microemulsions) and liposomes. The most common way of classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in Pharmaceutical Dosage Forms, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

[0555] If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical and cosmetic products and are usable over a wide range of pH values. In general, their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

[0556] If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

[0557] If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

[0558] If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

[0559] The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in Pharmaceutical Dosage Forms, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

[0560] The RNAi agent for use in the methods of the disclosure can also be provided as micellar formulations. "Micelles" are defined herein as a particular type of molecular assembly in which amphipathic molecules are arranged in a spherical structure such that all the hydrophobic portions of the molecules are directed inward, leaving the hydrophilic portions in contact with the surrounding aqueous phase. The converse arrangement exists if the environment is hydrophobic.

[0561] A mixed micellar formulation suitable for delivery through transdermal membranes may be prepared by mixing an aqueous solution of the siRNA composition, an alkali metal C_8 to C_{22} alkyl sulphate, and a micelle forming compounds. Exemplary micelle forming compounds include lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof. The micelle forming compounds may be added at the same time or after addition of the alkali metal alkyl sulphate. Mixed micelles will form with substantially any kind of mixing of the ingredients but vigorous mixing in order to provide smaller size micelles.

[0562] In one method a first micellar composition is prepared which contains the siRNA composition and at least the alkali metal alkyl sulphate. The first micellar composition is then mixed with at least three micelle forming compounds to form a mixed micellar composition. In another method, the micellar composition is prepared by mixing the siRNA composition, the alkali metal alkyl sulphate and at least one of the micelle forming compounds, followed by addition of the remaining micelle forming compounds, with vigorous mixing.

[0563] Phenol or m-cresol may be added to the mixed micellar composition to stabilize the formulation and protect against bacterial growth. Alternatively, phenol or m-cresol may be added with the micelle forming ingredients. An isotonic agent such as glycerin may also be added after formation of the mixed micellar composition.

[0564] For delivery of the micellar formulation as a spray, the formulation can be put into an aerosol dispenser and the dispenser is charged with a propellant. The propellant, which is under pressure, is in liquid form in the dispenser. The ratios of the ingredients are adjusted so that the aqueous and propellant phases become one, *i.e.,* there is one phase. If there are two phases, it is necessary to shake the dispenser prior to dispensing a portion of the contents, *e.g.,* through a metered valve. The dispensed dose of pharmaceutical agent is propelled from the metered valve in a fine spray.

[0565] Propellants may include hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl ether. In certain embodiments, HFA 134a (1,1,1,2 tetrafluoroethane) may be used.

[0566] The specific concentrations of the essential ingredients can be determined by relatively straightforward experimentation. For absorption through the oral cavities, it is often desirable to increase, *e.g.,* at least double or triple, the dosage for through injection or administration through the gastrointestinal tract.

B. Lipid particles

[0567] RNAi agents, *e.g.,* dsRNAs of in the disclosure may be fully encapsulated in a lipid formulation, *e.g.,* a LNP, or other nucleic acid-lipid particle.

[0568] As used herein, the term "LNP" refers to a stable nucleic acid-lipid particle. LNPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (*e.g.*, a PEG-lipid conjugate). LNPs are extremely useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous (i.v.) injection and accumulate at distal sites (*e.g.*, sites physically separated from the administration site). LNPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in WO 00/03683. The particles of the present disclosure typically have a mean diameter of about 50 nm to about 150 nm, more typically about 60 nm to about 130 nm, more typically about 70 nm to about 110 nm, most typically about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid- lipid particles of the present disclosure are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, *e.g.*, U.S. Patent Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; United States Patent publication No. 2010/0324120 and WO 96/40964.

[0569] In one embodiment, the lipid to drug ratio (mass/mass ratio) (*e.g.*, lipid to dsRNA ratio) will be in the range of from about 1:1 to about 50:1, from about 1:1 to about 25:1, from about 3:1 to about 15:1, from about 4:1 to about 10:1, from about 5:1 to about 9:1, or about 6:1 to about 9:1. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

[0570] Certain specific LNP formulations for delivery of RNAi agents have been described in the art, including, *e.g.*, "LNP01" formulations as described in, *e.g.*, WO 2008/042973, which is hereby incorporated by reference.

[0571] Additional exemplary lipid-dsRNA formulations are identified in the table below.

	Ionizable/Cationic Lipid	**cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio**
SNALP-1	l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA ~ 7:1
2-XTC	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DPPC/Cholesterol/PEG-cDMA 57.1/7.1/34.4/1.4 lipid:siRNA ~ 7:1

LNP05	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 6:1
LNP06	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 11:1
LNP07	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 6:1
LNP08	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 11:1
LNP09	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP10	(3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100)	ALN100/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP11	(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3)	MC-3/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP12	1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyl)didodecan-2-ol (Tech G1)	Tech G1/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP13	XTC	XTC/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 33:1
LNP14	MC3	MC3/DSPC/Chol/PEG-DMG 40/15/40/5 Lipid:siRNA: 11:1
LNP15	MC3	MC3/DSPC/Chol/PEG-DSG/GalNAc-PEG-DSG 50/10/35/4.5/0.5 Lipid:siRNA: 11:1

LNP16	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP17	MC3	MC3/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP18	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 12:1
LNP19	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/35/5 Lipid:siRNA: 8:1
LNP20	MC3	MC3/DSPC/Chol/PEG-DPG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP21	C12-200	C12-200/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP22	XTC	XTC/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1

DSPC: distearoylphosphatidylcholine

DPPC: dipalmitoylphosphatidylcholine

PEG-DMG: PEG-didimyristoyl glycerol (C14-PEG, or PEG-C14) (PEG with avg mol wt of 2000)

PEG-DSG: PEG-distyryl glycerol (C18-PEG, or PEG-C18) (PEG with avg mol wt of 2000)

PEG-cDMA: PEG-carbamoyl-1,2-dimyristyloxypropylamine (PEG with avg mol wt of 2000)

[0572] SNALP (l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in WO 2009/127060, which is hereby incorporated by reference.

[0573] XTC comprising formulations are described in WO 2010/088537, the entire contents of which are hereby incorporated herein by reference.

[0574] MC3 comprising formulations are described, *e.g.*, in United States Patent Publication No. 2010/0324120, the entire contents of which are hereby incorporated by reference.

[0575] ALNY-100 comprising formulations are described in WO 2010/054406, the entire contents of which are hereby incorporated herein by reference.

[0576] C12-200 comprising formulations are described in WO 2010/129709, the entire contents of which are hereby incorporated herein by reference.

[0577] Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules,

gel capsules, sachets, tablets or minitablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders can be desirable. In some embodiments, oral formulations are those in which dsRNAs featured in the disclosure are administered in conjunction with one or more penetration enhancer surfactants and chelators. Suitable surfactants include fatty acids or esters or salts thereof, bile acids or salts thereof. Suitable bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (*e.g.,* sodium). In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. DsRNAs featured in the disclosure can be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. DsRNA complexing agents include poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pollulans, celluloses and starches. Suitable complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylaminomethylethylene P(TDAE), polyaminostyrene (*e.g.,* p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcynaoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for dsRNAs and their preparation are described in detail in U.S. Patent 6,887,906, U.S. 2003/0027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference.

[0578] Compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intraventricular or intrahepatic administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

[0579] Pharmaceutical compositions of the present disclosure include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions can be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Particularly preferred are formulations that target the brain when treating HTT-associated diseases or disorders.

[0580] The pharmaceutical formulations of the present disclosure, which can conveniently be presented in unit dosage form, can be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0581] The compositions of the present disclosure can be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present disclosure can also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions can further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol or dextran. The suspension can also contain stabilizers.

C. Additional Formulations

i. Emulsions

[0582] The compositions of the present disclosure can be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1μm in diameter (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions can be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions can contain additional components in addition to the dispersed phases, and the active drug which can be present as a solution in either aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants can also be present in emulsions as needed. Pharmaceutical emulsions can also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise, a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

[0583] Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion can be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that can be incorporated into either phase of the emulsion. Emulsifiers can broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

[0584] Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants can be classified into different classes based on the nature of the hydrophilic group: nonionic, anionic, cationic and amphoteric (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

[0585] Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

[0586] A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives and antioxidants (Block, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc.,

New York, N.Y., volume 1, p. 335; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

[0587] Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed-phase droplets and by increasing the viscosity of the external phase.

[0588] Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols and phosphatides that can readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used can be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

[0589] The application of emulsion formulations *via* dermatological, oral and parenteral routes and methods for their manufacture have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Emulsion formulations for oral delivery have been very widely used because of ease of formulation, as well as efficacy from an absorption and bioavailability standpoint (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Mineral-oil base laxatives, oil-soluble vitamins and high fat nutritive preparations are among the materials that have commonly been administered orally as o/w emulsions.

ii. Microemulsions

[0590] In one embodiment of the present disclosure, the compositions of RNAi agents and nucleic acids are formulated as microemulsions. A microemulsion can be defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY;

Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically, microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotropically clear dispersions of two immiscible liquids that are stabilized by interfacial films of surface-active molecules (Leung and Shah, in: Controlled Release of Drugs: Polymers and Aggregate Systems, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215). Microemulsions commonly are prepared *via* a combination of three to five components that include oil, water, surfactant, cosurfactant and electrolyte. Whether the microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used, and on the structure and geometric packing of the polar heads and hydrocarbon tails of the surfactant molecules (Schott, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 271).

[0591] The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Block, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

[0592] Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions can, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase can typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase can include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

[0593] Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both o/w and w/o) have been proposed to enhance the oral bioavailability of drugs, including peptides (see *e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, Pharmaceutical Research, 1994, 11, 1385-1390; Ritschel, Meth. Find. Exp. Clin. Pharmacol., 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (see *e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, Pharmaceutical Research, 1994, 11, 1385; Ho *et al.*, J. Pharm. Sci., 1996, 85, 138-143). Often microemulsions can form spontaneously when their components are brought together at ambient temperature. This can be particularly advantageous when formulating thermolabile drugs, peptides or RNAi agents. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present disclosure will facilitate the increased systemic absorption of RNAi agents and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of RNAi agents and nucleic acids.

[0594] Microemulsions of the present disclosure can also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the RNAi agents and nucleic acids of the present disclosure. Penetration enhancers used in the microemulsions of the present disclosure can be classified as belonging to one of five broad categories--surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p. 92). Each of these classes has been discussed above.

iii. Microparticles

[0595] An RNAi agent of the disclosure may be incorporated into a particle, *e.g.*, a microparticle. Microparticles can be produced by spray-drying, but may also be produced by other methods including lyophilization, evaporation, fluid bed drying, vacuum drying, or a combination of these techniques.

iv. Penetration Enhancers

[0596] In one embodiment, the present disclosure employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly RNAi agents, to the skin of animals. Most drugs are present in solution in both ionized and nonionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs can cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

[0597] Penetration enhancers can be classified as belonging to one of five broad categories, *i.e.*, surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92). Each of the above mentioned classes of penetration enhancers are described below in greater detail.

[0598] Surfactants (or "surface-active agents") are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of RNAi agents through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92); and perfluorochemical emulsions, such as FC-43. Takahashi *et al.*, J. Pharm. Pharmacol., 1988, 40, 252).

[0599] Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein (1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C_{1-20} alkyl esters thereof (*e.g.*, methyl, isopropyl and t-butyl), and mono- and di-glycerides thereof (*i.e.*, oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, *etc.*) (see *e.g.*, Touitou, E., *et al.* Enhancement in Drug Delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; El Hariri *et al.*, J. Pharm. Pharmacol., 1992, 44, 651-654).

[0600] The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Brunton, Chapter 38 in: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., Hardman *et al.* Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. Suitable bile salts include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucholic acid (sodium glucholate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Swinyard, Chapter 39 In: Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa.,

1990, pages 782-783; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Yamamoto *et al.*, J. Pharm. Exp. Ther., 1992, 263, 25; Yamashita *et al.*, J. Pharm. Sci., 1990, 79, 579-583).

[0601] Chelating agents, as used in connection with the present disclosure, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of RNAi agents through the mucosa is enhanced. With regards to their use as penetration enhancers in the present disclosure, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, J. Chromatogr., 1993, 618, 315-339). Suitable chelating agents include but are not limited to disodium ethylenediaminetetraacetate (EDTA), citric acid, salicylates (*e.g.*, sodium salicylate, 5-methoxysalicylate and homovanilate), N-acyl derivatives of collagen, laureth-9 and N-amino acyl derivatives of beta-diketones (enamines)(see *e.g.*, Katdare, A. *et al.*, Excipient development for pharmaceutical, biotechnology, and drug delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Buur *et al.*, J. Control Rel., 1990, 14, 43-51).

[0602] As used herein, non-chelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of RNAi agents through the alimentary mucosa (see *e.g.*, Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). This class of penetration enhancers includes, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin and phenylbutazone (Yamashita *et al.*, J. Pharm. Pharmacol., 1987, 39, 621-626).

[0603] Agents that enhance uptake of RNAi agents at the cellular level can also be added to the pharmaceutical and other compositions of the present disclosure. For example, cationic lipids, such as lipofectin (Junichi *et al*, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (WO 97/30731), are also known to enhance the cellular uptake of dsRNAs.

[0604] Other agents can be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

vi. Excipients

[0605] In contrast to a carrier compound, a "pharmaceutical carrier" or "excipient" is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient can be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, *etc.*, when combined with a nucleic acid and the other components of a given

pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, *etc.*); fillers (*e.g.*, lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, *etc.*); lubricants (*e.g.*, magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, *etc.*); disintegrants (*e.g.*, starch, sodium starch glycolate, *etc.*); and wetting agents (*e.g.*, sodium lauryl sulphate, *etc*).

[0606] Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present disclosure. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

[0607] Formulations for topical administration of nucleic acids can include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions can also contain buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can be used.

[0608] Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

vii. Other Components

[0609] The compositions of the present disclosure can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or can contain additional materials useful in physically formulating various dosage forms of the compositions of the present disclosure, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present disclosure. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

[0610] Aqueous suspensions can contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol or dextran. The suspension can also contain stabilizers.

[0611] In some embodiments, pharmaceutical compositions featured in the disclosure include (a) one or more RNAi agents and (b) one or more agents which function by a non-RNAi mechanism and which are useful in treating an HTT-associated disorder. Examples of such agents include, but are not lmited to, monoamine inhibitors, reserpine, anticonvulsants, antipsychotic agents, and antidepressants.

[0612] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds that exhibit high therapeutic indices are preferred.

[0613] The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured herein in the disclosure lies generally within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods featured in the disclosure, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target sequence (*e.g.*, achieving a decreased concentration of the polypeptide) that includes the IC_{50} (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

[0614] In addition to their administration, as discussed above, the RNAi agents featured in the disclosure can be administered in combination with other known agents effective in treatment of pathological processes mediated by nucleotide repeat expression. In any event, the administering physician can adjust the amount and timing of RNAi agent administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

VII. Kits

[0615] In certain aspects, the instant disclosure provides kits that include a suitable container containing a pharmaceutical formulation of a siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, (*e.g.*, a precursor, *e.g.*, a larger siRNA compound which can be processed into a ssiRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, or precursor thereof).

[0616] Such kits include one or more dsRNA agent(s) and instructions for use, *e.g.*, instructions for administering a prophylactically or therapeutically effective amount of a dsRNA agent(s). The dsRNA agent may be in a vial or a pre-filled syringe. The kits may optionally further comprise means for administering the dsRNA agent (*e.g.*, an injection device, such as a pre-filled syringe), or means for measuring the inhibition of C3 (*e.g.,* means for measuring the inhibition of HTT mRNA, HTT

protein, and/or HTT activity). Such means for measuring the inhibition of HTT may comprise a means for obtaining a sample from a subject, such as, *e.g.*, a CSF and/or plasma sample. The kits of the invention may optionally further comprise means for determining the therapeutically effective or prophylactically effective amount.

[0617] In certain embodiments the individual components of the pharmaceutical formulation may be provided in one container, *e.g.*, a vial or a pre-filled syringe. Alternatively, it may be desirable to provide the components of the pharmaceutical formulation separately in two or more containers, *e.g.*, one container for a siRNA compound preparation, and at least another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

VII. Methods for Inhibiting HTT Expression

[0618] The present disclosure also provides methods of inhibiting expression of an HTT gene in a cell. The methods include contacting a cell with an RNAi agent, *e.g.*, double stranded RNAi agent, or a pharmaceutical compostion comprising a dsRNA agent of the invention, in an amount effective to inhibit expression of HTT in the cell, thereby inhibiting expression of HTT in the cell. In certain embodiments of the disclosure, HTT is inhibited preferentially in CNS (*e.g.*, brain) cells.

[0619] Contacting of a cell with an RNAi agent, *e.g.*, a double stranded RNAi agent, may be done *in vitro* or *in vivo*. Contacting a cell *in vivo* with the RNAi agent includes contacting a cell or group of cells within a subject, *e.g.*, a human subject, with the RNAi agent. Combinations of *in vitro* and *in vivo* methods of contacting a cell are also possible.

[0620] Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished *via* a targeting ligand, including any ligand described herein or known in the art. In some embodiments, the targeting ligand is a carbohydrate moiety, *e.g.*, a GalNAc ligand, or any other ligand that directs the RNAi agent to a site of interest.

[0621] The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating," "suppressing" and other similar terms, and includes any level of inhibition. In certain embodiments, a level of inhibition, *e.g.*, for an RNAi agent of the instant disclosure, can be assessed in cell culture conditions, *e.g.*, wherein cells in cell culture are transfected *via* Lipofectamine™-mediated transfection at a concentration in the vicinity of a cell of 10 nM or less, 1 nM or less, *etc*. Knockdown of a given RNAi agent can be determined *via* comparison of pre-treated levels in cell culture versus post-treated levels in cell culture, optionally also comparing against cells treated in parallel with a scrambled or other form of control RNAi agent. Knockdown in cell culture of, *e.g.*, preferably 50% or more, can thereby be identified as indicative of "inhibiting" or "reducing", "downregulating" or "suppressing", *etc*. having occurred. It is expressly contemplated that assessment of targeted mRNA or encoded protein levels (and therefore an extent of "inhibiting", *etc*. caused by an

RNAi agent of the disclosure) can also be assessed in *in vivo* systems for the RNAi agents of the instant disclosure, under properly controlled conditions as described in the art.

[0622] The phrase "inhibiting expression of an HTT gene" or "inhibiting expression of HTT," as used herein, includes inhibition of expression of any HTT gene (such as, *e.g.*, a mouse HTT gene, a rat HTT gene, a monkey HTT gene, or a human HTT gene) as well as variants or mutants of an HTT gene that encode an HTT protein. Thus, the HTT gene may be a wild-type HTT gene, a mutant HTT gene, or a transgenic HTT gene in the context of a genetically manipulated cell, group of cells, or organism.

[0623] "Inhibiting expression of an HTT gene" includes any level of inhibition of an HTT gene, *e.g.*, at least partial suppression of the expression of an HTT gene, such as an inhibition by at least 20%. In certain embodiments, inhibition is by at least 30%, at least 40%, preferably at least 50%, at least about 60%, at least 70%, at least about 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%; or to below the level of detection of the assay method.

[0624] The expression of an HTT gene may be assessed based on the level of any variable associated with HTT gene expression, *e.g.*, HTT mRNA level or HTT protein level, or, for example, the level of HTT expanded protein.

[0625] Inhibition may be assessed by a decrease in an absolute or relative level of one or more of these variables compared with a control level. The control level may be any type of control level that is utilized in the art, *e.g.*, a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, *e.g.*, buffer only control or inactive agent control).

[0626] In some embodiments of the methods of the disclosure, expression of an HTT gene is inhibited by at least 20%, 30%, 40%, preferably at least 50%, 60%, 70%, 80%, 85%, 90%, or 95%, or to below the level of detection of the assay. In certain embodiments, the methods include a clinically relevant inhibition of expression of HTT, *e.g.* as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of HTT.

[0627] Inhibition of the expression of an HTT gene may be manifested by a reduction of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which an HTT gene is transcribed and which has or have been treated (*e.g.*, by contacting the cell or cells with an RNAi agent of the disclosure, or by administering an RNAi agent of the disclosure to a subject in which the cells are or were present) such that the expression of an HTT gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s) not treated with an RNAi agent or not treated with an RNAi agent targeted to the gene of interest). The degree of inhibition may be expressed in terms of:

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} \bullet 100\%$$

[0628] In other embodiments, inhibition of the expression of an HTT gene may be assessed in terms of a reduction of a parameter that is functionally linked to an HTT gene expression, *e.g.*, HTT protein expression. HTT gene silencing may be determined in any cell expressing HTT, either endogenous or heterologous from an expression construct, and by any assay known in the art.

[0629] Inhibition of the expression of an HTT protein may be manifested by a reduction in the level of the HTT protein that is expressed by a cell or group of cells (*e.g.*, the level of protein expressed in a sample derived from a subject). As explained above, for the assessment of mRNA suppression, the inhibiton of protein expression levels in a treated cell or group of cells may similarly be expressed as a percentage of the level of protein in a control cell or group of cells.

[0630] A control cell or group of cells that may be used to assess the inhibition of the expression of an HTT gene includes a cell or group of cells that has not yet been contacted with an RNAi agent of the disclosure. For example, the control cell or group of cells may be derived from an individual subject (*e.g.*, a human or animal subject) prior to treatment of the subject with an RNAi agent.

[0631] The level of HTT mRNA that is expressed by a cell or group of cells may be determined using any method known in the art for assessing mRNA expression. In one embodiment, the level of expression of HTT in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.,* mRNA of the HTT gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasy™ RNA preparation kits (Qiagen®) or PAXgene (PreAnalytix, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays, northern blotting, *in situ* hybridization, and microarray analysis. Circulating HTT mRNA may be detected using methods the described in WO2012/177906, the entire contents of which are hereby incorporated herein by reference.

[0632] In some embodiments, the level of expression of HTT is determined using a nucleic acid probe. The term "probe", as used herein, refers to any molecule that is capable of selectively binding to a specific HTT nucleic acid or protein, or fragment thereof. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

[0633] Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or northern analyses, polymerase chain reaction (PCR) analyses and probe arrays. One method for the determination of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to HTT mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix® gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of HTT mRNA.

[0634] An alternative method for determining the level of expression of HTT in a sample involves the process of nucleic acid amplification or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, *e.g.*, by RT-PCR (the experimental embodiment set forth in Mullis, 1987, US Patent No. 4,683,202), ligase chain reaction (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88:189-193), self sustained sequence replication (Guatelli *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.* (1988) *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, US Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the disclosure, the level of expression of HTT is determined by quantitative fluorogenic RT-PCR (*i.e.*, the TaqMan™ System), by a Dual-Glo® Luciferase assay, or by other art-recognized method for measurement of HTT expression or mRNA level.

[0635] The expression level of HTT mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See US Patent Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by reference. The determination of HTT expression level may also comprise using nucleic acid probes in solution.

[0636] In some embodiments, the level of mRNA expression is assessed using branched DNA (bDNA) assays or real time PCR (qPCR). The use of this PCR method is described and exemplified in the Examples presented herein. Such methods can also be used for the detection of HTT nucleic acids.

[0637] The level of HTT protein expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, and the like. Such assays can also be used for the detection of proteins indicative of the presence or replication of HTT proteins.

[0638] In some embodiments, the efficacy of the methods of the disclosure in the treatment of an HTT-related disease is assessed by a decrease in HTT mRNA level (*e.g*, by assessment of a CSF sample and/or plasma sample for HTT level, by brain biopsy, or otherwise).

[0639] In some embodiments of the methods of the disclosure, the RNAi agent is administered to a subject such that the RNAi agent is delivered to a specific site within the subject. The inhibition of expression of HTT may be assessed using measurements of the level or change in the level of HTT mRNA or HTT protein in a sample derived from a specific site within the subject, *e.g.*, CNS cells. In

certain embodiments, the methods include a clinically relevant inhibition of expression of HTT, *e.g.* as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of HTT, suchas, for example, stabilization or inhibition of caudate atrophy (*e.g.,* as assessed by volumetric MRI (vMRI)), a stabilization or reduction in neurofilament light chain (Nfl) levels in a CSF sample from a subject, a reduction in mutant HTT mRNA or a cleaved mutant HTT protein, *e.g.,* one or both of full-length mutant HTT mRNA or protein and a cleaved mutant HTT mRNA or protein, and a stabilization or improvement in Unified Huntington's Disease Rating Scale (UHDRS) score.

[0640] As used herein, the terms detecting or determining a level of an analyte are understood to mean performing the steps to determine if a material, *e.g.*, protein, RNA, is present. As used herein, methods of detecting or determining include detection or determination of an analyte level that is below the level of detection for the method used.

IX. Methods of Treating or Preventing HTT-Associated Diseases

[0641] The present disclosure also provides methods of using an RNAi agent of the disclosure to reduce or inhibit HTT expression in a cell. The methods include contacting the cell with a dsRNA of the disclosure, or a pharmaceutical composition of the disclosure, and maintaining the cell for a time sufficient to obtain degradation of the mRNA transcript of an HTT gene, thereby inhibiting expression of the HTT gene in the cell. Reduction in gene expression can be assessed by any methods known in the art. For example, a reduction in the expression of HTT may be determined by determining the mRNA expression level of HTT using methods routine to one of ordinary skill in the art, *e.g.,* northern blotting, qRT-PCR; by determining the protein level of HTT using methods routine to one of ordinary skill in the art, such as western blotting, immunological techniques.

[0642] In the methods of the disclosure the cell may be contacted *in vitro* or *in vivo, i.e.,* the cell may be within a subject.

[0643] A cell suitable for treatment using the methods of the disclosure may be any cell that expresses an HTT gene. A cell suitable for use in the methods of the disclosure may be a mammalian cell, *e.g.,* a primate cell (such as a human cell or a non-human primate cell, *e.g.*, a monkey cell or a chimpanzee cell), a non-primate cell (such as a a rat cell, or a mouse cell). In one embodiment, the cell is a human cell, *e.g.,* a human CNS cell.

[0644] HTT expression is inhibited in the cell by at least about 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or about 100%, *i.e.*, to below the level of detection. In preferred embodiments, HTT expression is inhibited by at least 50 %.

[0645] The *in vivo* methods of the disclosure may include administering to a subject a composition containing an RNAi agent, where the RNAi agent includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the HTT gene of the mammal to be treated.

[0646] When the organism to be treated is a mammal such as a human, the composition can be administered by any means known in the art including, but not limited to oral, intraperitoneal, or parenteral routes, including intracranial (*e.g.*, intraventricular, intraparenchymal, and intrathecal),

intravenous, intramuscular, intravitreal, subcutaneous, transdermal, airway (aerosol), nasal, rectal, and topical (including buccal and sublingual) administration. In certain embodiments, the compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection. In certain embodiments, the compositions are administered by intrathecal injection.

[0647] In some embodiments, the administration is *via* a depot injection. A depot injection may release the RNAi agent in a consistent way over a prolonged time period. Thus, a depot injection may reduce the frequency of dosing needed to obtain a desired effect, *e.g.*, a desired inhibition of HTT, or a therapeutic or prophylactic effect. A depot injection may also provide more consistent serum concentrations. Depot injections may include subcutaneous injections or intramuscular injections. In preferred embodiments, the depot injection is a subcutaneous injection.

[0648] In some embodiments, the administration is *via* a pump. The pump may be an external pump or a surgically implanted pump. In certain embodiments, the pump is a subcutaneously implanted osmotic pump. In other embodiments, the pump is an infusion pump. An infusion pump may be used for intracranial, intravenous, subcutaneous, arterial, or epidural infusions. In preferred embodiments, the infusion pump is a subcutaneous infusion pump. In other embodiments, the pump is a surgically implanted pump that delivers the RNAi agent to the CNS.

[0649] The mode of administration may be chosen based upon whether local or systemic treatment is desired and based upon the area to be treated. The route and site of administration may be chosen to enhance targeting.

[0650] In one aspect, the present disclosure also provides methods for inhibiting the expression of an HTT gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets an HTT gene in a cell of the mammal and maintaining the mammal for a time sufficient to obtain degradation of the mRNA transcript of the HTT gene, thereby inhibiting expression of the HTT gene in the cell. Reduction in gene expression can be assessed by any methods known it the art and by methods, *e.g.* qRT-PCR, described herein. In some embodiments, the dsRNA is present in a composition, such as a pharmaceutical composition.

[0651] Reduction in protein production can be assessed by any methods known it the art and by methods, *e.g.* ELISA, described herein. In one embodiment, a CNS biopsy sample or a cerebrospinal fluid (CSF) sample serves as the tissue material for monitoring the reduction in HTT gene or protein expression (or of a proxy therefore).

[0652] The present disclosure further provides methods of treatment of a subject in need thereof. The treatment methods of the disclosure include administering an RNAi agent of the disclosure to a subject, *e.g.*, a subject that would benefit from inhibition of HTT expression, in a therapeutically effective amount of an RNAi agent targeting an HTT gene or a pharmaceutical composition comprising an RNAi agent targeting aHTT gene.

[0653] In addition, the present disclosure provides methods of preventing, treating or inhibiting the progression of an HTT-associated disease or disorder (*e.g.*, Huntington's disease), in a subject, such as the progression of an HTT-associated disease or disorder. The methods include administering

to the subject a therapeutically effective amount of any of the RNAi agent, *e.g.,* dsRNA agents, or the pharmaceutical composition provided herein, thereby preventing, treating or inhibiting the progression of an HTT-associated disease or disorder in the subject.

[0654] An RNAi agent of the disclosure may be administered as a "free RNAi agent." A free RNAi agent is administered in the absence of a pharmaceutical composition. The naked RNAi agent may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution containing the RNAi agent can be adjusted such that it is suitable for administering to a subject.

[0655] Alternatively, an RNAi agent of the disclosure may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

[0656] Subjects that would benefit from a reduction or inhibition of HTT gene expression are those having an HTT-associated disease, *e.g.,* Huntington's disease.

[0657] The disclosure further provides methods for the use of an RNAi agent or a pharmaceutical composition thereof, *e.g.*, for treating a subject that would benefit from reduction or inhibition of HTT expression, *e.g.,* a subject having an HTT-associated disorder, in combination with other pharmaceuticals or other therapeutic methods, *e.g.*, with known pharmaceuticals or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders. For example, in certain embodiments, an RNAi agent targeting HTT is administered in combination with, *e.g.*, an agent useful in treating an HTT-associated disorder as described elsewhere herein or as otherwise known in the art. For example, additional agents suitable for treating a subject that would benefit from reducton in HTT expression, *e.g.,* a subject having an HTT-associated disorder, may include agents currently used to treat symptoms of HTT. The RNAi agent and additional therapeutic agents may be administered at the same time or in the same combination, *e.g.*, intrathecally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times or by another method known in the art or described herein.

[0658] Exemplary additional therapeutics include, for example, a monoamine inhibitor, *e.g.,*tetrabenazine (Xenazine), deutetrabenazine (Austedo), and reserpine, an anticonvulsant, *e.g.,*valproic acid (Depakote, Depakene, Depacon), and clonazepam (Klonopin), an antipsychotic agent, *e.g.,* risperidone (Risperdal), and haloperidol (Haldol), and an antidepressant, *e.g.,* paroxetine (Paxil).

[0659] In one embodiment, the method includes administering a composition featured herein such that expression of the target HTT gene is decreased, for at least one month. In preferred embodiments, expression is decreased for at least 2 months, 3 months, or 6 months.

[0660] Preferably, the RNAi agents useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target HTT gene. Compositions and methods for inhibiting the expression of these genes using RNAi agents can be prepared and performed as described herein.

[0661] Administration of the dsRNA according to the methods of the disclosure may result in a reduction of the severity, signs, symptoms, or markers of such diseases or disorders in a patient with an HTT-associated disorder. By "reduction" in this context is meant a statistically significant or clinically significant decrease in such level. The reduction can be, for example, at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or about 100%.

[0662] Efficacy of treatment or prevention of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. For example, efficacy of treatment of an HTT-associated disorder may be assessed, for example, by periodic monitoring of a subject's. Comparisons of the later readings with the initial readings provide a physician an indication of whether the treatment is effective. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of an RNAi agent targeting HTT or pharmaceutical composition thereof, "effective against" an HTT-associated disorder indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating HTT-associated disorders and the related causes.

[0663] A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given RNAi agent drug or formulation of that drug can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant reduction in a marker or symptom is observed.

[0664] Alternatively, the efficacy can be measured by a reduction in the severity of disease as determined by one skilled in the art of diagnosis based on a clinically accepted disease severity grading scale. Any positive change resulting in *e.g.*, lessening of severity of disease measured using the appropriate scale, represents adequate treatment using an RNAi agent or RNAi agent formulation as described herein.

[0665] Subjects can be administered a therapeutic amount of dsRNA, such as about 0.01 mg/kg to about 200 mg/kg.

[0666] The RNAi agent can be administered intrathecally, *via* intravitreal injection, or by intravenous infusion over a period of time, on a regular basis. In certain embodiments, after an initial

treatment regimen, the treatments can be administered on a less frequent basis. Administration of the RNAi agent can reduce HTT levels, *e.g.*, in a cell, tissue, blood, CSF sample or other compartment of the patient by at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70,% 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or at least about 99% or more. In a preferred embodiment, administration of the RNAi agent can reduce HTT levels, *e.g.*, in a cell, tissue, blood, CSF sample or other compartment of the patient by at least 50%.

[0667] Before administration of a full dose of the RNAi agent, patients can be administered a smaller dose, such as a 5% infusion reaction, and monitored for adverse effects, such as an allergic reaction. In another example, the patient can be monitored for unwanted immunostimulatory effects, such as increased cytokine (*e.g.*, TNF-alpha or INF-alpha) levels.

[0668] Alternatively, the RNAi agent can be administered subcutaneously, *i.e.*, by subcutaneous injection. One or more injections may be used to deliver the desired, *e.g.*, monthly dose of RNAi agent to a subject. The injections may be repeated over a period of time. The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimine may include administration of a therapeutic amount of RNAi agent on a regular basis, such as monthly or extending to once a quarter, twice per year, once per year. In certain embodiments, the RNAi agent is administered about once per month to about once per quarter (*i.e.*, about once every three months).

[0669] 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 RNAi agents and methods featured in the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

EXAMPLES

Example 1. RNAi Agent Design, Synthesis, Selection, and *In vitro* Evaluation

[0670] This Example describes methods for the design, synthesis, selection, and *in vitro* evaluation of HTT RNAi agents.

Source of reagents

[0671] Where the source of a reagent is not specifically given herein, such reagent can be obtained from any supplier of reagents for molecular biology at a quality/purity standard for application in molecular biology.

Bioinformatics

[0672] siRNAs targeting intron 1 of the human huntingtin transcript (HTT; NCBI Reference Sequence: NG_009378.1 (Homo sapiens huntingtin (HTT), RefSeqGene (LRG_763) on chromosome 4); or NCBI Reference Sequence: NC_000004.12 (Homo sapiens chromosome 4, GRCh38.p13 Primary Assembly)) were designed using custom R and Python scripts.

[0673] A detailed list of the unmodified HTT sense and antisense strand nucleotide sequences are shown in Table 2. A detailed list of the modified HTT sense and antisense strand nucleotide sequences are shown in Table 3.

[0674] It is to be understood that, throughout the application, a duplex name without a decimal is equivalent to a duplex name with a decimal which merely references the batch number of the duplex. For example, AD-564727 is equivalent to AD-564727.1.

Cell culture and transfections

[0675] Cos7 were cultured according to standard methods and were transfected with the iRNA duplex of interest.

[0676] Briefly, cells were transfected by adding 7.5 µL of Opti-MEM plus 0.1 µL of RNAiMAX per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 2.5 µL of each siRNA duplex to an individual well in a 384-well plate. The cells were then incubated at room temperature for 15 minutes. Forty µL of MEDIA containing ~1.5 x10^4 cells was then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed in A549 cells at 10nM. Single dose experiments were performed in at 10 nM, 3 nM, 1 nM, and 0.1nM.

In vitro Dual-Luciferase and Endogenous Screening Assays

[0677] Cos7 cells were transfected by adding 50 µL of siRNA duplexes and 75 ng of a plasmid, comprising human HTT target sequence, nucleotides 5001 – 6271 of NG_009378.1, per well along with 100 µL of Opti-MEM plus 0.5 µL of Lipofectamine 2000 per well (Invitrogen, Carlsbad CA. cat # 13778-150) and then incubated at room temperature for 15 minutes. The mixture was then added to the cells which are re-suspended in 35 µL of fresh complete media. The transfected cells were incubated at 37°C in an atmosphere of 5% CO2. Single-dose experiments were performed at 10 nM or 50 nM.

[0678] Twenty-four hours after the siRNAs and psiCHECK2 plasmid are transfected; Firefly (transfection control) and Renilla (fused to HTT target sequence comprising nucleotides 5001 – 6271 of NG_009378.1) luciferase were measured. First, media was removed from cells. Then Firefly luciferase activity was measured by adding 75 µL of Dual-Glo® Luciferase Reagent equal to the culture medium volume to each well and mix. The mixture was incubated at room temperature for 30 minutes before luminescense (500nm) was measured on a Spectramax (Molecular Devices) to detect the Firefly luciferase signal. Renilla luciferase activity was measured by adding 75 µL of room temperature of Dual-Glo® Stop & Glo® Reagent to each well and the plates were incubated for 10-15 minutes before luminescence was again measured to determine the Renilla luciferase signal. The

Dual-Glo® Stop & Glo® Reagent quenches the firefly luciferase signal and sustained luminescence for the Renilla luciferase reaction. siRNA activity was determined by normalizing the Renilla (MUC5B) signal to the Firefly (control) signal within each well. The magnitude of siRNA activity was then assessed relative to cells that were transfected with the same vector but were not treated with siRNA or were treated with a non-targeting siRNA. All transfections were done with n=4.

Total RNA isolation using DYNABEADS mRNA Isolation Kit

[0679] RNA is isolated using an automated protocol on a BioTek-EL406 platform using DYNABEADs (Invitrogen, cat#61012). Briefly, 70 µL of Lysis/Binding Buffer and 10 µL of lysis buffer containing 3 µL of magnetic beads is added to the plate with cells. Plates are incubated on an electromagnetic shaker for 10 minutes at room temperature and then magnetic beads are captured and the supernatant was removed. Bead-bound RNA are then washed 2 times with 150 µL Wash Buffer A and once with Wash Buffer B. Beads are then washed with 150 µL Elution Buffer, re-captured and supernatant removed.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813)

[0680] Ten µL of a master mix containing 1 µL 10X Buffer, 0.4 µL 25X dNTPs, 1 µL 10x Random primers, 0.5 µL Reverse Transcriptase, 0.5 µL RNase inhibitor and 6.6 µL of H_2O per reaction is added to RNA isolated above. Plates are sealed, mixed, and incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by 2 hour incubation at 37°C.

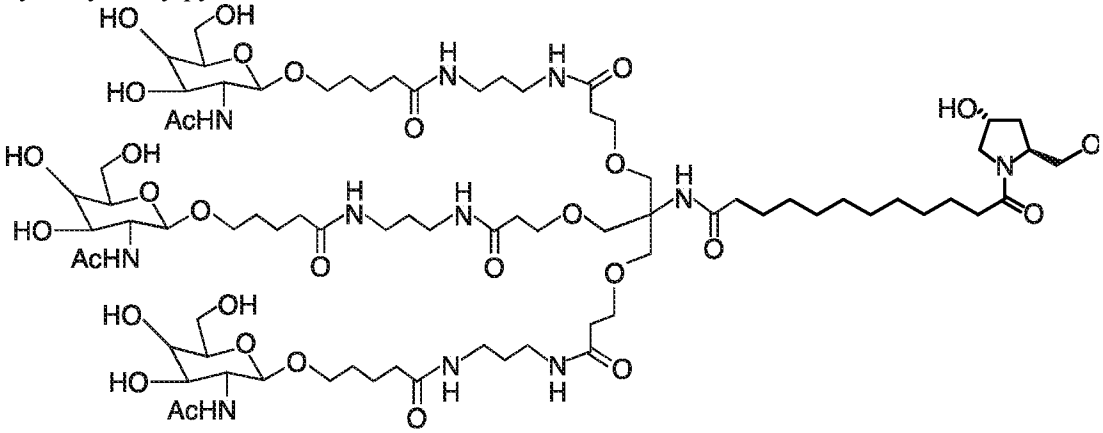
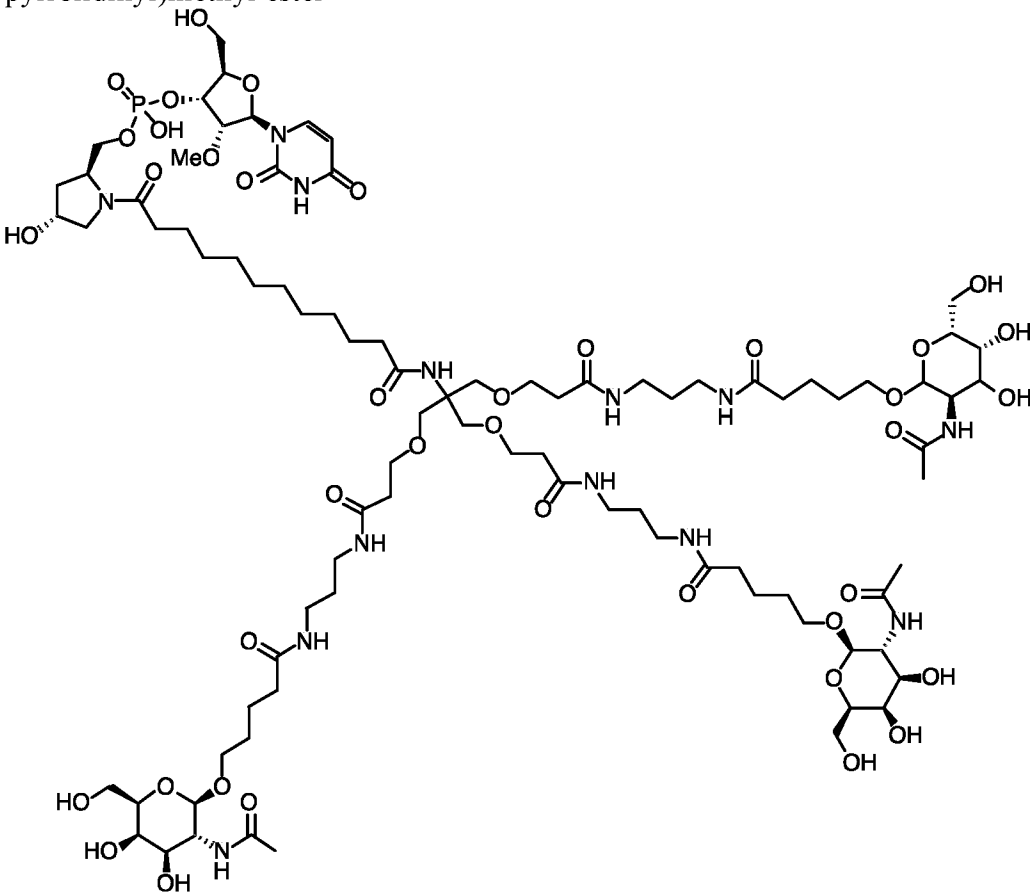
Real time PCR

[0681] Two µL of cDNA is added to a master mix containing 0.5 µL of human or mouse GAPDH TaqMan Probe (ThermoFisher cat 4352934E or 4351309) and 0.5 µL of appropriate HTT probe (commercially available, *e.g.*, from Thermo Fisher) and 5 µL Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR is done in a LightCycler480 Real Time PCR system (Roche). Each duplex is tested with N=4 and data are normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data are analyzed using the ΔΔCt method and normalized to assays performed with an appropriate control.

[0682] The results of the dual-luciferase assays of the agents are provided in Table 4.

Table 1. Abbreviations of nucleotide monomers used in nucleic acid sequence representation. It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds; and it is understood that when the nucleotide contains a 2'-fluoro modification, then the fluoro replaces the hydroxy at that position in the parent nucleotide (i.e., it is a 2'-deoxy-2'-fluoronucleotide). It is to be further understood that the nucleotide abbreviations in the table omit the 3'-phosphate (i.e., they are 3'-OH) when placed at the 3'-terminal position of an oligonucleotide.

Abbre*via*tion	**Nucleotide(s)**
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3`-phosphate
Abs	beta-L-adenosine-3`-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3`-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
G	guanosine-3'-phosphate
Gb	beta-L-guanosine-3`-phosphate
Gbs	beta-L-guanosine-3`-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
Us	uridine -3'-phosphorothioate
N	any nucleotide, modified or unmodified
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'- phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'- phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'- phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
s	phosphorothioate linkage

Abbreviation	Nucleotide(s)
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol Hyp-(GalNAc-alkyl)3 (2S,4R)-1-[29-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-14,14-bis[[3-[[3-[[5-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-1-oxopentyl]amino]propyl]amino]-3-oxopropoxy]methyl]-1,12,19,25-tetraoxo-16-oxa-13,20,24-triazanonacos-1-yl]-4-hydroxy-2-hydroxymethylpyrrolidine 
uL96	2'-O-methyluridine-3'-phosphate ((2S,4R)-1-[29-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-14,14-bis[[3-[[3-[[5-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-1-oxopentyl]amino]propyl]amino]-3-oxopropoxy]methyl]-1,12,19,25-tetraoxo-16-oxa-13,20,24-triazanonacos-1-yl]-4-hydroxy-2-pyrrolidinyl)methyl ester 

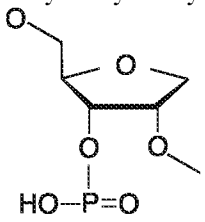
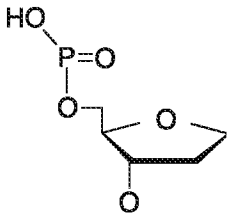
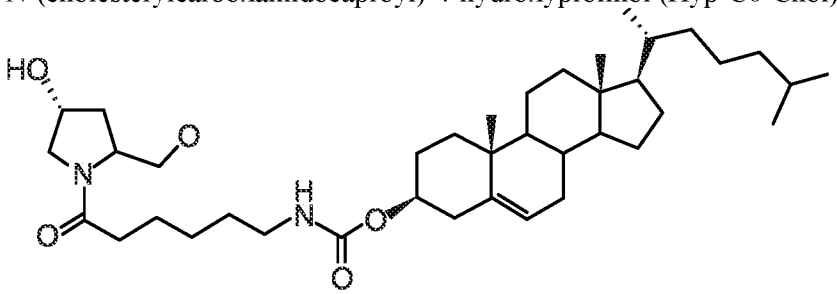
Abbreviation	Nucleotide(s)
Y34	2-hydroxymethyl-tetrahydrofurane-4-methoxy-3-phosphate (abasic 2'-OMe furanose) 
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofurane-5-phosphate) 
L10	N-(cholesterylcarboxamidocaproyl)-4-hydroxyprolinol (Hyp-C6-Chol) 
(Agn)	Adenosine-glycol nucleic acid (GNA) S-Isomer
(Cgn)	Cytidine-glycol nucleic acid (GNA) S-Isomer
(Ggn)	Guanosine-glycol nucleic acid (GNA) S-Isomer
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
P	Phosphate
VP	Vinyl-phosphonate
dA	2`-deoxyadenosine-3`-phosphate
dAs	2`-deoxyadenosine-3`-phosphorothioate
dC	2`-deoxycytidine-3`-phosphate
dCs	2`-deoxycytidine-3`-phosphorothioate
dG	2`-deoxyguanosine-3`-phosphate
dGs	2`-deoxyguanosine-3`-phosphorothioate
dT	2`-deoxythymidine-3`-phosphate
dTs	2`-deoxythymidine-3`-phosphorothioate
dU	2`-deoxyuridine
dUs	2`-deoxyuridine-3`-phosphorothioate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ahds)	2'-O-hexadecyl-adenosine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Ghds)	2'-O-hexadecyl-guanosine-3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate
(C2p)	cytidine-2`-phosphate
(G2p)	guanosine-2`-phosphate
(U2p)	uridine-2`-phosphate
(A2p)	adenosine-2`-phosphate

Table 2. Unmodified Sense and Antisense Strand Sequences of Intron 1 Targeting HTT dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640313	GGCGGUAACCCUGCAGCCUGA		3075147-3075167	5473-5493	UCAGGCTGCAGGGUUACCGCCAU		3075145-3075167	5471-5493
AD-1640314	GCAGAGACAGAGUGACCCAGA		3075195-3075215	5521-5541	UCUGGGTCACUCUGUCUCUGCGG		3075193-3075215	5519-5541
AD-1640315	AGACAGAGUGACCCAGCAACA		3075199-3075219	5525-5545	UGUUGCTGGGUCACUCUGUCUCU		3075197-3075219	5523-5545
AD-1640316	CAGAGUGACCCAGCAACCCAA		3075202-3075222	5528-5548	UUGGGUTGCUGGGUCACUCUGUC		3075200-3075222	5526-5548
AD-1640317	AGAGUGACCCAGCAACCCAGA		3075203-3075223	5529-5549	UCUGGGTUGCUGGGUCACUCUGU		3075201-3075223	5527-5549
AD-1640318	AGCAACCCAGAGCCCAUGAGA		3075213-3075233	5539-5559	UCUCAUGGGCUCUGGGUUGCUGG		3075211-3075233	5537-5559
AD-1640319	AGCAACCCAGAGCCCAUGAGA		3075213-3075233	5539-5559	UCUCAUGGGCUCUGGGUUGCUGG		3075211-3075233	5537-5559
AD-1640320	GCAACCCAGAGCCCAUGAGGA		3075214-3075234	5540-5560	UCCUCAUGGGCUCUGGGUUGCUG		3075212-3075234	5538-5560
AD-1640321	GCAACCCAGAGCCCAUGAGGA		3075214-3075234	5540-5560	UCCUCATGGGCTCUGGGUUGCUG		3075212-3075234	5538-5560
AD-1640322	CAACCCAGAGCCCAUGAGGGA		3075215-3075235	5541-5561	UCCCTCAUGGGCUCUGGGUUGCU		3075213-3075235	5539-5561
AD-1640323	CAACCCAGAGCCCAUGAGGGA		3075215-3075235	5541-5561	UCCCUCAUGGGCUCUGGGUUGCU		3075213-3075235	5539-5561
AD-1640324	CAACCCAGAGCCCAUGAGGGA		3075215-3075235	5541-5561	UCCCTCAUGGGCUCUGGGUUGCU		3075213-3075235	5539-5561
AD-1640325	ACCCAGAGCCCAUGAGGGACA		3075217-3075237	5543-5563	UGUCCCTCAUGGGCUCUGGGUUG		3075215-3075237	5541-5563
AD-1640326	CGCUCCCUCACUUGGGUCUUA		3075279-3075299	5605-5625	UAAGACCCAAGUGAGGGAGCGGG		3075277-3075299	5603-5625
AD-1640327	CGCUCCCUCACUUGGGUCUUA		3075279-3075299	5605-5625	UAAGACCCAAGTGAGGGAGCGGG		3075277-3075299	5603-5625
AD-	CUCCCUCACUUGG		3075281-	5607-5627	UGGAAGACCCAA		3075279-3075301	5605-5627

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640328	GUCUUCCA		3075301		GUGAGGGAGCG			
AD-1640329	CCCUCACUUGGGU CUUCCCUA		3075283-3075303	5609-5629	UAGGGAAGACCC AAGUGAGGGAG		3075281-3075303	5607-5629
AD-1640330	CCUCACUUGGGUC UUCCCUUA		3075284-3075304	5610-5630	UAAGGGAAGACC CAAGUGAGGGA		3075282-3075304	5608-5630
AD-1640331	CCUCACUUGGGUC UUCCCUUA		3075284-3075304	5610-5630	UAAGGGAAGACC CAAGUGAGGGA		3075282-3075304	5608-5630
AD-1640332	CCUCACUUGGGUC UUCCCUUA		3075284-3075304	5610-5630	UAAGGGAAGACC CAAGUGAGGGA		3075282-3075304	5608-5630
AD-1640333	CACUUGGGUCUUC CCUUGUCA		3075287-3075307	5613-5633	UGACAAGGGAAG ACCCAAGUGAG		3075285-3075307	5611-5633
AD-1640334	CACUUGGGUCUUC CCUUGUCA		3075287-3075307	5613-5633	UGACAAGGGAAG ACCCAAGUGAG		3075285-3075307	5611-5633
AD-1640335	ACUUGGGUCUUCC CUUGUCCA		3075288-3075308	5614-5634	UGGACAAGGGAA GACCCAAGUGA		3075286-3075308	5612-5634
AD-1640336	ACUUGGGUCUUCC CUUGUCCA		3075288-3075308	5614-5634	UGGACAAGGGAA GACCCAAGUGA		3075286-3075308	5612-5634
AD-1640337	ACUUGGGUCUUCC CUUGUCCA		3075288-3075308	5614-5634	UGGACAAGGGAA GACCCAAGUGA		3075286-3075308	5612-5634
AD-1640338	CUUGGGUCUUCCC UUGUCCUA		3075289-3075309	5615-5635	UAGGACAAGGGA AGACCCAAGUG		3075287-3075309	5613-5635
AD-1640339	CUUGGGUCUUCCC UUGUCCUA		3075289-3075309	5615-5635	UAGGACAAGGGA AGACCCAAGUG		3075287-3075309	5613-5635
AD-1640340	UGGGUCUUCCCUU GUCCUCUA		3075291-3075311	5617-5637	UAGAGGACAAGG GAAGACCCAAG		3075289-3075311	5615-5637
AD-1640341	GUCUUCCCUUGUC CUCUCGCA		3075294-3075314	5620-5640	UGCGAGAGGACA AGGGAAGACCC		3075292-3075314	5618-5640
AD-1640342	UCUUCCCUUGUCC UCUCGCGA		3075295-3075315	5621-5641	UCGCGAGAGGAC AAGGGAAGACC		3075293-3075315	5619-5641
AD-1640343	UCUUCCCUUGUCC UCUCGCGA		3075295-3075315	5621-5641	UCGCGAGAGGAC AAGGGAAGACC		3075293-3075315	5619-5641
AD-1640344	CUUCCCUUGUCCU CUCGCGAA		3075296-3075316	5622-5642	UUCGCGAGAGGA CAAGGGAAGAC		3075294-3075316	5620-5642

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640345	CUUCCCUUGUCCUCUCGCGAA		3075296-3075316	5622-5642	UUCGCGAGAGGGACAAGGGAAGAC		3075294-3075316	5620-5642
AD-1640346	UUCCCUUGUCCUCUCGCGAGA		3075297-3075317	5623-5643	UCUCGCGAGAGGACAAGGGAAGA		3075295-3075317	5621-5643
AD-1640347	UUCCCUUGUCCUCUCGCGAGA		3075297-3075317	5623-5643	UCUCGCGAGAGGACAAGGGAAGA		3075295-3075317	5621-5643
AD-1640348	UCCCUUGUCCUCUCGCGAGGA		3075298-3075318	5624-5644	UCCUCGCGAGAGGACAAGGGAAG		3075296-3075318	5622-5644
AD-1640349	UCCCUUGUCCUCUCGCGAGGA		3075298-3075318	5624-5644	UCCUCGCGAGAGGACAAGGGAAG		3075296-3075318	5622-5644
AD-1640350	CCCUUGUCCUCUCGCGAGGGA		3075299-3075319	5625-5645	UCCCUCGCGAGAGGACAAGGGAA		3075297-3075319	5623-5645
AD-1640351	CCCUUGUCCUCUCGCGAGGGA		3075299-3075319	5625-5645	UCCCTCGCGAGAGGACAAGGGAA		3075297-3075319	5623-5645
AD-1640352	CCUGUCCUGAAUUCACCGAGA		3075339-3075359	5665-5685	UCUCGGUGAAUUCAGGACAGGCC		3075337-3075359	5663-5685
AD-1640353	CCUGUCCUGAAUUCACCGAGA		3075339-3075359	5665-5685	UCUCGGTGAAUTCAGGACAGGCC		3075337-3075359	5663-5685
AD-1640354	CUGUCCUGAAUUCACCGAGGA		3075340-3075360	5666-5686	UCCUCGGUGAAUUCAGGACAGGC		3075338-3075360	5664-5686
AD-1640355	CUGUCCUGAAUUCACCGAGGA		3075340-3075360	5666-5686	UCCUCGGUGAATUCAGGACAGGC		3075338-3075360	5664-5686
AD-1640356	UGUCCUGAAUUCACCGAGGGA		3075341-3075361	5667-5687	UCCCUCGGUGAAUUCAGGACAGG		3075339-3075361	5665-5687
AD-1640357	UGUCCUGAAUUCACCGAGGGA		3075341-3075361	5667-5687	UCCCTCGGUGAAUUCAGGACAGG		3075339-3075361	5665-5687
AD-1640358	UCGCCCUUCGCAGGAUGCGAA		3075381-3075401	5707-5727	UUCGCATCCUGCGAAGGGCGAGA		3075379-3075401	5705-5727
AD-1640359	CGCCCUUCGCAGGAUGCGAAA		3075382-3075402	5708-5728	UUUCGCAUCCUGCGAAGGGCGAG		3075380-3075402	5706-5728
AD-1640360	GCCCUUCGCAGGAUGCGAAGA		3075383-3075403	5709-5729	UCUUCGCAUCCUGCGAAGGGCGA		3075381-3075403	5707-5729
AD-	GCCCUUCGCAGGA		3075383-	5709-5729	UCUUCGCAUCCTG		3075381-3075403	5707-5729

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640361	UGCGAAGA		3075403		CGAAGGGCGA			
AD-1640362	CCUUCGCAGGAUG CGAAGAGA		3075385-3075405	5711-5731	UCUCUUCGCAUCC UGCGAAGGGC		3075383-3075405	5709-5731
AD-1640363	CCUUCGCAGGAUG CGAAGAGA		3075385-3075405	5711-5731	UCUCUUCGCAUCC UGCGAAGGGC		3075383-3075405	5709-5731
AD-1640364	CUUCGCAGGAUGC GAAGAGUA		3075386-3075406	5712-5732	UACUCUUCGCAUC CUGCGAAGGG		3075384-3075406	5710-5732
AD-1640365	UUCGCAGGAUGC GAAGAGUUA		3075387-3075407	5713-5733	UAACUCUUCGCAU CCUGCGAAGG		3075385-3075407	5711-5733
AD-1640366	UCGCAGGAUGCG AAGAGUUGA		3075388-3075408	5714-5734	UCAACUCUUCGCA UCCUGCGAAG		3075386-3075408	5712-5734
AD-1640367	UCGCAGGAUGCG AAGAGUUGA		3075388-3075408	5714-5734	UCAACUCUUCGCA UCCUGCGAAG		3075386-3075408	5712-5734
AD-1640368	CGCAGGAUGCGA AGAGUUGGA		3075389-3075409	5715-5735	UCCAACUCUUCGC AUCCUGCGAA		3075387-3075409	5713-5735
AD-1640369	CGCAGGAUGCGA AGAGUUGGA		3075389-3075409	5715-5735	UCCAACUCUUCGC AUCCUGCGAA		3075387-3075409	5713-5735
AD-1640370	GCAGGAUGCGAA GAGUUGGGA		3075390-3075410	5716-5736	UCCCAACUCUUCG CAUCCUGCGA		3075388-3075410	5714-5736
AD-1640371	GCAGGAUGCGAA GAGUUGGGA		3075390-3075410	5716-5736	UCCCAACUCUUCG CAUCCUGCGA		3075388-3075410	5714-5736
AD-1640372	AUUUGCGAGAAA CCAGGGCGA		3075430-3075450	5756-5776	UCGCCCTGGUUUC UCGCAAAUAA		3075428-3075450	5754-5776
AD-1640373	AUUUGCGAGAAA CCAGGGCGA		3075430-3075450	5756-5776	UCGCCCUGGUUUC UCGCAAAUAA		3075428-3075450	5754-5776
AD-1640374	AUUUGCGAGAAA CCAGGGCGA		3075430-3075450	5756-5776	UCGCCCTGGUUTC UCGCAAAUAA		3075428-3075450	5754-5776
AD-1640375	UUUGCGAGAAAC CAGGGCGGA		3075431-3075451	5757-5777	UCCGCCCUGGUUU CUCGCAAAUA		3075429-3075451	5755-5777
AD-1640376	UUUGCGAGAAAC CAGGGCGGA		3075431-3075451	5757-5777	UCCGCCCCUGGUTU CUCGCAAAUA		3075429-3075451	5755-5777
AD-1640377	UUGCGAGAAACC AGGGCGGGA		3075432-3075452	5758-5778	UCCCGCCCCUGGUU UCUCGCAAAU		3075430-3075452	5756-5778

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640378	UUGCGAGAAACC AGGGCGGGA		3075432-3075452	5758-5778	UCCCGCCCUGGTU UCUCGCAAAU		3075430-3075452	5756-5778
AD-1640379	UAACUGCGUUGU GAAGAGAAA		3075460-3075480	5786-5806	UUUCTCTUCACAA CGCAGUUAAA		3075458-3075480	5784-5806
AD-1640380	ACUGCGUUGUGA AGAGAACUA		3075462-3075482	5788-5808	UAGUTCTCUUCAC AACGCAGUUA		3075460-3075482	5786-5808
AD-1640381	UGCGUUGUGAAG AGAACUUGA		3075464-3075484	5790-5810	UCAAGUTCUCUUC ACAACGCAGU		3075462-3075484	5788-5810
AD-1640382	UGCGUUGUGAAG AGAACUUGA		3075464-3075484	5790-5810	UCAAGUUCUCUUC ACAACGCAGU		3075462-3075484	5788-5810
AD-1640383	UGCGUUGUGAAG AGAACUUGA		3075464-3075484	5790-5810	UCAAGUTCUCUTC ACAACGCAGU		3075462-3075484	5788-5810
AD-1640384	GCGUUGUGAAGA GAACUUGGA		3075465-3075485	5791-5811	UCCAAGUUCUCUU CACAACGCAG		3075463-3075485	5789-5811
AD-1640385	GCGUUGUGAAGA GAACUUGGA		3075465-3075485	5791-5811	UCCAAGTUCUCTU CACAACGCAG		3075463-3075485	5789-5811
AD-1640386	GUUGUGAAGAGA ACUUGGAGA		3075467-3075487	5793-5813	UCUCCAAGUUCUC UUCACAACGC		3075465-3075487	5791-5813
AD-1640387	GUUGUGAAGAGA ACUUGGAGA		3075467-3075487	5793-5813	UCUCCAAGUUCTC UUCACAACGC		3075465-3075487	5791-5813
AD-1640388	GUGAAGAGAACU UGGAGGAGA		3075470-3075490	5796-5816	UCUCCUCCAAGUU CUCUUCACAA		3075468-3075490	5794-5816
AD-1640389	GUGAAGAGAACU UGGAGGAGA		3075470-3075490	5796-5816	UCUCCUCCAAGTU CUCUUCACAA		3075468-3075490	5794-5816
AD-1640390	UGAAGAGAACUU GGAGGAGCA		3075471-3075491	5797-5817	UGCUCCTCCAAGU UCUCUUCACA		3075469-3075491	5795-5817
AD-1640391	AGAGAACUUGGA GGAGCCGAA		3075474-3075494	5800-5820	UUCGGCTCCUCCA AGUUCUCUUC		3075472-3075494	5798-5820
AD-1640392	GAGAACUUGGAG GAGCCGAGA		3075475-3075495	5801-5821	UCUCGGCUCCUCC AAGUUCUCUU		3075473-3075495	5799-5821
AD-1640393	GAGAACUUGGAG GAGCCGAGA		3075475-3075495	5801-5821	UCUCGGCUCCUCC AAGUUCUCUU		3075473-3075495	5799-5821
AD-	CUUGGAGGAGCC		3075480-	5806-5826	UCAAAUCUCGGCU		3075478-3075500	5804-5826

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640394	GAGAUUUUGA		3075500		CCUCCAAGUU			
AD-1640395	CUUGGAGGAGCC GAGAUUUUGA		3075480-3075500	5806-5826	UCAAAUCUCGGCU CCUCCAAGUU		3075478-3075500	5804-5826
AD-1640396	UUGGAGGAGCCG AGAUUUGCA		3075481-3075501	5807-5827	UGCAAAUCUCGGC UCCUCCAAGU		3075479-3075501	5805-5827
AD-1640397	UUGGAGGAGCCG AGAUUUGCA		3075481-3075501	5807-5827	UGCAAATCUCGGC UCCUCCAAGU		3075479-3075501	5805-5827
AD-1640398	UGGAGGAGCCGA GAUUUGCUA		3075482-3075502	5808-5828	UAGCAAAUCUCG GCUCCUCCAAG		3075480-3075502	5806-5828
AD-1640399	UGGAGGAGCCGA GAUUUGCUA		3075482-3075502	5808-5828	UAGCAAAUCUCG GCUCCUCCAAG		3075480-3075502	5806-5828
AD-1640400	GGAGGAGCCGAG AUUUGCUCA		3075483-3075503	5809-5829	UGAGCAAAUCUC GGCUCCUCCAA		3075481-3075503	5807-5829
AD-1640401	GGAGGAGCCGAG AUUUGCUCA		3075483-3075503	5809-5829	UGAGCAAAUCUC GGCUCCUCCAA		3075481-3075503	5807-5829
AD-1640402	GGAGGAGCCGAG AUUUGCUCA		3075483-3075503	5809-5829	UGAGCAAAUCUC GGCUCCUCCAA		3075481-3075503	5807-5829
AD-1640403	GAGGAGCCGAGA UUUGCUCAA		3075484-3075504	5810-5830	UUGAGCAAAUCU CGGCUCCUCCA		3075482-3075504	5808-5830
AD-1640404	GAGCCGAGAUUU GCUCAGUGA		3075487-3075507	5813-5833	UCACTGAGCAAAU CUCGGCUCCU		3075485-3075507	5811-5833
AD-1640405	GCCGAGAUUUGC UCAGUGCCA		3075489-3075509	5815-5835	UGGCACTGAGCAA AUCUCGGCUC		3075487-3075509	5813-5835
AD-1640406	CGAGAUUUGCUC AGUGCCACA		3075491-3075511	5817-5837	UGUGGCACUGAG CAAAUCUCGGC		3075489-3075511	5815-5837
AD-1640407	AUUUGCUCAGUG CCACUUCCA		3075495-3075515	5821-5841	UGGAAGTGGCACU GAGCAAAUCU		3075493-3075515	5819-5841
AD-1640408	UUGCUCAGUGCCA CUUCCCUA		3075497-3075517	5823-5843	UAGGGAAGUGGC ACUGAGCAAAU		3075495-3075517	5821-5843
AD-1640409	UUGCUCAGUGCCA CUUCCCUA		3075497-3075517	5823-5843	UAGGGAAGUGGC ACUGAGCAAAU		3075495-3075517	5821-5843
AD-1640410	UUGCUCAGUGCCA CUUCCCUA		3075497-3075517	5823-5843	UAGGGAAGUGGC ACUGAGCAAAU		3075495-3075517	5821-5843

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640411	UGCUCAGUGCCAC UUCCCUCA		3075498-3075518	5824-5844	UGAGGGAAGUGG CACUGAGCAAA		3075496-3075518	5822-5844
AD-1640412	UGCUCAGUGCCAC UUCCCUCA		3075498-3075518	5824-5844	UGAGGGAAGUGG CACUGAGCAAA		3075496-3075518	5822-5844
AD-1640413	UGCUCAGUGCCAC UUCCCUCA		3075498-3075518	5824-5844	UGAGGGAAGUGG CACUGAGCAAA		3075496-3075518	5822-5844
AD-1640414	AGUGCCACUUCCC UCUUCUAA		3075503-3075523	5829-5849	UUAGAAGAGGGA AGUGGCACUGA		3075501-3075523	5827-5849
AD-1640415	AGUGCCACUUCCC UCUUCUAA		3075503-3075523	5829-5849	UTAGAAGAGGGA AGUGGCACUGA		3075501-3075523	5827-5849
AD-1640416	GCCACUUCCCUCU UCUAGUCA		3075506-3075526	5832-5852	UGACUAGAAGAG GGAAGUGGCAC		3075504-3075526	5830-5852
AD-1640417	GCCACUUCCCUCU UCUAGUCA		3075506-3075526	5832-5852	UGACTAGAAGAG GGAAGUGGCAC		3075504-3075526	5830-5852
AD-1640418	CCACUUCCCUCUU CUAGUCUA		3075507-3075527	5833-5853	UAGACUAGAAGA GGGAAGUGGCA		3075505-3075527	5831-5853
AD-1640419	CCACUUCCCUCUU CUAGUCUA		3075507-3075527	5833-5853	UAGACUAGAAGA GGGAAGUGGCA		3075505-3075527	5831-5853
AD-1640420	CCACUUCCCUCUU CUAGUCUA		3075507-3075527	5833-5853	UAGACUAGAAGA GGGAAGUGGCA		3075505-3075527	5831-5853
AD-1640421	CACUUCCCUCUUC UAGUCUGA		3075508-3075528	5834-5854	UCAGACTAGAAGA GGGAAGUGGC		3075506-3075528	5832-5854
AD-1640422	CACUUCCCUCUUC UAGUCUGA		3075508-3075528	5834-5854	UCAGACUAGAAG AGGGAAGUGGC		3075506-3075528	5832-5854
AD-1640429	CACUUCCCUCUUC UAGUCUGA		3075508-3075528	5834-5854	UCAGACTAGAAGA GGGAAGUGGC		3075506-3075528	5832-5854
AD-1640430	ACUUCCCUCUUCU AGUCUGAA		3075509-3075529	5835-5855	UUCAGACUAGAA GAGGGAAGUGG		3075507-3075529	5833-5855
AD-1640431	CUUCCCUCUUCUA GUCUGAGA		3075510-3075530	5836-5856	UCUCAGACUAGA AGAGGGAAGUG		3075508-3075530	5834-5856
AD-1640432	CUUCCCUCUUCUA GUCUGAGA		3075510-3075530	5836-5856	UCUCAGACUAGA AGAGGGAAGUG		3075508-3075530	5834-5856
AD-	CUUCCCUCUUCUA		3075510-	5836-5856	UCUCAGACUAGA		3075508-3075530	5834-5856

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640433	GUCUGAGA		3075530		AGAGGGAAGUG			
AD-1640434	UCCCUCUUCUAGUCUGAGAGA		3075512-3075532	5838-5858	UCUCTCAGACUAGAAGAGGGAAG		3075510-3075532	5836-5858
AD-1640435	CCUCUUCUAGUCUGAGAGGGA		3075514-3075534	5840-5860	UCCCTCTCAGACUAGAAGAGGGA		3075512-3075534	5838-5860
AD-1640436	CCUCUUCUAGUCUGAGAGGGA		3075514-3075534	5840-5860	UCCCUCUCAGACUAGAAGAGGGA		3075512-3075534	5838-5860
AD-1640437	CCUCUUCUAGUCUGAGAGGGA		3075514-3075534	5840-5860	UCCCTCTCAGACUAGAAGAGGGA		3075512-3075534	5838-5860
AD-1640438	UCUUCUAGUCUGAGAGGGAAA		3075516-3075536	5842-5862	UUUCCCTCUCAGACUAGAAGAGG		3075514-3075536	5840-5862
AD-1640439	CUUCUAGUCUGAGAGGGAAGA		3075517-3075537	5843-5863	UCUUCCCUCUCAGACUAGAAGAG		3075515-3075537	5841-5863
AD-1640440	CUUCUAGUCUGAGAGGGAAGA		3075517-3075537	5843-5863	UCUUCCCUCUCAGACUAGAAGAG		3075515-3075537	5841-5863
AD-1640441	UCUAGUCUGAGAGGGAAGAGA		3075519-3075539	5845-5865	UCUCUUCCCUCUCAGACUAGAAG		3075517-3075539	5843-5865
AD-1640442	UCUAGUCUGAGAGGGAAGAGA		3075519-3075539	5845-5865	UCUCTUCCCUCTCAGACUAGAAG		3075517-3075539	5843-5865
AD-1640443	CUAGUCUGAGAGGGAAGAGGA		3075520-3075540	5846-5866	UCCUCUTCCCUCTCAGACUAGAA		3075518-3075540	5844-5866
AD-1640444	CUAGUCUGAGAGGGAAGAGGA		3075520-3075540	5846-5866	UCCUCUUCCCUCTCAGACUAGAA		3075518-3075540	5844-5866
AD-1640445	CUAGUCUGAGAGGGAAGAGGA		3075520-3075540	5846-5866	UCCUCUTCCCUCTCAGACUAGAA		3075518-3075540	5844-5866
AD-1640446	UAGUCUGAGAGGGAAGAGGGA		3075521-3075541	5847-5867	UCCCTCTUCCCUCUCAGACUAGA		3075519-3075541	5845-5867
AD-1640447	UAGUCUGAGAGGGAAGAGGGA		3075521-3075541	5847-5867	UCCCUCUUCCCUCUCAGACUAGA		3075519-3075541	5845-5867
AD-1640448	GUCUGAGAGGGAAGAGGGCUA		3075523-3075543	5849-5869	UAGCCCTCUUCCCUCUCAGACUA		3075521-3075543	5847-5869
AD-1640449	UCUGAGAGGGAAGAGGGCUGA		3075524-3075544	5850-5870	UCAGCCCUCUUCCCUCUCAGACU		3075522-3075544	5848-5870

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AD-1640450	UCUGAGAGGGAA GAGGGCUGA		3075524-3075544	5850-5870	UCAGCCCUCUUCC CUCUCAGACU		3075522-3075544	5848-5870
AD-1640451	CUGAGAGGGAAG AGGGCUGGA		3075525-3075545	5851-5871	UCCAGCCCUCUUC CCUCUCAGAC		3075523-3075545	5849-5871
AD-1640452	CUGAGAGGGAAG AGGGCUGGA		3075525-3075545	5851-5871	UCCAGCCCUCUTC CCUCUCAGAC		3075523-3075545	5849-5871
AD-1640453	UUUGGAGCUGGA GAGAUGUGA		3075575-3075595	5901-5921	UCACAUCUCUCCA GCUCCAAACC		3075573-3075595	5899-5921
AD-1640454	UUUGGAGCUGGA GAGAUGUGA		3075575-3075595	5901-5921	UCACAUCUCUCCA GCUCCAAACC		3075573-3075595	5899-5921
AD-1640455	UUGGAGCUGGAG AGAUGUGGA		3075576-3075596	5902-5922	UCCACAUCUCUCC AGCUCCAAAC		3075574-3075596	5900-5922
AD-1640456	UUGGAGCUGGAG AGAUGUGGA		3075576-3075596	5902-5922	UCCACATCUCUCC AGCUCCAAAC		3075574-3075596	5900-5922
AD-1640457	GCAGUGGAUGAC AUAAUGCUA		3075598-3075618	5924-5944	UAGCAUUAUGUC AUCCACUGCCC		3075596-3075618	5922-5944
AD-1640458	GCAGUGGAUGAC AUAAUGCUA		3075598-3075618	5924-5944	UAGCAUTAUGUCA UCCACUGCCC		3075596-3075618	5922-5944
AD-1640459	CAGUGGAUGACA UAAUGCUUA		3075599-3075619	5925-5945	UAAGCATUAUGUC AUCCACUGCC		3075597-3075619	5923-5945
AD-1640460	CAGUGGAUGACA UAAUGCUUA		3075599-3075619	5925-5945	UAAGCAUUAUGU CAUCCACUGCC		3075597-3075619	5923-5945
AD-1640461	CAGUGGAUGACA UAAUGCUUA		3075599-3075619	5925-5945	UAAGCATUAUGTC AUCCACUGCC		3075597-3075619	5923-5945
AD-1640462	UAGGACGCCUCGG CGGGAGUA		3075620-3075640	5946-5966	UACUCCCGCCGAG GCGUCCUAAA		3075618-3075640	5944-5966
AD-1640463	UGAGGGCGCGUCC AAUGGGAA		3075665-3075685	5991-6011	UUCCCATUGGACG CGCCCUCACU		3075663-3075685	5989-6011
AD-1640464	UGAGGGCGCGUCC AAUGGGAA		3075665-3075685	5991-6011	UUCCCAUUGGACG CGCCCUCACU		3075663-3075685	5989-6011
AD-1640465	UGAGGGCGCGUCC AAUGGGAA		3075665-3075685	5991-6011	UTCCCATUGGACG CGCCCUCACU		3075663-3075685	5989-6011
AD-	GCGUCCAAUGGG		3075672-	5998-6018	UAGAAATCUCCCA		3075670-3075692	5996-6018

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1640466	AGAUUUCUA		3075692		UUGGACGCGC			
AD-1640467	GCGUCCAAUGGG AGAUUUCUA		3075672-3075692	5998-6018	UAGAAAUCUCCCA UUGGACGCGC		3075670-3075692	5996-6018
AD-1640468	GCGUCCAAUGGG AGAUUUCUA		3075672-3075692	5998-6018	UAGAAATCUCCCA UUGGACGCGC		3075670-3075692	5996-6018
AD-1640469	CGUCCAAUGGGA GAUUUCUUA		3075673-3075693	5999-6019	UAAGAAAUCUCCC AUUGGACGCG		3075671-3075693	5997-6019
AD-1640470	CGUCCAAUGGGA GAUUUCUUA		3075673-3075693	5999-6019	UAAGAAAUCUCCC AUUGGACGCG		3075671-3075693	5997-6019
AD-1640471	CAGCCUGAGAUU UGAGGCUCA		3075712-3075732	6038-6058	UGAGCCTCAAAUC UCAGGCUGUU		3075710-3075732	6036-6058
AD-1640472	CUGAGAUUUGAG GCUCUUCCA		3075716-3075736	6042-6062	UGGAAGAGCCUC AAAUCUCAGGC		3075714-3075736	6040-6062
AD-1640473	UGAGAUUUGAGG CUCUUCCUA		3075717-3075737	6043-6063	UAGGAAGAGCCU CAAAUCUCAGG		3075715-3075737	6041-6063
AD-1640474	UGAGAUUUGAGG CUCUUCCUA		3075717-3075737	6043-6063	UAGGAAGAGCCTC AAAUCUCAGG		3075715-3075737	6041-6063
AD-1640475	GAGAUUUGAGGC UCUUCCUAA		3075718-3075738	6044-6064	UUAGGAAGAGCC UCAAAUCUCAG		3075716-3075738	6042-6064
AD-1640476	GAGAUUUGAGGC UCUUCCUAA		3075718-3075738	6044-6064	UUAGGAAGAGCC UCAAAUCUCAG		3075716-3075738	6042-6064
AD-1640477	GAGAUUUGAGGC UCUUCCUAA		3075718-3075738	6044-6064	UTAGGAAGAGCCU CAAAUCUCAG		3075716-3075738	6042-6064
AD-1640478	AGAUUUGAGGCU CUUCCUACA		3075719-3075739	6045-6065	UGUAGGAAGAGC CUCAAAUCUCA		3075717-3075739	6043-6065
AD-1640479	UUUGAGGCUCUU CCUACAUUA		3075722-3075742	6048-6068	UAAUGUAGGAAG AGCCUCAAAUC		3075720-3075742	6046-6068
AD-1640480	UGAGGCUCUUCCU ACAUUGUA		3075724-3075744	6050-6070	UACAAUGUAGGA AGAGCCUCAAA		3075722-3075744	6048-6070
AD-1640481	UGAGGCUCUUCCU ACAUUGUA		3075724-3075744	6050-6070	UACAAUGUAGGA AGAGCCUCAAA		3075722-3075744	6048-6070
AD-1640482	GAGGCUCUUCCUA CAUUGUCA		3075725-3075745	6051-6071	UGACAAUGUAGG AAGAGCCUCAA		3075723-3075745	6049-6071

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AD-1640483	GAGGCUCUUCCUACAUUGUCA		3075725-3075745	6051-6071	UGACAATGUAGGAAGAGCCUCAA		3075723-3075745	6049-6071
AD-1640484	AGGCUCUUCCUACAUUGUCAA		3075726-3075746	6052-6072	UUGACAAUGUAGGAAGAGCCUCA		3075724-3075746	6050-6072
AD-1640485	AGGCUCUUCCUACAUUGUCAA		3075726-3075746	6052-6072	UUGACAAUGUAGGAAGAGCCUCA		3075724-3075746	6050-6072
AD-1640486	AGGCUCUUCCUACAUUGUCAA		3075726-3075746	6052-6072	UUGACAAUGUAGGAAGAGCCUCA		3075724-3075746	6050-6072
AD-1640487	GGCUCUUCCUACAUUGUCAGA		3075727-3075747	6053-6073	UCUGACAAUGUAGGAAGAGCCUC		3075725-3075747	6051-6073
AD-1640488	GGCUCUUCCUACAUUGUCAGA		3075727-3075747	6053-6073	UCUGACAAUGUAGGAAGAGCCUC		3075725-3075747	6051-6073
AD-1640489	GCUCUUCCUACAUUGUCAGGA		3075728-3075748	6054-6074	UCCUGACAAUGUAGGAAGAGCCU		3075726-3075748	6052-6074
AD-1640490	GCUCUUCCUACAUUGUCAGGA		3075728-3075748	6054-6074	UCCUGACAAUGUAGGAAGAGCCU		3075726-3075748	6052-6074
AD-1640491	CUCUUCCUACAUUGUCAGGAA		3075729-3075749	6055-6075	UUCCUGACAAUGUAGGAAGAGCC		3075727-3075749	6053-6075
AD-1640492	CUUCCUACAUUGUCAGGACAA		3075731-3075751	6057-6077	UUGUCCUGACAAUGUAGGAAGAG		3075729-3075751	6055-6077
AD-1640493	UACAUUGUCAGGACAUUUCAA		3075736-3075756	6062-6082	UUGAAATGUCCUGACAAUGUAGG		3075734-3075756	6060-6082
AD-1640494	UACAUUGUCAGGACAUUUCAA		3075736-3075756	6062-6082	UUGAAAUGUCCUGACAAUGUAGG		3075734-3075756	6060-6082
AD-1640495	UACAUUGUCAGGACAUUUCAA		3075736-3075756	6062-6082	UUGAAATGUCCUGACAAUGUAGG		3075734-3075756	6060-6082
AD-1640496	ACAUUGUCAGGACAUUUCAUA		3075737-3075757	6063-6083	UAUGAAAUGUCCUGACAAUGUAG		3075735-3075757	6061-6083
AD-1640497	ACAUUGUCAGGACAUUUCAUA		3075737-3075757	6063-6083	UAUGAAAUGUCCUGACAAUGUAG		3075735-3075757	6061-6083
AD-1640498	CAUUGUCAGGACAUUUCAUUA		3075738-3075758	6064-6084	UAAUGAAAUGUCCUGACAAUGUA		3075736-3075758	6062-6084
AD-	CAUUGUCAGGAC		3075738-	6064-6084	UAAUGAAAUGUC		3075736-3075758	6062-6084

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1640499	AUUUCAUUA		3075758		CUGACAAUGUA			
AD-1640500	UUGUCAGGACAUUUCAUUAA		3075740-3075760	6066-6086	UUAAAUGAAAUGUCCUGACAAUG		3075738-3075760	6064-6086
AD-1640501	UUGUCAGGACAUUUCAUUAA		3075740-3075760	6066-6086	UTAAAUGAAAUGUCCUGACAAUG		3075738-3075760	6064-6086
AD-1640502	UCAGGACAUUUCAUUUAGUUA		3075743-3075763	6069-6089	UAACUAAAUGAAAUGUCCUGACA		3075741-3075763	6067-6089
AD-1640503	UCAGGACAUUUCAUUUAGUUA		3075743-3075763	6069-6089	UAACTAAAUGAAAUGUCCUGACA		3075741-3075763	6067-6089
AD-1640504	CAGGACAUUUCAUUUAGUUCA		3075744-3075764	6070-6090	UGAACUAAAUGAAAUGUCCUGAC		3075742-3075764	6068-6090
AD-1640505	CAGGACAUUUCAUUUAGUUCA		3075744-3075764	6070-6090	UGAACUAAAUGAAAUGUCCUGAC		3075742-3075764	6068-6090
AD-1640506	AGGACAUUUCAUUUAGUUCAA		3075745-3075765	6071-6091	UUGAACTAAAUGAAAUGUCCUGA		3075743-3075765	6069-6091
AD-1640507	GGACAUUUCAUUUAGUUCAUA		3075746-3075766	6072-6092	UAUGAACUAAAUGAAAUGUCCUG		3075744-3075766	6070-6092
AD-1640508	GGACAUUUCAUUUAGUUCAUA		3075746-3075766	6072-6092	UAUGAACUAAATGAAAUGUCCUG		3075744-3075766	6070-6092
AD-1640509	ACAUUUCAUUUAGUUCAUGAA		3075748-3075768	6074-6094	UUCATGAACUAAAUGAAAUGUCC		3075746-3075768	6072-6094
AD-1640510	ACAUUUCAUUUAGUUCAUGAA		3075748-3075768	6074-6094	UUCAUGAACUAAAUGAAAUGUCC		3075746-3075768	6072-6094
AD-1640511	UUUCAUUUAGUUCAUGAUCAA		3075751-3075771	6077-6097	UUGATCAUGAACUAAAUGAAAUG		3075749-3075771	6075-6097
AD-1640512	UCAUUUAGUUCAUGAUCACGA		3075753-3075773	6079-6099	UCGUGATCAUGAACUAAAUGAAA		3075751-3075773	6077-6099
AD-1640513	UCAUUUAGUUCAUGAUCACGA		3075753-3075773	6079-6099	UCGUGAUCAUGAACUAAAUGAAA		3075751-3075773	6077-6099
AD-1640514	CAUUUAGUUCAUGAUCACGGA		3075754-3075774	6080-6100	UCCGTGAUCAUGAACUAAAUGAA		3075752-3075774	6078-6100
AD-1640515	CAUUUAGUUCAUGAUCACGGA		3075754-3075774	6080-6100	UCCGUGAUCAUGAACUAAAUGAA		3075752-3075774	6078-6100

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AD-1640516	CAUUUAGUUCAUGAUCACGGA		3075754-3075774	6080-6100	UCCGUGAUCAUGAACUAAAUGAA		3075752-3075774	6078-6100
AD-1640517	AUUUAGUUCAUGAUCACGGUA		3075755-3075775	6081-6101	UACCGUGAUCAUGAACUAAAUGA		3075753-3075775	6079-6101
AD-1640518	AUUUAGUUCAUGAUCACGGUA		3075755-3075775	6081-6101	UACCGUGAUCAUGAACUAAAUGA		3075753-3075775	6079-6101
AD-1640519	UUUAGUUCAUGAUCACGGUGA		3075756-3075776	6082-6102	UCACCGUGAUCAUGAACUAAAUG		3075754-3075776	6080-6102
AD-1640520	UUUAGUUCAUGAUCACGGUGA		3075756-3075776	6082-6102	UCACCGUGAUCAUGAACUAAAUG		3075754-3075776	6080-6102
AD-1640521	UUAGUUCAUGAUCACGGUGGA		3075757-3075777	6083-6103	UCCACCGUGAUCAUGAACUAAAU		3075755-3075777	6081-6103
AD-1640522	UUAGUUCAUGAUCACGGUGGA		3075757-3075777	6083-6103	UCCACCGUGAUCAUGAACUAAAU		3075755-3075777	6081-6103
AD-1640523	UAGUUCAUGAUCACGGUGGUA		3075758-3075778	6084-6104	UACCACCGUGAUCAUGAACUAAA		3075756-3075778	6082-6104
AD-1640524	UAGUUCAUGAUCACGGUGGUA		3075758-3075778	6084-6104	UACCACCGUGATCAUGAACUAAA		3075756-3075778	6082-6104
AD-1640525	AGUUCAUGAUCACGGUGGUAA		3075759-3075779	6085-6105	UUACCACCGUGAUCAUGAACUAA		3075757-3075779	6083-6105
AD-1640526	GUUCAUGAUCACGGUGGUAGA		3075760-3075780	6086-6106	UCUACCACCGUGAUCAUGAACUA		3075758-3075780	6084-6106
AD-1640527	GUUCAUGAUCACGGUGGUAGA		3075760-3075780	6086-6106	UCUACCACCGUGAUCAUGAACUA		3075758-3075780	6084-6106
AD-1640528	CAUGAUCACGGUGGUAGUAAA		3075763-3075783	6089-6109	UUUACUACCACCGUGAUCAUGAA		3075761-3075783	6087-6109
AD-1640529	AUGAUCACGGUGGUAGUAACA		3075764-3075784	6090-6110	UGUUACTACCACCGUGAUCAUGA		3075762-3075784	6088-6110
AD-1640530	GAUCACGGUGGUAGUAACACA		3075766-3075786	6092-6112	UGUGTUACUACCACCGUGAUCAU		3075764-3075786	6090-6112
AD-1640531	GAUCACGGUGGUAGUAACACA		3075766-3075786	6092-6112	UGUGUUACUACCACCGUGAUCAU		3075764-3075786	6090-6112
AD-	GAUCACGGUGGU		3075766-	6092-6112	UGUGTUACUACCA		3075764-3075786	6090-6112

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640532	AGUAACACA		3075786		CCGUGAUCAU			
AD-1640533	AUCACGGUGGUA GUAACACGA		3075767-3075787	6093-6113	UCGUGUTACUACC ACCGUGAUCA		3075765-3075787	6091-6113
AD-1640534	AUCACGGUGGUA GUAACACGA		3075767-3075787	6093-6113	UCGUGUUACUACC ACCGUGAUCA		3075765-3075787	6091-6113
AD-1640535	AUCACGGUGGUA GUAACACGA		3075767-3075787	6093-6113	UCGUGUTACUACC ACCGUGAUCA		3075765-3075787	6091-6113
AD-1640536	UCACGGUGGUAG UAACACGAA		3075768-3075788	6094-6114	UUCGTGTUACUAC CACCGUGAUC		3075766-3075788	6092-6114
AD-1640537	CACGGUGGUAGU AACACGAUA		3075769-3075789	6095-6115	UAUCGUGUUACU ACCACCGUGAU		3075767-3075789	6093-6115
AD-1640538	ACGGUGGUAGUA ACACGAUUA		3075770-3075790	6096-6116	UAAUCGUGUUAC UACCACCGUGA		3075768-3075790	6094-6116
AD-1640539	ACGGUGGUAGUA ACACGAUUA		3075770-3075790	6096-6116	UAAUCGTGUUACU ACCACCGUGA		3075768-3075790	6094-6116
AD-1640540	GCACCACCUAAGA GAUCUGCA		3075794-3075814	6120-6140	UGCAGATCUCUUA GGUGGUGCUU		3075792-3075814	6118-6140
AD-1640541	CACCACCUAAGAG AUCUGCUA		3075795-3075815	6121-6141	UAGCAGAUCUCU UAGGUGGUGCU		3075793-3075815	6119-6141
AD-1640542	CCACCUAAGAGAU CUGCUCAA		3075797-3075817	6123-6143	UUGAGCAGAUCU CUUAGGUGGUG		3075795-3075817	6121-6143
AD-1640543	CCUAAGAGAUCU GCUCAUCUA		3075800-3075820	6126-6146	UAGATGAGCAGA UCUCUUAGGUG		3075798-3075820	6124-6146
AD-1640544	UAAGAGAUCUGC UCAUCUAAA		3075802-3075822	6128-6148	UUUAGATGAGCA GAUCUCUUAGG		3075800-3075822	6126-6148
AD-1640545	AAGAGAUCUGCU CAUCUAAGA		3075803-3075823	6129-6149	UCUUAGAUGAGC AGAUCUCUUAG		3075801-3075823	6127-6149
AD-1640546	AAGAGAUCUGCU CAUCUAAGA		3075803-3075823	6129-6149	UCUUAGAUGAGC AGAUCUCUUAG		3075801-3075823	6127-6149
AD-1640547	AAGAGAUCUGCU CAUCUAAGA		3075803-3075823	6129-6149	UCUUAGAUGAGC AGAUCUCUUAG		3075801-3075823	6127-6149
AD-1640548	AGAGAUCUGCUC AUCUAAGCA		3075804-3075824	6130-6150	UGCUUAGAUGAG CAGAUCUCUUA		3075802-3075824	6128-6150

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640549	AGAGAUCUGCUCAUCUAAGCA		3075804-3075824	6130-6150	UGCUTAGAUGAGCAGAUCUCUUA		3075802-3075824	6128-6150
AD-1640550	GAGAUCUGCUCAUCUAAGCCA		3075805-3075825	6131-6151	UGGCTUAGAUGAGCAGAUCUCUU		3075803-3075825	6129-6151
AD-1640551	GAGAUCUGCUCAUCUAAGCCA		3075805-3075825	6131-6151	UGGCUUAGAUGAGCAGAUCUCUU		3075803-3075825	6129-6151
AD-1640552	AGAUCUGCUCAUCUAAGCCUA		3075806-3075826	6132-6152	UAGGCUTAGAUGAGCAGAUCUCU		3075804-3075826	6130-6152
AD-1640553	GAUCUGCUCAUCUAAGCCUAA		3075807-3075827	6133-6153	UUAGGCTUAGAUGAGCAGAUCUC		3075805-3075827	6131-6153
AD-1640554	CUGCUCAUCUAAGCCUAAGUA		3075810-3075830	6136-6156	UACUUAGGCUUAGAUGAGCAGAU		3075808-3075830	6134-6156
AD-1640555	CUGCUCAUCUAAGCCUAAGUA		3075810-3075830	6136-6156	UACUTAGGCUUAGAUGAGCAGAU		3075808-3075830	6134-6156
AD-1640556	UGCUCAUCUAAGCCUAAGUUA		3075811-3075831	6137-6157	UAACTUAGGCUUAGAUGAGCAGA		3075809-3075831	6135-6157
AD-1640557	UGCUCAUCUAAGCCUAAGUUA		3075811-3075831	6137-6157	UAACUUAGGCUUAGAUGAGCAGA		3075809-3075831	6135-6157
AD-1640558	UGCUCAUCUAAGCCUAAGUUA		3075811-3075831	6137-6157	UAACTUAGGCUTAGAUGAGCAGA		3075809-3075831	6135-6157
AD-1640559	GCUCAUCUAAGCCUAAGUUGA		3075812-3075832	6138-6158	UCAACUUAGGCUUAGAUGAGCAG		3075810-3075832	6136-6158
AD-1640560	GCUCAUCUAAGCCUAAGUUGA		3075812-3075832	6138-6158	UCAACUTAGGCTUAGAUGAGCAG		3075810-3075832	6136-6158
AD-1640561	CUCAUCUAAGCCUAAGUUGGA		3075813-3075833	6139-6159	UCCAACUUAGGCUUAGAUGAGCA		3075811-3075833	6137-6159
AD-1640562	CUCAUCUAAGCCUAAGUUGGA		3075813-3075833	6139-6159	UCCAACTUAGGCUUAGAUGAGCA		3075811-3075833	6137-6159
AD-1640563	UCAUCUAAGCCUAAGUUGGUA		3075814-3075834	6140-6160	UACCAACUUAGGCUUAGAUGAGC		3075812-3075834	6138-6160
AD-1640564	UCAUCUAAGCCUAAGUUGGUA		3075814-3075834	6140-6160	UACCAACUUAGGCUUAGAUGAGC		3075812-3075834	6138-6160
AD-	CAUCUAAGCCUAA		3075815-	6141-6161	UGACCAACUUAG		3075813-3075835	6139-6161

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640565	GUUGGUCA		3075835		GCUUAGAUGAG			
AD-1640566	CAUCUAAGCCUAA GUUGGUCA		3075815-3075835	6141-6161	UGACCAACUUAG GCUUAGAUGAG		3075813-3075835	6139-6161
AD-1640567	CAUCUAAGCCUAA GUUGGUCA		3075815-3075835	6141-6161	UGACCAACUUAG GCUUAGAUGAG		3075813-3075835	6139-6161
AD-1640568	AUCUAAGCCUAA GUUGGUCUA		3075816-3075836	6142-6162	UAGACCAACUUA GGCUUAGAUGA		3075814-3075836	6140-6162
AD-1640569	AUCUAAGCCUAA GUUGGUCUA		3075816-3075836	6142-6162	UAGACCAACUUA GGCUUAGAUGA		3075814-3075836	6140-6162
AD-1640570	UCUAAGCCUAAG UUGGUCUGA		3075817-3075837	6143-6163	UCAGACCAACUUA GGCUUAGAUG		3075815-3075837	6141-6163
AD-1640571	UCUAAGCCUAAG UUGGUCUGA		3075817-3075837	6143-6163	UCAGACCAACUTA GGCUUAGAUG		3075815-3075837	6141-6163
AD-1640572	CUAAGCCUAAGU UGGUCUGCA		3075818-3075838	6144-6164	UGCAGACCAACUU AGGCUUAGAU		3075816-3075838	6142-6164
AD-1640573	UAAGCCUAAGUU GGUCUGCAA		3075819-3075839	6145-6165	UUGCAGACCAACU UAGGCUUAGA		3075817-3075839	6143-6165
AD-1640574	AGCCUAAGUUGG UCUGCAGGA		3075821-3075841	6147-6167	UCCUGCAGACCAA CUUAGGCUUA		3075819-3075841	6145-6167
AD-1640575	CCUAAGUUGGUC UGCAGGCGA		3075823-3075843	6149-6169	UCGCCUGCAGACC AACUUAGGCU		3075821-3075843	6147-6169
AD-1640576	CUAAGUUGGUCU GCAGGCGUA		3075824-3075844	6150-6170	UACGCCTGCAGAC CAACUUAGGC		3075822-3075844	6148-6170
AD-1640577	UAAGUUGGUCUG CAGGCGUUA		3075825-3075845	6151-6171	UAACGCCUGCAGA CCAACUUAGG		3075823-3075845	6149-6171
AD-1640578	UAAGUUGGUCUG CAGGCGUUA		3075825-3075845	6151-6171	UAACGCCUGCAGA CCAACUUAGG		3075823-3075845	6149-6171
AD-1640579	AGUUGGUCUGCA GGCGUUUGA		3075827-3075847	6153-6173	UCAAACGCCUGCA GACCAACUUA		3075825-3075847	6151-6173
AD-1640580	AGUUGGUCUGCA GGCGUUUGA		3075827-3075847	6153-6173	UCAAACGCCUGCA GACCAACUUA		3075825-3075847	6151-6173
AD-1640581	UGGUCUGCAGGC GUUUGAAUA		3075830-3075850	6156-6176	UAUUCAAACGCCU GCAGACCAAC		3075828-3075850	6154-6176

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640582	UGGUCUGCAGGC GUUUGAAUA		3075830-3075850	6156-6176	UAUUCAAACGCCU GCAGACCAAC		3075828-3075850	6154-6176
AD-1640583	GGUCUGCAGGCG UUUGAAUGA		3075831-3075851	6157-6177	UCAUUCAAACGCC UGCAGACCAA		3075829-3075851	6155-6177
AD-1640584	GGUCUGCAGGCG UUUGAAUGA		3075831-3075851	6157-6177	UCAUUCAAACGCC UGCAGACCAA		3075829-3075851	6155-6177
AD-1640585	GGUCUGCAGGCG UUUGAAUGA		3075831-3075851	6157-6177	UCAUUCAAACGCC UGCAGACCAA		3075829-3075851	6155-6177
AD-1640586	UCUGCAGGCGUU UGAAUGAGA		3075833-3075853	6159-6179	UCUCAUUCAAACG CCUGCAGACC		3075831-3075853	6157-6179
AD-1640587	UCUGCAGGCGUU UGAAUGAGA		3075833-3075853	6159-6179	UCUCAUTCAAACG CCUGCAGACC		3075831-3075853	6157-6179
AD-1640588	CUGCAGGCGUUU GAAUGAGUA		3075834-3075854	6160-6180	UACUCATUCAAAC GCCUGCAGAC		3075832-3075854	6158-6180
AD-1640589	CUGCAGGCGUUU GAAUGAGUA		3075834-3075854	6160-6180	UACUCAUUCAAAC GCCUGCAGAC		3075832-3075854	6158-6180
AD-1640590	CUGCAGGCGUUU GAAUGAGUA		3075834-3075854	6160-6180	UACUCATUCAAAC GCCUGCAGAC		3075832-3075854	6158-6180
AD-1640591	UGCAGGCGUUUG AAUGAGUUA		3075835-3075855	6161-6181	UAACTCAUUCAAA CGCCUGCAGA		3075833-3075855	6159-6181
AD-1640592	GCAGGCGUUUGA AUGAGUUGA		3075836-3075856	6162-6182	UCAACUCAUUCAA ACGCCUGCAG		3075834-3075856	6160-6182
AD-1640593	GCAGGCGUUUGA AUGAGUUGA		3075836-3075856	6162-6182	UCAACUCAUUCAA ACGCCUGCAG		3075834-3075856	6160-6182
AD-1640594	CAGGCGUUUGAA UGAGUUGUA		3075837-3075857	6163-6183	UACAACTCAUUCA AACGCCUGCA		3075835-3075857	6161-6183
AD-1640595	CAGGCGUUUGAA UGAGUUGUA		3075837-3075857	6163-6183	UACAACUCAUUCA AACGCCUGCA		3075835-3075857	6161-6183
AD-1640596	CAGGCGUUUGAA UGAGUUGUA		3075837-3075857	6163-6183	UACAACTCAUUCA AACGCCUGCA		3075835-3075857	6161-6183
AD-1640597	AGGCGUUUGAAU GAGUUGUGA		3075838-3075858	6164-6184	UCACAACUCAUUC AAACGCCUGC		3075836-3075858	6162-6184
AD-	AGGCGUUUGAAU		3075838-	6164-6184	UCACAACUCAUTC		3075836-3075858	6162-6184

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640598	GAGUUGUGA		3075858		AAACGCCUGC			
AD-1640599	GCGUUUGAAUGAGUUGUGGUA		3075840-3075860	6166-6186	UACCACAACUCAUUCAAACGCCU		3075838-3075860	6164-6186
AD-1640600	GCGUUUGAAUGAGUUGUGGUA		3075840-3075860	6166-6186	UACCACAACUCAUUCAAACGCCU		3075838-3075860	6164-6186
AD-1640601	GUUUGAAUGAGUUGUGGUUGA		3075842-3075862	6168-6188	UCAACCACAACUCAUUCAAACGC		3075840-3075862	6166-6188
AD-1640602	GUUUGAAUGAGUUGUGGUUGA		3075842-3075862	6168-6188	UCAACCACAACTCAUUCAAACGC		3075840-3075862	6166-6188
AD-1640603	UUUGAAUGAGUUGUGGUUGCA		3075843-3075863	6169-6189	UGCAACCACAACUCAUUCAAACG		3075841-3075863	6167-6189
AD-1640604	UUUGAAUGAGUUGUGGUUGCA		3075843-3075863	6169-6189	UGCAACCACAACUCAUUCAAACG		3075841-3075863	6167-6189
AD-1640605	UUGAAUGAGUUGUGGUUGCCA		3075844-3075864	6170-6190	UGGCAACCACAACUCAUUCAAAC		3075842-3075864	6168-6190
AD-1640606	UUGAAUGAGUUGUGGUUGCCA		3075844-3075864	6170-6190	UGGCAACCACAACUCAUUCAAAC		3075842-3075864	6168-6190
AD-1640607	UGAAUGAGUUGUGGUUGCCAA		3075845-3075865	6171-6191	UUGGCAACCACAACUCAUUCAAA		3075843-3075865	6169-6191
AD-1640608	GAGUUGUGGUUGCCAAGUAAA		3075850-3075870	6176-6196	UUUACUTGGCAACCACAACUCAU		3075848-3075870	6174-6196
AD-1640609	AGUUGUGGUUGCCAAGUAAAA		3075851-3075871	6177-6197	UUUUACTUGGCAACCACAACUCA		3075849-3075871	6175-6197
AD-1640610	GUUGUGGUUGCCAAGUAAAGA		3075852-3075872	6178-6198	UCUUUACUUGGCAACCACAACUC		3075850-3075872	6176-6198
AD-1640611	GUUGUGGUUGCCAAGUAAAGA		3075852-3075872	6178-6198	UCUUTACUUGGCAACCACAACUC		3075850-3075872	6176-6198
AD-1640612	UUGUGGUUGCCAAGUAAAGUA		3075853-3075873	6179-6199	UACUUUACUUGGCAACCACAACU		3075851-3075873	6177-6199
AD-1640613	UUGUGGUUGCCAAGUAAAGUA		3075853-3075873	6179-6199	UACUTUACUUGGCAACCACAACU		3075851-3075873	6177-6199
AD-1640614	UGGUUGCCAAGUAAAGUGGUA		3075856-3075876	6182-6202	UACCACTUUACUUGGCAACCACA		3075854-3075876	6180-6202

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640615	UGGUUGCCAAGUAAAGUGGUA		3075856-3075876	6182-6202	UACCACUUUACUUGGCAACCACA		3075854-3075876	6180-6202
AD-1640616	UGGUUGCCAAGUAAAGUGGUA		3075856-3075876	6182-6202	UACCACTUUACTUGGCAACCACA		3075854-3075876	6180-6202
AD-1640617	GGUUGCCAAGUAAAGUGGUGA		3075857-3075877	6183-6203	UCACCACUUUACUUGGCAACCAC		3075855-3075877	6181-6203
AD-1640618	GGUUGCCAAGUAAAGUGGUGA		3075857-3075877	6183-6203	UCACCACUUUACUUGGCAACCAC		3075855-3075877	6181-6203
AD-1640619	GCCAAGUAAAGUGGUGAACUA		3075861-3075881	6187-6207	UAGUTCACCACUUUACUUGGCAA		3075859-3075881	6185-6207
AD-1640620	CAAGUAAAGUGGUGAACUUAA		3075863-3075883	6189-6209	UUAAGUTCACCACUUUACUUGGC		3075861-3075883	6187-6209
AD-1640621	AAGUAAAGUGGUGAACUUACA		3075864-3075884	6190-6210	UGUAAGTUCACCACUUUACUUGG		3075862-3075884	6188-6210
AD-1640622	AGUAAAGUGGUGAACUUACGA		3075865-3075885	6191-6211	UCGUAAGUUCACCACUUUACUUG		3075863-3075885	6189-6211
AD-1640623	AGUAAAGUGGUGAACUUACGA		3075865-3075885	6191-6211	UCGUAAGUUCACCACUUUACUUG		3075863-3075885	6189-6211
AD-1640624	GUAAAGUGGUGAACUUACGUA		3075866-3075886	6192-6212	UACGUAAGUUCACCACUUUACUU		3075864-3075886	6190-6212
AD-1640625	GUAAAGUGGUGAACUUACGUA		3075866-3075886	6192-6212	UACGTAAGUUCACCACUUUACUU		3075864-3075886	6190-6212
AD-1640626	UAAAGUGGUGAACUUACGUGA		3075867-3075887	6193-6213	UCACGUAAGUUCACCACUUUACU		3075865-3075887	6191-6213
AD-1640627	UAAAGUGGUGAACUUACGUGA		3075867-3075887	6193-6213	UCACGUAAGUUCACCACUUUACU		3075865-3075887	6191-6213
AD-1640628	AAAGUGGUGAACUUACGUGGA		3075868-3075888	6194-6214	UCCACGUAAGUUCACCACUUUAC		3075866-3075888	6192-6214
AD-1640629	AAAGUGGUGAACUUACGUGGA		3075868-3075888	6194-6214	UCCACGTAAGUTCACCACUUUAC		3075866-3075888	6192-6214
AD-1640630	AAGUGGUGAACUUACGUGGUA		3075869-3075889	6195-6215	UACCACGUAAGUUCACCACUUUA		3075867-3075889	6193-6215
AD-	AAGUGGUGAACU		3075869-	6195-6215	UACCACGUAAGTU		3075867-3075889	6193-6215

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640631	UACGUGGUA		3075889		CACCACUUUA			
AD-1640632	AGUGGUGAACUUACGUGGUGA		3075870-3075890	6196-6216	UCACCACGUAAGUUCACCACUUU		3075868-3075890	6194-6216
AD-1640633	AGUGGUGAACUUACGUGGUGA		3075870-3075890	6196-6216	UCACCACGUAAGUUCACCACUUU		3075868-3075890	6194-6216
AD-1640634	GUGGUGAACUUACGUGGUGAA		3075871-3075891	6197-6217	UUCACCACGUAAGUUCACCACUU		3075869-3075891	6195-6217
AD-1640635	GUGGUGAACUUACGUGGUGAA		3075871-3075891	6197-6217	UUCACCACGUAAGUUCACCACUU		3075869-3075891	6195-6217
AD-1640636	GUGGUGAACUUACGUGGUGAA		3075871-3075891	6197-6217	UTCACCACGUAAGUUCACCACUU		3075869-3075891	6195-6217
AD-1640637	GUGAACUUACGUGGGGUGAUUAA		3075874-3075894	6200-6220	UUAATCACCACGUAAGUUCACCA		3075872-3075894	6198-6220
AD-1640638	GAACUUACGUGGUGAUUAAUA		3075876-3075896	6202-6222	UAUUAATCACCACGUAAGUUCAC		3075874-3075896	6200-6222
AD-1640639	GAACUUACGUGGUGAUUAAUA		3075876-3075896	6202-6222	UAUUAAUCACCACGUAAGUUCAC		3075874-3075896	6200-6222
AD-1640640	GAACUUACGUGGUGAUUAAUA		3075876-3075896	6202-6222	UAUUAATCACCACGUAAGUUCAC		3075874-3075896	6200-6222
AD-1640641	AACUUACGUGGUGAUUAAUGA		3075877-3075897	6203-6223	UCAUUAAUCACCACGUAAGUUCA		3075875-3075897	6201-6223
AD-1640642	AACUUACGUGGUGAUUAAUGA		3075877-3075897	6203-6223	UCAUTAAUCACCACGUAAGUUCA		3075875-3075897	6201-6223
AD-1640643	ACUUACGUGGUGAUUAAUGAA		3075878-3075898	6204-6224	UUCAUUAAUCACCACGUAAGUUC		3075876-3075898	6202-6224
AD-1640644	ACUUACGUGGUGAUUAAUGAA		3075878-3075898	6204-6224	UTCATUAAUCACCACGUAAGUUC		3075876-3075898	6202-6224
AD-1640645	CUUACGUGGUGAUUAAUGAAA		3075879-3075899	6205-6225	UUUCAUTAAUCACCACGUAAGUU		3075877-3075899	6203-6225
AD-1640646	CUUACGUGGUGAUUAAUGAAA		3075879-3075899	6205-6225	UUUCAUUAAUCACCACGUAAGUU		3075877-3075899	6203-6225
AD-1640647	CUUACGUGGUGAUUAAUGAAA		3075879-3075899	6205-6225	UTUCAUTAAUCACCACGUAAGUU		3075877-3075899	6203-6225

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640648	UUACGUGGUGAUUAAUGAAAA		3075880-3075900	6206-6226	UUUUCATUAAUCACCACGUAAGU		3075878-3075900	6204-6226
AD-1640649	UACGUGGUGAUUAAUGAAAUA		3075881-3075901	6207-6227	UAUUTCAUUAAUCACCACGUAAG		3075879-3075901	6205-6227
AD-1640650	UGGUGAUUAAUGAAAUUAUCA		3075885-3075905	6211-6231	UGAUAATUUCAUUAACACCACG		3075883-3075905	6209-6231
AD-1640651	UGGUGAUUAAUGAAAUUAUCA		3075885-3075905	6211-6231	UGAUAAUUUCAUUAACACCACG		3075883-3075905	6209-6231
AD-1640652	UGGUGAUUAAUGAAAUUAUCA		3075885-3075905	6211-6231	UGAUAATUUCATUAAUCACCACG		3075883-3075905	6209-6231
AD-1640653	AGUUUGGGCCCGCUGCAGCUA		3075092-3075112	5418-5438	UAGCTGCAGCGGGCCCAACUCA		3075090-3075112	5416-5438
AD-1640654	UGGCGGUAACCCUGCAGCCUA		3075146-3075166	5472-5492	UAGGCUGCAGGGUUACCGCCAUC		3075144-3075166	5470-5492
AD-1640655	CAGAGACAGAGUGACCCAGCA		3075196-3075216	5522-5542	UGCUGGGUCACUCUGUCUCUGCG		3075194-3075216	5520-5542
AD-1640656	AGAGACAGAGUGACCCAGCAA		3075197-3075217	5523-5543	UUGCTGGGUCACUCUGUCUGC		3075195-3075217	5521-5543
AD-1640657	GAGACAGAGUGACCCAGCAAA		3075198-3075218	5524-5544	UUUGCUGGGUCACUCUGUCUCUG		3075196-3075218	5522-5544
AD-1640658	GACAGAGUGACCCAGCAACCA		3075200-3075220	5526-5546	UGGUTGCUGGGUCACUCUGUCUC		3075198-3075220	5524-5546
AD-1640659	ACAGAGUGACCCAGCAACCCA		3075201-3075221	5527-5547	UGGGTUGCUGGGUCACUCUGUCU		3075199-3075221	5525-5547
AD-1640660	GAGUGACCCAGCAACCCAGAA		3075204-3075224	5530-5550	UUCUGGGUUGCUGGGUCACUCUG		3075202-3075224	5528-5550
AD-1640661	AGUGACCCAGCAACCCAGAGA		3075205-3075225	5531-5551	UCUCTGGGUUGCUGGGUCACUCU		3075203-3075225	5529-5551
AD-1640662	AGCAACCCAGAGCCCAUGAGA		3075213-3075233	5539-5559	UCUCAUGGGCUCUGGGUUGCUGG		3075211-3075233	5537-5559
AD-1640663	AACCCAGAGCCCAUGAGGGAA		3075216-3075236	5542-5562	UUCCCUCAUGGGCUCUGGGUUGC		3075214-3075236	5540-5562
AD-	CCCAGAGCCCAUG		3075218-	5544-5564	UUGUCCCUCAUGG		3075216-3075238	5542-5564

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640664	AGGGACAA		3075238		GCUCUGGGUU			
AD-1640665	CCAGAGCCCAUGAGGGACACA		3075219-3075239	5545-5565	UGUGTCCCUCAUGGGCUCUGGGU		3075217-3075239	5543-5565
AD-1640666	CGCUCCCUCACUUGGGUCUUA		3075279-3075299	5605-5625	UAAGACCCAAGUGAGGGAGCGGG		3075277-3075299	5603-5625
AD-1640667	GCUCCCUCACUUGGGUCUUCA		3075280-3075300	5606-5626	UGAAGACCCAAGUGAGGGAGCGG		3075278-3075300	5604-5626
AD-1640668	UCCCUCACUUGGGUCUUCCCA		3075282-3075302	5608-5628	UGGGAAGACCCAAGUGAGGGAGC		3075280-3075302	5606-5628
AD-1640669	UCACUUGGGUCUUCCCUUGUA		3075286-3075306	5612-5632	UACAAGGGAAGACCCAAGUGAGG		3075284-3075306	5610-5632
AD-1640670	CACUUGGGUCUUCCCUUGUCA		3075287-3075307	5613-5633	UGACAAGGGAAGACCCAAGUGAG		3075285-3075307	5611-5633
AD-1640671	UUGGGUCUUCCCUUGUCCUCA		3075290-3075310	5616-5636	UGAGGACAAGGGAAGACCCAAGU		3075288-3075310	5614-5636
AD-1640672	GGGUCUUCCCUUGUCCUCUCA		3075292-3075312	5618-5638	UGAGAGGACAAGGGAAGACCCAA		3075290-3075312	5616-5638
AD-1640673	GGUCUUCCCUUGUCCUCUCGA		3075293-3075313	5619-5639	UCGAGAGGACAAGGGAAGACCCA		3075291-3075313	5617-5639
AD-1640674	CCCUUGUCCUCUCGCGAGGGA		3075299-3075319	5625-5645	UCCCTCGCGAGAGGACAAGGGAA		3075297-3075319	5623-5645
AD-1640675	GCCUGUCCUGAAUUCACCGAA		3075338-3075358	5664-5684	UUCGGUGAAUUCAGGACAGGCCC		3075336-3075358	5662-5684
AD-1640676	CUGUCCUGAAUUCACCGAGGA		3075340-3075360	5666-5686	UCCUCGGUGAAUUCAGGACAGGC		3075338-3075360	5664-5686
AD-1640677	GCCCUUCGCAGGAUGCGAAGA		3075383-3075403	5709-5729	UCUUCGCAUCCUGCGAAGGGCGA		3075381-3075403	5707-5729
AD-1640678	CCCUUCGCAGGAUGCGAAGAA		3075384-3075404	5710-5730	UUCUTCGCAUCCUGCGAAGGGCG		3075382-3075404	5708-5730
AD-1640679	CCUUCGCAGGAUGCGAAGAGA		3075385-3075405	5711-5731	UCUCTUCGCAUCCUGCGAAGGGC		3075383-3075405	5709-5731
AD-1640680	UCGCAGGAUGCGAAGAGUUGA		3075388-3075408	5714-5734	UCAACUCUUCGCAUCCUGCGAAG		3075386-3075408	5712-5734

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640681	UAUUUGCGAGAA ACCAGGGCA		3075429-3075449	5755-5775	UGCCCUGGUUUCU CGCAAAUAAA		3075427-3075449	5753-5775
AD-1640682	AACUGCGUUGUG AAGAGAACA		3075461-3075481	5787-5807	UGUUCUCUUCACA ACGCAGUUAA		3075459-3075481	5785-5807
AD-1640683	CUGCGUUGUGAA GAGAACUUA		3075463-3075483	5789-5809	UAAGTUCUCUUCA CAACGCAGUU		3075461-3075483	5787-5809
AD-1640684	CGUUGUGAAGAG AACUUGGAA		3075466-3075486	5792-5812	UUCCAAGUUCUCU UCACAACGCA		3075464-3075486	5790-5812
AD-1640685	GUGAAGAGAACU UGGAGGAGA		3075470-3075490	5796-5816	UCUCCUCCAAGUU CUCUUCACAA		3075468-3075490	5794-5816
AD-1640686	GAAGAGAACUUG GAGGAGCCA		3075472-3075492	5798-5818	UGGCTCCUCCAAG UUCUCUUCAC		3075470-3075492	5796-5818
AD-1640687	AAGAGAACUUGG AGGAGCCGA		3075473-3075493	5799-5819	UCGGCUCCUCCAA GUUCUCUUCA		3075471-3075493	5797-5819
AD-1640688	GAGAACUUGGAG GAGCCGAGA		3075475-3075495	5801-5821	UCUCGGCUCCUCC AAGUUCUCUU		3075473-3075495	5799-5821
AD-1640689	AGAACUUGGAGG AGCCGAGAA		3075476-3075496	5802-5822	UUCUCGGCUCCUC CAAGUUCUCU		3075474-3075496	5800-5822
AD-1640690	GAACUUGGAGGA GCCGAGAUA		3075477-3075497	5803-5823	UAUCTCGGCUCCU CCAAGUUCUC		3075475-3075497	5801-5823
AD-1640691	AACUUGGAGGAG CCGAGAUUA		3075478-3075498	5804-5824	UAAUCUCGGCUCC UCCAAGUUCU		3075476-3075498	5802-5824
AD-1640692	AGGAGCCGAGAU UUGCUCAGA		3075485-3075505	5811-5831	UCUGAGCAAAUC UCGGCUCCUCC		3075483-3075505	5809-5831
AD-1640693	GGAGCCGAGAUU UGCUCAGUA		3075486-3075506	5812-5832	UACUGAGCAAAU CUCGGCUCCUC		3075484-3075506	5810-5832
AD-1640694	AGCCGAGAUUUG CUCAGUGCA		3075488-3075508	5814-5834	UGCACUGAGCAA AUCUCGGCUCC		3075486-3075508	5812-5834
AD-1640695	CCGAGAUUUGCUC AGUGCCAA		3075490-3075510	5816-5836	UUGGCACUGAGC AAAUCUCGGCU		3075488-3075510	5814-5836
AD-1640696	GAGAUUUGCUCA GUGCCACUA		3075492-3075512	5818-5838	UAGUGGCACUGA GCAAAUCUCGG		3075490-3075512	5816-5838
AD-	AGAUUUGCUCAG		3075493-	5819-5839	UAAGTGGCACUGA		3075491-3075513	5817-5839

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640697	UGCCACUUA		3075513		GCAAAUCUCG			
AD-1640698	GAUUUGCUCAGU GCCACUUCA		3075494-3075514	5820-5840	UGAAGUGGCACU GAGCAAAUCUC		3075492-3075514	5818-5840
AD-1640699	UUUGCUCAGUGCC ACUUCCCA		3075496-3075516	5822-5842	UGGGAAGUGGCA CUGAGCAAAUC		3075494-3075516	5820-5842
AD-1640700	GCUCAGUGCCACU UCCCUCUA		3075499-3075519	5825-5845	UAGAGGGAAGUG GCACUGAGCAA		3075497-3075519	5823-5845
AD-1640701	CUCAGUGCCACUU CCCUCUUA		3075500-3075520	5826-5846	UAAGAGGGAAGU GGCACUGAGCA		3075498-3075520	5824-5846
AD-1640702	AGUGCCACUUCCC UCUUCUAA		3075503-3075523	5829-5849	UUAGAAGAGGGA AGUGGCACUGA		3075501-3075523	5827-5849
AD-1640703	GCCACUUCCCUCU UCUAGUCA		3075506-3075526	5832-5852	UGACTAGAAGAG GGAAGUGGCAC		3075504-3075526	5830-5852
AD-1640704	ACUUCCCUCUUCU AGUCUGAA		3075509-3075529	5835-5855	UUCAGACUAGAA GAGGGAAGUGG		3075507-3075529	5833-5855
AD-1640705	UUCCCUCUUCUAG UCUGAGAA		3075511-3075531	5837-5857	UUCUCAGACUAG AAGAGGGAAGU		3075509-3075531	5835-5857
AD-1640706	CCCUCUUCUAGUC UGAGAGGA		3075513-3075533	5839-5859	UCCUCUCAGACUA GAAGAGGGAA		3075511-3075533	5837-5859
AD-1640707	CUCUUCUAGUCUG AGAGGGAA		3075515-3075535	5841-5861	UUCCCUCUCAGAC UAGAAGAGGG		3075513-3075535	5839-5861
AD-1640708	CUUCUAGUCUGA GAGGGAAGA		3075517-3075537	5843-5863	UCUUCCCUCUCAG ACUAGAAGAG		3075515-3075537	5841-5863
AD-1640709	UUCUAGUCUGAG AGGGAAGAA		3075518-3075538	5844-5864	UUCUTCCCUCUCA GACUAGAAGA		3075516-3075538	5842-5864
AD-1640711	AGUCUGAGAGGG AAGAGGGCA		3075522-3075542	5848-5868	UGCCCUCUUCCCU CUCAGACUAG		3075520-3075542	5846-5868
AD-1640712	UCUGAGAGGGAA GAGGGCUGA		3075524-3075544	5850-5870	UCAGCCCUCUUCC CUCUCAGACU		3075522-3075544	5848-5870
AD-1640713	CUGAGAGGGAAG AGGGCUGGA		3075525-3075545	5851-5871	UCCAGCCCUCUUC CCUCUCAGAC		3075523-3075545	5849-5871
AD-1640714	UUUGGAGCUGGA GAGAUGUGA		3075575-3075595	5901-5921	UCACAUCUCUCCA GCUCCAAACC		3075573-3075595	5899-5921

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640715	UAGGACGCCUCGGCGGAGUA		3075620-3075640	5946-5966	UACUCCCGCCGAGGCGUCCUAAA		3075618-3075640	5944-5966
AD-1640716	AGGGCGCGUCCAAUGGGAGAA		3075667-3075687	5993-6013	UUCUCCCAUUGGACGCGCCCUCA		3075665-3075687	5991-6013
AD-1640717	GGCGCGUCCAAUGGGAGAUA		3075668-3075688	5994-6014	UAUCTCCCAUUGGACGCGCCCUC		3075666-3075688	5992-6014
AD-1640718	GGCGCGUCCAAUGGGAGAUUA		3075669-3075689	5995-6015	UAAUCUCCCAUUGGACGCGCCCU		3075667-3075689	5993-6015
AD-1640719	CGCGUCCAAUGGGAGAUUUCA		3075671-3075691	5997-6017	UGAAAUCUCCCAUUGGACGCGCC		3075669-3075691	5995-6017
AD-1640720	ACAGCCUGAGAUUUGAGGCUA		3075711-3075731	6037-6057	UAGCCUCAAAUCUCAGGCUGUUU		3075709-3075731	6035-6057
AD-1640721	AGCCUGAGAUUUGAGGCUCUA		3075713-3075733	6039-6059	UAGAGCCUCAAAUCUCAGGCUGU		3075711-3075733	6037-6059
AD-1640722	GCCUGAGAUUUGAGGCUCUUA		3075714-3075734	6040-6060	UAAGAGCCUCAAAUCUCAGGCUG		3075712-3075734	6038-6060
AD-1640723	CCUGAGAUUUGAGGCUCUUCA		3075715-3075735	6041-6061	UGAAGAGCCUCAAAUCUCAGGCU		3075713-3075735	6039-6061
AD-1640724	UGAGAUUUGAGGCUCUUCCUA		3075717-3075737	6043-6063	UAGGAAGAGCCUCAAAUCUCAGG		3075715-3075737	6041-6063
AD-1640725	GAUUUGAGGCUCUUCCUACAA		3075720-3075740	6046-6066	UUGUAGGAAGAGCCUCAAAUCUC		3075718-3075740	6044-6066
AD-1640726	AUUUGAGGCUCUUCCUACAUA		3075721-3075741	6047-6067	UAUGTAGGAAGAGCCUCAAAUCU		3075719-3075741	6045-6067
AD-1640727	UGAGGCUCUUCCUACAUUGUA		3075724-3075744	6050-6070	UACAAUGUAGGAAGAGCCUCAAA		3075722-3075744	6048-6070
AD-1640728	GCUCUUCCUACAUUGUCAGGA		3075728-3075748	6054-6074	UCCUGACAAUGUAGGAAGAGCCU		3075726-3075748	6052-6074
AD-1640729	UCUUCCUACAUUGUCAGGACA		3075730-3075750	6056-6076	UGUCCUGACAAUGUAGGAAGAGC		3075728-3075750	6054-6076
AD-1640730	UUCCUACAUUGUCAGGACAUA		3075732-3075752	6058-6078	UAUGTCCUGACAAUGUAGGAAGA		3075730-3075752	6056-6078
AD-	UCCUACAUUGUCA		3075733-	6059-6079	UAAUGUCCUGAC		3075731-3075753	6057-6079

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640731	GGACAUUA		3075753		AAUGUAGGAAG			
AD-1640732	CUACAUUGUCAG GACAUUUCA		3075735-3075755	6061-6081	UGAAAUGUCCUG ACAAUGUAGGA		3075733-3075755	6059-6081
AD-1640733	UUGUCAGGACAU UUCAUUUAA		3075740-3075760	6066-6086	UUAAAUGAAAUG UCCUGACAAUG		3075738-3075760	6064-6086
AD-1640734	GGACAUUUCAUU UAGUUCAUA		3075746-3075766	6072-6092	UAUGAACUAAAU GAAAUGUCCUG		3075744-3075766	6070-6092
AD-1640735	UUCAUUUAGUUC AUGAUCACA		3075752-3075772	6078-6098	UGUGAUCAUGAA CUAAAUGAAAU		3075750-3075772	6076-6098
AD-1640736	AGUUCAUGAUCA CGGUGGUAA		3075759-3075779	6085-6105	UUACCACCGUGAU CAUGAACUAA		3075757-3075779	6083-6105
AD-1640737	UUCAUGAUCACG GUGGUAGUA		3075761-3075781	6087-6107	UACUACCACCGUG AUCAUGAACU		3075759-3075781	6085-6107
AD-1640738	UCAUGAUCACGG UGGUAGUAA		3075762-3075782	6088-6108	UUACTACCACCGU GAUCAUGAAC		3075760-3075782	6086-6108
AD-1640739	UGAUCACGGUGG UAGUAACAA		3075765-3075785	6091-6111	UUGUTACUACCAC CGUGAUCAUG		3075763-3075785	6089-6111
AD-1640740	CACGGUGGUAGU AACACGAUA		3075769-3075789	6095-6115	UAUCGUGUUACU ACCACCGUGAU		3075767-3075789	6093-6115
AD-1640741	UAAGCACCACCUA AGAGAUCA		3075791-3075811	6117-6137	UGAUCUCUUAGG UGGUGCUUAAA		3075789-3075811	6115-6137
AD-1640742	ACCACCUAAGAGA UCUGCUCA		3075796-3075816	6122-6142	UGAGCAGAUCUC UUAGGUGGUGC		3075794-3075816	6120-6142
AD-1640743	CACCUAAGAGAUC UGCUCAUA		3075798-3075818	6124-6144	UAUGAGCAGAUC UCUUAGGUGGU		3075796-3075818	6122-6144
AD-1640744	ACCUAAGAGAUC UGCUCAUCA		3075799-3075819	6125-6145	UGAUGAGCAGAU CUCUUAGGUGG		3075797-3075819	6123-6145
AD-1640745	CUAAGAGAUCUG CUCAUCUAA		3075801-3075821	6127-6147	UUAGAUGAGCAG AUCUCUUAGGU		3075799-3075821	6125-6147
AD-1640746	AGAGAUCUGCUC AUCUAAGCA		3075804-3075824	6130-6150	UGCUTAGAUGAGC AGAUCUCUUA		3075802-3075824	6128-6150
AD-1640747	AUCUGCUCAUCUA AGCCUAAA		3075808-3075828	6134-6154	UUUAGGCUUAGA UGAGCAGAUCU		3075806-3075828	6132-6154

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
AD-1640748	CUGCUCAUCUAAG CCUAAGUA		3075810-3075830	6136-6156	UACUTAGGCUUAG AUGAGCAGAU		3075808-3075830	6134-6156
AD-1640749	UCUAAGCCUAAG UUGGUCUGA		3075817-3075837	6143-6163	UCAGACCAACUUA GGCUUAGAUG		3075815-3075837	6141-6163
AD-1640750	CUAAGCCUAAGU UGGUCUGCA		3075818-3075838	6144-6164	UGCAGACCAACUU AGGCUUAGAU		3075816-3075838	6142-6164
AD-1640751	AAGCCUAAGUUG GUCUGCAGA		3075820-3075840	6146-6166	UCUGCAGACCAAC UUAGGCUUAG		3075818-3075840	6144-6166
AD-1640752	GCCUAAGUUGGU CUGCAGGCA		3075822-3075842	6148-6168	UGCCTGCAGACCA ACUUAGGCUU		3075820-3075842	6146-6168
AD-1640753	CCUAAGUUGGUC UGCAGGCGA		3075823-3075843	6149-6169	UCGCCUGCAGACC AACUUAGGCU		3075821-3075843	6147-6169
AD-1640754	UAAGUUGGUCUG CAGGCGUUA		3075825-3075845	6151-6171	UAACGCCUGCAGA CCAACUUAGG		3075823-3075845	6149-6171
AD-1640755	GUCUGCAGGCGU UUGAAUGAA		3075832-3075852	6158-6178	UUCATUCAAACGC CUGCAGACCA		3075830-3075852	6156-6178
AD-1640756	GCAGGCGUUUGA AUGAGUUGA		3075836-3075856	6162-6182	UCAACUCAUUCAA ACGCCUGCAG		3075834-3075856	6160-6182
AD-1640757	UUUGAAUGAGUU GUGGUUGCA		3075843-3075863	6169-6189	UGCAACCACAACU CAUUCAAACG		3075841-3075863	6167-6189
AD-1640758	UUGAAUGAGUUG UGGUUGCCA		3075844-3075864	6170-6190	UGGCAACCACAAC UCAUUCAAAC		3075842-3075864	6168-6190
AD-1640759	AAUGAGUUGUGG UUGCCAAGA		3075847-3075867	6173-6193	UCUUGGCAACCAC AACUCAUUCA		3075845-3075867	6171-6193
AD-1640760	AUGAGUUGUGGU UGCCAAGUA		3075848-3075868	6174-6194	UACUTGGCAACCA CAACUCAUUC		3075846-3075868	6172-6194
AD-1640761	UGAGUUGUGGUU GCCAAGUAA		3075849-3075869	6175-6195	UUACTUGGCAACC ACAACUCAUU		3075847-3075869	6173-6195
AD-1640762	UUGCCAAGUAAA GUGGUGAAA		3075859-3075879	6185-6205	UUUCACCACACUUUA CUUGGCAACC		3075857-3075879	6183-6205
AD-1640763	UGCCAAGUAAAG UGGUGAACA		3075860-3075880	6186-6206	UGUUCACCACACUUU ACUUGGCAAC		3075858-3075880	6184-6206
AD-	CCAAGUAAAGUG		3075862-	6188-6208	UAAGTUCACCACU		3075860-3075882	6186-6208

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Range (NC_000004.12)	Sense Range (NG_009378.1)	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Range (NC_000004.12)	Antisense Range (NG_009378.1)
1640764	GUGAACUUA		3075882		UUACUUGGCA			
AD-1640765	AGUAAAGUGGUG AACUUACGA		3075865-3075885	6191-6211	UCGUAAGUUCACC ACUUUACUUG		3075863-3075885	6189-6211
AD-1640766	UGGUGAACUUAC GUGGUGAUA		3075872-3075892	6198-6218	UAUCACCACGUAA GUUCACCACU		3075870-3075892	6196-6218
AD-1640767	UGAACUUACGUG GUGAUUAAA		3075875-3075895	6201-6221	UUUAAUCACCACG UAAGUUCACC		3075873-3075895	6199-6221
AD-1640768	ACGUGGUGAUUA AUGAAAUUA		3075882-3075902	6208-6228	UAAUUUCAUUAA UCACCACGUAA		3075880-3075902	6206-6228

Table 3. Modified Sense and Antisense Strand Sequences of Intron 1 Targeting HTT dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640313	gsgscgg(Uhd)AfaCfCfCfugcagccuga L96		VPusCfsagdGc(Tgn)gcagggUfuAfcc gccsasu		ATGGCGGTAACCCTGCAGC CTGC	
AD-1640314	gscsaga(Ghd)AfcAfGfAfgugacccaga L96		VPusCfsugdGg(Tgn)cacucuGfuCfuc ugcsgsg		CCGCAGAGACAGAGTGACC CAGC	
AD-1640315	asgsaca(Ghd)AfgUfGfAfcccagcaacaL 96		VPusGfsuudGc(Tgn)gggucaCfuCfug ucuscsu		AGAGACAGAGTGACCCAGC AACC	
AD-1640316	csasgag(Uhd)GfaCfCfCfagcaacccaaL 96		VPusUfsggdGu(Tgn)gcugggUfcAfcu cugsusc		GACAGAGTGACCCAGCAAC CCAG	
AD-1640317	asgsagu(Ghd)AfcCfCfAfgcaacccagaL 96		VPusCfsugdGg(Tgn)ugcuggGfuCfac ucusgsu		ACAGAGTGACCCAGCAACC CAGA	
AD-1640318	asgscaa(Chd)CfcAfGfAfgcccaugagaL 96		VPusCfsucaUfgGfGfcucuGfgGfuugc usgsg		CCAGCAACCCAGAGCCCAT GAGG	
AD-1640319	asgscaa(Chd)ccAfGfAfgcccaugagaL9 6		VPusdCsucdAudGggcudCuGfgguugc usgsg		CCAGCAACCCAGAGCCCAT GAGG	
AD-1640320	gscsaac(Chd)CfaGfAfGfcccaugaggaL 96		VPusCfscucAfuGfGfgcucUfgGfguug csusg		CAGCAACCCAGAGCCCATG AGGG	
AD-1640321	gscsaac(Chd)caGfAfGfcccaugaggaL9 6		VPusdCscudCadTgggcdTcUfggguug csusg		CAGCAACCCAGAGCCCATG AGGG	
AD-1640322	csasacc(Chd)AfgAfGfCfccaugaggga L96		VPusCfsccdTc(Agn)ugggcuCfuGfgg uugscsu		AGCAACCCAGAGCCCATGA GGGA	
AD-1640323	csasacc(Chd)AfgAfGfCfccaugaggga L96		VPusCfsccuCfaUfGfggcuCfuGfgguu gscsu		AGCAACCCAGAGCCCATGA GGGA	
AD-1640324	csasacc(Chd)agAfGfCfccaugagggaL9 6		VPusdCsccdTcdAugggdCuCfuggguu gscsu		AGCAACCCAGAGCCCATGA GGGA	
AD-1640325	ascscca(Ghd)AfgCfCfCfaugagggacaL 96		VPusGfsucdCc(Tgn)caugggCfuCfug ggususg		CAACCCAGAGCCCATGAGG GACA	
AD-1640326	csgscuc(Chd)CfuCfAfCfuugggucuua L96		VPusAfsagaCfcCfAfagugAfgGfgagc gsgsg		CCCGCTCCCTCACTTGGGTC TTC	
AD-1640327	csgscuc(Chd)cuCfAfCfuugggucuuaL 96		VPusdAsagdAcdCcaagdTgAfgggagc gsgsg		CCCGCTCCCTCACTTGGGTC TTC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640328	csuscccc(Uhd)CfaCfUfUfgggucuucca L96		VPusGfsgadAg(Agn)cccaagUfgAfgg gagscsg		CGCTCCCTCACTTGGGTCTT CCC	
AD-1640329	cscscuc(Ahd)CfuUfGfGfgucuucccua L96		VPusAfsggdGa(Agn)gacccaAfgUfga gggsasg		CTCCCTCACTTGGGTCTTCC CTT	
AD-1640330	cscsuca(Chd)UfuGfGfGfucuucccuua L96		VPusAfsagdGg(Agn)agacccAfaGfug aggsgsa		TCCCTCACTTGGGTCTTCCC TTG	
AD-1640331	cscsuca(Chd)UfuGfGfGfucuucccuua L96		VPusAfsaggGfaAfGfacccAfaGfugag gsgsa		TCCCTCACTTGGGTCTTCCC TTG	
AD-1640332	cscsuca(Chd)uuGfGfGfucuucccuuaL 96		VPusdAsagdGgdAagacdCcAfagugag gsgsa		TCCCTCACTTGGGTCTTCCC TTG	
AD-1640333	csascuu(Ghd)GfgUfCfUfucccuuguca L96		VPusGfsacaAfgGfGfaagaCfcCfaagug sasg		CTCACTTGGGTCTTCCCTTG TCC	
AD-1640334	csascuu(Ghd)ggUfCfUfucccuugucaL 96		VPusdGsacdAadGggaadGaCfccaagu gsasg		CTCACTTGGGTCTTCCCTTG TCC	
AD-1640335	ascsuug(Ghd)GfuCfUfUfcccuugucca L96		VPusGfsgadCa(Agn)gggaagAfcCfcaa gusgsa		TCACTTGGGTCTTCCCTTGT CCT	
AD-1640336	ascsuug(Ghd)GfuCfUfUfcccuugucca L96		VPusGfsgacAfaGfGfgaagAfcCfcaag usgsa		TCACTTGGGTCTTCCCTTGT CCT	
AD-1640337	ascsuug(Ghd)guCfUfUfcccuuguccaL 96		VPusdGsgadCadAgggadAgAfcccaag usgsa		TCACTTGGGTCTTCCCTTGT CCT	
AD-1640338	csusugg(Ghd)UfcUfUfCfccuuguccua L96		VPusAfsggaCfaAfGfggaaGfaCfccaag susg		CACTTGGGTCTTCCCTTGTC CTC	
AD-1640339	csusugg(Ghd)ucUfUfUfCfccuuguccuaL 96		VPusdAsggdAcdAagggdAaGfacccaa gsusg		CACTTGGGTCTTCCCTTGTC CTC	
AD-1640340	usgsggu(Chd)UfuCfCfCfuuguccucua L96		VPusAfsgadGg(Agn)caagggAfaGfac ccasasg		CTTGGGTCTTCCCTTGTCCT CTC	
AD-1640341	gsuscuu(Chd)CfcUfUfUfGfucccucgca L96		VPusGfscgdAg(Agn)ggacaaGfgGfaa gacscsc		GGGTCTTCCCTTGTCCTCTC GCG	
AD-1640342	uscsuuc(Chd)CfuUfGfUfcccucgcga L96		VPusCfsgcgAfgAfGfgacaAfgGfgaag ascsc		GGTCTTCCCTTGTCCTCTCG CGA	
AD-	uscsuuc(Chd)cuUfGfUfcccucgcgaL		VPusdCsgcdGadGaggadCaAfgggaag		GGTCTTCCCTTGTCCTCTCG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640343	96		ascsc		CGA	
AD-1640344	csusucc(Chd)UfuGfUfCfcucucgcgaaL96		VPusUfscgcGfaGfAfggacAfaGfggaagsasc		GTCTTCCCTTGTCCTCTCGCGAG	
AD-1640345	csusucc(Chd)uuGfUfCfcucucgcgaaL96		VPusdTscgdCgdAgaggdAcAfagggaagsasc		GTCTTCCCTTGTCCTCTCGCGAG	
AD-1640346	ususccc(Uhd)UfgUfCfCfucucgcgagaL96		VPusCfsucgCfgAfGfaggaCfaAfgggaasgsa		TCTTCCCTTGTCCTCTCGCGAGG	
AD-1640347	ususccc(Uhd)ugUfCfCfucucgcgagaL96		VPusdCsucdGcdGagagdGaCfaagggaasgsa		TCTTCCCTTGTCCTCTCGCGAGG	
AD-1640348	uscsccu(Uhd)GfuCfCfUfcucgcgaggaL96		VPusCfscucGfcGfAfgaggAfcAfagggasasg		CTTCCCTTGTCCTCTCGCGAGGG	
AD-1640349	uscsccu(Uhd)guCfCfUfcucgcgaggaL96		VPusdCscudCgdCgagadGgAfcaagggasasg		CTTCCCTTGTCCTCTCGCGAGGG	
AD-1640350	cscscuu(Ghd)UfcCfUfCfucgcgaggggaL96		VPusCfsccuCfgCfGfagagGfaCfaagggsasa		TTCCCTTGTCCTCTCGCGAGGG	
AD-1640351	cscscuu(Ghd)ucCfUfCfucgcgaggggaL96		VPusdCsccdTcdGcgagdAgGfacaagggsasa		TTCCCTTGTCCTCTCGCGAGGG	
AD-1640352	cscsugu(Chd)CfuGfAfAfuucaccgagaL96		VPusCfsucgGfuGfAfauucAfgGfacaggscsc		GGCCTGTCCTGAATTCACCGAGG	
AD-1640353	cscsugu(Chd)cuGfAfAfuucaccgagaL96		VPusdCsucdGgdTgaaudTcAfggacagscsc		GGCCTGTCCTGAATTCACCGAGG	
AD-1640354	csusguc(Chd)UfgAfAfUfucaccgaggaL96		VPusCfscucGfgUfGfaauuCfaGfgacagsgsc		GCCTGTCCTGAATTCACCGAGGG	
AD-1640355	csusguc(Chd)ugAfAfUfucaccgaggaL96		VPusdCscudCgdGugaadTuCfaggacagsgsc		GCCTGTCCTGAATTCACCGAGGG	
AD-1640356	usgsucc(Uhd)GfaAfUfUfUfcaccgaggggaL96		VPusCfsccuCfgGfUfgaauUfcAfggacasgsg		CCTGTCCTGAATTCACCGAGGG	
AD-1640357	usgsucc(Uhd)gaAfUfUfUfcaccgaggggaL96		VPusdCsccdTcdGgugadAuUfcaggacasgsg		CCTGTCCTGAATTCACCGAGGG	
AD-1640358	uscsgcc(Chd)UfuCfGfCfaggaugcgaaL96		VPusUfscgdCa(Tgn)ccugcgAfaGfggcgasgsa		TCTCGCCCTTCGCAGGATGCGAA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640359	csgscccc(Uhd)UfcGfCfAfggaugcgaaaL96		VPusUfsucdGc(Agn)uccugcGfaAfgggcgsasg		CTCGCCCTTCGCAGGATGCGAAG	
AD-1640360	gscscccu(Uhd)CfgCfAfGfgaugcgaagaL96		VPusCfsuucGfcAfUfccugCfgAfagggcsgsa		TCGCCCTTCGCAGGATGCGAAGA	
AD-1640361	gscscccu(Uhd)cgCfAfGfgaugcgaagaL96		VPusdCsuudCgdCauccdTgCfgaaggcsgsa		TCGCCCTTCGCAGGATGCGAAGA	
AD-1640362	cscsuuc(Ghd)CfaGfGfAfugcgaagagaL96		VPusCfsucuUfcGfCfauccUfgCfgaaggsgsc		GCCCTTCGCAGGATGCGAAGAGT	
AD-1640363	cscsuuc(Ghd)caGfGfAfugcgaagagaL96		VPusdCsucdTudCgcaudCcUfgcgaaggsgsc		GCCCTTCGCAGGATGCGAAGAGT	
AD-1640364	csusucg(Chd)AfgGfAfUfgcgaagaguaL96		VPusAfscudCu(Tgn)cgcaucCfuGfcgaagsgsg		CCCTTCGCAGGATGCGAAGAGTT	
AD-1640365	ususcgc(Ahd)GfgAfUfGfcgaagaguuaL96		VPusAfsacdTc(Tgn)ucgcauCfcUfgcgaasgsg		CCTTCGCAGGATGCGAAGAGTTG	
AD-1640366	uscsgca(Ghd)GfaUfGfCfgaagauugaL96		VPusCfsaacUfcUfUfcgcaUfcCfugcgasasg		CTTCGCAGGATGCGAAGAGTTGG	
AD-1640367	uscsgca(Ghd)gaUfGfCfgaagauugaL96		VPusdCsaadCudCuucgdCaUfccugcgasasg		CTTCGCAGGATGCGAAGAGTTGG	
AD-1640368	csgscag(Ghd)AfuGfCfGfaagauuggaL96		VPusCfscaaCfuCfUfucgcAfuCfcugcgsasa		TTCGCAGGATGCGAAGAGTTGGG	
AD-1640369	csgscag(Ghd)auGfCfGfaagauuggaL96		VPusdCscadAcdTcuucdGcAfuccugcgsasa		TTCGCAGGATGCGAAGAGTTGGG	
AD-1640370	gscsagg(Ahd)UfgCfGfAfagauuggga L96		VPusCfsccaAfcUfCfuucgCfaUfccugcsgsa		TCGCAGGATGCGAAGAGTTGGGG	
AD-1640371	gscsagg(Ahd)ugCfGfAfagauuggga L96		VPusdCsccdAadCucuudCgCfauccugcsgsa		TCGCAGGATGCGAAGAGTTGGGG	
AD-1640372	asusuug(Chd)GfaGfAfAfaccagggcgaL96		VPusCfsgcdCc(Tgn)gguuucUfcGfcaaausasa		TTATTTGCGAGAAACCAGGGCGG	
AD-1640373	asusuug(Chd)GfaGfAfAfaccagggcgaL96		VPusCfsgccCfuGfGfuuucUfcGfcaaausasa		TTATTTGCGAGAAACCAGGGCGG	
AD-	asusuug(Chd)gaGfAfAfaccagggcgaL		VPusdCsgcdCcdTgguudTcUfcgcaaauu		TTATTTGCGAGAAACCAGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640374	96		sasa		GCGG	
AD-1640375	usususgc(Ghd)AfgAfAfAfAfccagggcgga L96		VPusCfscgcCfcUfGfguuuCfuCfgcaaa susa		TATTTGCGAGAAACCAGGG CGGG	
AD-1640376	usususgc(Ghd)agAfAfAfAfccagggcggaL 96		VPusdCscgdCcdCuggudTuCfucgcaaa susa		TATTTGCGAGAAACCAGGG CGGG	
AD-1640377	ususgcg(Ahd)GfaAfAfAfCfcagggcggga L96		VPusCfsccgCfcCfUfgguuUfcUfcgcaa sasu		ATTTGCGAGAAACCAGGGC GGGG	
AD-1640378	ususgcg(Ahd)gaAfAfAfCfcagggcgggaL 96		VPusdCsccdGcdCcuggdTuUfcucgcaa sasu		ATTTGCGAGAAACCAGGGC GGGG	
AD-1640379	usasacu(Ghd)CfgUfUfUfGfugaagagaaa L96		VPusUfsucdTc(Tgn)ucacaaCfgCfagu uasasa		TTTAACTGCGTTGTGAAGAG AAC	
AD-1640380	ascsugc(Ghd)UfuGfUfUfGfaagagaacua L96		VPusAfsgudTc(Tgn)cuucacAfaCfgca gususa		TAACTGCGTTGTGAAGAGA ACTT	
AD-1640381	usgscgu(Uhd)GfuGfAfAfAfgagaacuuga L96		VPusCfsaadGu(Tgn)cucuucAfcAfacg casgsu		ACTGCGTTGTGAAGAGAAC TTGG	
AD-1640382	usgscgu(Uhd)GfuGfAfAfgagaacuuga L96		VPusCfsaagUfuCfUfcuucAfcAfacgca sgsu		ACTGCGTTGTGAAGAGAAC TTGG	
AD-1640383	usgscgu(Uhd)guGfAfAfgagaacuugaL 96		VPusdCsaadGudTcucudTcAfcaacgca sgsu		ACTGCGTTGTGAAGAGAAC TTGG	
AD-1640384	gscsguu(Ghd)UfgAfAfGfagaacuugga L96		VPusCfscaaGfuUfCfucuuCfaCfaacgc sasg		CTGCGTTGTGAAGAGAACT TGGA	
AD-1640385	gscsguu(Ghd)ugAfAfGfagaacuuggaL 96		VPusdCscadAgdTucucdTuCfacaacgc sasg		CTGCGTTGTGAAGAGAACT TGGA	
AD-1640386	gsusugu(Ghd)AfaGfAfGfaacuuggaga L96		VPusCfsuccAfaGfUfucuCfuCfacaac sgsc		GCGTTGTGAAGAGAACTTG GAGG	
AD-1640387	gsusugu(Ghd)aaGfAfGfaacuuggagaL 96		VPusdCsucdCadAguucdTcUfucacaac sgsc		GCGTTGTGAAGAGAACTTG GAGG	
AD-1640388	gsusgaa(Ghd)AfgAfAfCfuuggaggaga L96		VPusCfsuccUfcCfAfaguuCfuCfuucac sasa		TTGTGAAGAGAACTTGGAG GAGC	
AD-1640389	gsusgaa(Ghd)agAfAfCfuuggaggagaL 96		VPusdCsucdCudCcaagdTuCfucuucac sasa		TTGTGAAGAGAACTTGGAG GAGC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640390	usgsaag(Ahd)GfaAfCfUfuggaggagca L96		VPusGfscudCc(Tgn)ccaaguUfcUfcuu cascsa		TGTGAAGAGAACTTGGAGG AGCC	
AD-1640391	asgsaga(Ahd)CfuUfGfGfaggagccgaa L96		VPusUfscgdGc(Tgn)ccuccaAfgUfucu cususc		GAAGAGAACTTGGAGGAGC CGAG	
AD-1640392	gsasgaa(Chd)UfuGfGfAfggagccgaga L96		VPusCfsucgGfcUfCfcuccAfaGfuucu csusu		AAGAGAACTTGGAGGAGCC GAGA	
AD-1640393	gsasgaa(Chd)uuGfGfAfggagccgagaL 96		VPusdCsucdGgdCuccudCcAfaguucu csusu		AAGAGAACTTGGAGGAGCC GAGA	
AD-1640394	csusugg(Ahd)GfgAfGfCfcgagauuuga L96		VPusCfsaaaUfcUfCfggcuCfcUfccaag susu		AACTTGGAGGAGCCGAGAT TTGC	
AD-1640395	csusugg(Ahd)ggAfGfCfcgagauuugaL 96		VPusdCsaadAudCucggdCuCfcuccaa gsusu		AACTTGGAGGAGCCGAGAT TTGC	
AD-1640396	ususgga(Ghd)GfaGfCfCfgagauuugca L96		VPusGfscaaAfuCfUfcggcUfcCfuccaa sgsu		ACTTGGAGGAGCCGAGATT TGCT	
AD-1640397	ususgga(Ghd)gaGfCfCfgagauuugcaL 96		VPusdGscadAadTcucgdGcUfccuccaa sgsu		ACTTGGAGGAGCCGAGATT TGCT	
AD-1640398	usgsgag(Ghd)AfgCfCfGfagauuugcua L96		VPusAfsgcaAfaUfCfucggCfuCfcucca sasg		CTTGGAGGAGCCGAGATTT GCTC	
AD-1640399	usgsgag(Ghd)agCfCfGfagauuugcuaL 96		VPusdAsgcdAadAucucdGgCfuccucc asasg		CTTGGAGGAGCCGAGATTT GCTC	
AD-1640400	gsgsagg(Ahd)GfcCfGfAfgauuugcuca L96		VPusGfsagdCa(Agn)aucucgGfcUfcc uccsasa		TTGGAGGAGCCGAGATTTG CTCA	
AD-1640401	gsgsagg(Ahd)GfcCfGfAfgauuugcuca L96		VPusGfsagcAfaAfUfcucgGfcUfccuc csasa		TTGGAGGAGCCGAGATTTG CTCA	
AD-1640402	gsgsagg(Ahd)gcCfGfAfgauuugcucaL 96		VPusdGsagdCadAaucudCgGfcuccuc csasa		TTGGAGGAGCCGAGATTTG CTCA	
AD-1640403	gsasgga(Ghd)CfcGfAfGfauuugcucaa L96		VPusUfsgadGc(Agn)aaucucGfgCfuc cucscsa		TGGAGGAGCCGAGATTTGC TCAG	
AD-1640404	gsasgcc(Ghd)AfgAfUfUfugcucaguga L96		VPusCfsacdTg(Agn)gcaaauCfuCfggc ucscsu		AGGAGCCGAGATTTGCTCA GTGC	
AD-	gscscga(Ghd)AfuUfUfGfcucagugcca		VPusGfsgcdAc(Tgn)gagcaaAfuCfucg		GAGCCGAGATTTGCTCAGT	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640405	L96		gcsusc		GCCA	
AD-1640406	csgsaga(Uhd)UfuGfCfUfcagugccaca L96		VPusGfsugdGc(Agn)cugagcAfaAfuc ucgsgsc		GCCGAGATTTGCTCAGTGCC ACT	
AD-1640407	asususug(Chd)UfcAfGfUfgccacuucca L96		VPusGfsgadAg(Tgn)ggcacuGfaGfcaa auscsu		AGATTTGCTCAGTGCCACTT CCC	
AD-1640408	ususgcu(Chd)AfgUfGfCfcacuucccua L96		VPusAfsggdGa(Agn)guggcaCfuGfag caasasu		ATTTGCTCAGTGCCACTTCC CTC	
AD-1640409	ususgcu(Chd)AfgUfGfCfcacuucccua L96		VPusAfsgggAfaGfUfggcaCfuGfagca asasu		ATTTGCTCAGTGCCACTTCC CTC	
AD-1640410	ususgcu(Chd)agUfGfCfcacuucccuaL 96		VPusdAsggdGadAguggdCaCfugagca asasu		ATTTGCTCAGTGCCACTTCC CTC	
AD-1640411	usgscuc(Ahd)GfuGfCfCfacuucccuca L96		VPusGfsagdGg(Agn)aguggcAfcUfga gcasasa		TTTGCTCAGTGCCACTTCCC TCT	
AD-1640412	usgscuc(Ahd)GfuGfCfCfacuucccuca L96		VPusGfsaggGfaAfGfuggcAfcUfgagc asasa		TTTGCTCAGTGCCACTTCCC TCT	
AD-1640413	usgscuc(Ahd)guGfCfCfacuucccucaL 96		VPusdGsagdGgdAagugdGcAfcugagc asasa		TTTGCTCAGTGCCACTTCCC TCT	
AD-1640414	asgsugc(Chd)AfcUfUfCfccucuucuaa L96		VPusUfsagaAfgAfGfggaaGfuGfgcac usgsa		TCAGTGCCACTTCCCTCTTC TAG	
AD-1640415	asgsugc(Chd)acUfUfCfccucuucuaaL9 6		VPusdTsagdAadGagggdAaGfuggcac usgsa		TCAGTGCCACTTCCCTCTTC TAG	
AD-1640416	gscscac(Uhd)UfcCfCfUfcuucuaguca L96		VPusGfsacuAfgAfAfgaggGfaAfgugg csasc		GTGCCACTTCCCTCTTCTAG TCT	
AD-1640417	gscscac(Uhd)ucCfCfUfcuucuagucaL9 6		VPusdGsacdTadGaagadGgGfaagugg csasc		GTGCCACTTCCCTCTTCTAG TCT	
AD-1640418	cscsacu(Uhd)CfcCfUfCfuucuagucua L96		VPusAfsgadCu(Agn)gaagagGfgAfag uggscsa		TGCCACTTCCCTCTTCTAGT CTG	
AD-1640419	cscsacu(Uhd)CfcCfUfCfuucuagucua L96		VPusAfsgacUfaGfAfagagGfgAfagug gscsa		TGCCACTTCCCTCTTCTAGT CTG	
AD-1640420	cscsacu(Uhd)ccCfUfCfuucuagucuaL9 6		VPusdAsgadCudAgaagdAgGfgaagug gscsa		TGCCACTTCCCTCTTCTAGT CTG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640421	csascuu(Chd)CfcUfCfCfUfucuagucuga L96		VPusCfsagdAc(Tgn)agaagaGfgGfaag ugsgsc		GCCACTTCCCTCTTCTAGTC TGA	
AD-1640422	csascuu(Chd)CfcUfCfCfUfucuagucuga L96		VPusCfsagaCfuAfGfaagaGfgGfaagu gsgsc		GCCACTTCCCTCTTCTAGTC TGA	
AD-1640429	csascuu(Chd)ccUfCfCfUfucuagucugaL 96		VPusdCsagdAcdTagaadGaGfggaagu gsgsc		GCCACTTCCCTCTTCTAGTC TGA	
AD-1640430	ascsuuc(Chd)CfuCfUfUfUfcuagucugaa L96		VPusUfscagAfcUfAfgaagAfgGfgaag usgsg		CCACTTCCCTCTTCTAGTCT GAG	
AD-1640431	csusucc(Chd)UfcUfUfUfCfuagucugaga L96		VPusCfsucdAg(Agn)cuagaaGfaGfgg aagsusg		CACTTCCCTCTTCTAGTCTG AGA	
AD-1640432	csusucc(Chd)UfcUfUfUfCfuagucugaga L96		VPusCfsucaGfaCfUfagaaGfaGfggaag susg		CACTTCCCTCTTCTAGTCTG AGA	
AD-1640433	csusucc(Chd)ucUfUfUfCfuagucugagaL 96		VPusdCsucdAgdAcuagdAaGfagggaa gsusg		CACTTCCCTCTTCTAGTCTG AGA	
AD-1640434	uscscccu(Chd)UfuCfUfUfAfgucugagaga L96		VPusCfsucdTc(Agn)gacuagAfaGfagg gasasg		CTTCCCTCTTCTAGTCTGAG AGG	
AD-1640435	cscsucu(Uhd)CfuAfGfUfUfcugagagggga L96		VPusCfscccdTc(Tgn)cagacuAfgAfaga ggsgsa		TCCCTCTTCTAGTCTGAGAG GGA	
AD-1640436	cscsucu(Uhd)CfuAfGfUfUfcugagagggga L96		VPusCfsccuCfuCfAfgacuAfgAfagag gsgsa		TCCCTCTTCTAGTCTGAGAG GGA	
AD-1640437	cscsucu(Uhd)cuAfGfUfUfcugagagggaL 96		VPusdCsccdTcdTcagadCuAfgaagagg sgsa		TCCCTCTTCTAGTCTGAGAG GGA	
AD-1640438	uscsuuc(Uhd)AfgUfCfUfUfgagagggaaa L96		VPusUfsucdCc(Tgn)cucagaCfuAfgaa gasgsg		CCTCTTCTAGTCTGAGAGGG AAG	
AD-1640439	csusucu(Ahd)GfuCfUfUfGfagagggaaga L96		VPusCfsuucCfcUfCfucagAfcUfagaag sasg		CTCTTCTAGTCTGAGAGGGA AGA	
AD-1640440	csusucu(Ahd)guCfUfUfGfagagggaagaL 96		VPusdCsuudCcdCucucdAgAfcuagaa gsasg		CTCTTCTAGTCTGAGAGGGA AGA	
AD-1640441	uscsuag(Uhd)CfuGfAfGfagggaagaga L96		VPusCfsucuUfcCfCfucucAfgAfcuag asasg		CTTCTAGTCTGAGAGGGAA GAGG	
AD-	uscsuag(Uhd)cuGfAfGfagggaagagaL		VPusdCsucdTudCccucdTcAfgacuaga		CTTCTAGTCTGAGAGGGAA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640442	96		sasg		GAGG	
AD-1640443	csusagu(Chd)UfgAfGfAfgggaagagga L96		VPusCfscudCu(Tgn)cccucuCfaGfacu agsasa		TTCTAGTCTGAGAGGGAAG AGGG	
AD-1640444	csusagu(Chd)UfgAfGfAfgggaagagga L96		VPusCfscucUfuCfCfcucuCfaGfacuag sasa		TTCTAGTCTGAGAGGGAAG AGGG	
AD-1640445	csusagu(Chd)ugAfGfAfgggaagaggaL 96		VPusdCscudCudTcccudCuCfagacuag sasa		TTCTAGTCTGAGAGGGAAG AGGG	
AD-1640446	usasguc(Uhd)GfaGfAfGfggaagaggga L96		VPusCfsccdTc(Tgn)ucccucUfcAfgac uasgsa		TCTAGTCTGAGAGGGAAGA GGGC	
AD-1640447	usasguc(Uhd)GfaGfAfGfggaagaggga L96		VPusCfsccuCfuUfCfccucUfcAfgacua sgsa		TCTAGTCTGAGAGGGAAGA GGGC	
AD-1640448	gsuscug(Ahd)GfaGfGfGfaagagggcua L96		VPusAfsgcdCc(Tgn)cuucccUfcUfcag acsusa		TAGTCTGAGAGGGAAGAGG GCTG	
AD-1640449	uscsuga(Ghd)AfgGfGfAfagagggcuga L96		VPusCfsagcCfcUfCfuuccCfuCfucaga scsu		AGTCTGAGAGGGAAGAGGG CTGG	
AD-1640450	uscsuga(Ghd)agGfGfAfagagggcugaL 96		VPusdCsagdCcdCucuudCcCfucucaga scsu		AGTCTGAGAGGGAAGAGGG CTGG	
AD-1640451	csusgag(Ahd)GfgGfAfAfgagggcugga L96		VPusCfscagCfcCfUfcuucCfcUfcucag sasc		GTCTGAGAGGGAAGAGGGC TGGG	
AD-1640452	csusgag(Ahd)ggGfAfAfgagggcuggaL 96		VPusdCscadGcdCcucudTcCfcucucag sasc		GTCTGAGAGGGAAGAGGGC TGGG	
AD-1640453	ususugg(Ahd)GfcUfGfGfagagauguga L96		VPusCfsacaUfcUfCfuccaGfcUfccaaa scsc		GGTTTGGAGCTGGAGAGAT GTGG	
AD-1640454	ususugg(Ahd)gcUfGfGfagagaugugaL 96		VPusdCsacdAudCucucdCaGfcuccaaa scsc		GGTTTGGAGCTGGAGAGAT GTGG	
AD-1640455	ususgga(Ghd)CfuGfGfGfAfgagaugugga L96		VPusCfscacAfuCfUfcuccAfgCfuccaa sasc		GTTTGGAGCTGGAGAGATG TGGG	
AD-1640456	ususgga(Ghd)cuGfGfGfAfgagauguggaL 96		VPusdCscadCadTcucudCcAfgcuccaa sasc		GTTTGGAGCTGGAGAGATG TGGG	
AD-1640457	gscsagu(Ghd)GfaUfGfAfcauaaugcua L96		VPusAfsgcaUfuAfUfgucaUfcCfacug cscsc		GGGCAGTGGATGACATAAT GCTT	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640458	gscsagu(Ghd)gaUfGfAfcauaaugcuaL96		VPusdAsgcdAudTaugudCaUfccacugcscsc		GGGCAGTGGATGACATAATGCTT	
AD-1640459	csasgug(Ghd)AfuGfAfCfauaaugcuua		VPusAfsagdCa(Tgn)uaugucAfuCfcacugscscsc		GGCAGTGGATGACATAATGCTTT	
AD-1640460	csasgug(Ghd)AfuGfAfCfauaaugcuua		VPusAfsagcAfuUfAfugucAfuCfcacugscsc		GGCAGTGGATGACATAATGCTTT	
AD-1640461	csasgug(Ghd)auGfAfCfauaaugcuuaL96		VPusdAsagdCadTuaugdTcAfuccacugscsc		GGCAGTGGATGACATAATGCTTT	
AD-1640462	usasgga(Chd)GfcCfUfCfggcgggagua		VPusAfscucCfcGfCfcgagGfcGfuccuasasa		TTTAGGACGCCTCGGCGGGAGTG	
AD-1640463	usgsagg(Ghd)CfgCfGfUfccaaugggaa		VPusUfsccdCa(Tgn)uggacgCfgCfccucascsu		AGTGAGGGCGCGTCCAATGGGAG	
AD-1640464	usgsagg(Ghd)CfgCfGfUfccaaugggaa		VPusUfscccAfuUfGfgacgCfgCfccucascsu		AGTGAGGGCGCGTCCAATGGGAG	
AD-1640465	usgsagg(Ghd)cgCfGfUfccaaugggaaL96		VPusdTsccdCadTuggadCgCfgcccucascsu		AGTGAGGGCGCGTCCAATGGGAG	
AD-1640466	gscsguc(Chd)AfaUfGfGfgagauuucua		VPusAfsgadAa(Tgm)cucccaUfuGfgacgcsgsc		GCGCGTCCAATGGGAGATTTCTT	
AD-1640467	gscsguc(Chd)AfaUfGfGfgagauuucua		VPusAfsgaaAfuCfUfcccaUfuGfgacgcsgsc		GCGCGTCCAATGGGAGATTTCTT	
AD-1640468	gscsguc(Chd)aaUfGfGfgagauuucuaL96		VPusdAsgadAadTcuccdCaUfuggacgcsgsc		GCGCGTCCAATGGGAGATTTCTT	
AD-1640469	csgsucc(Ahd)AfuGfGfGfagauuucuua		VPusAfsagaAfaUfCfucccAfuUfggacgscsg		CGCGTCCAATGGGAGATTTCTTT	
AD-1640470	csgsucc(Ahd)auGfGfGfagauuucuuaL96		VPusdAsagdAadAucucdCcAfuuggacgscsg		CGCGTCCAATGGGAGATTTCTTT	
AD-1640471	csasgcc(Uhd)GfaGfAfUfuugaggcucaL96		VPusGfsagdCc(Tgn)caaaucUfcAfggcugsusu		AACAGGCCTGAGATTTGAGGCTCT	
AD-1640472	csusgag(Ahd)UfuUfGfAfggcucuucca		VPusGfsgadAg(Agn)gccucaAfaUfcucagsgsc		GCCTGAGATTTGAGGCTCTTCCT	
AD-	usgsaga(Uhd)UfuGfAfGfgcucuuccua		VPusAfsggaAfgAfGfccucAfaAfucuc		CCTGAGATTTGAGGCTCTTC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640473	L96		asgsg		CTA	
AD-1640474	usgsaga(Uhd)uuGfAfGfgcucuuccuaL96		VPusdAsggdAadGagccdTcAfaaucucasgsg		CCTGAGATTTGAGGCTCTTCCTA	
AD-1640475	gsasgau(Uhd)UfgAfGfGfcucuuccuaaL96		VPusUfsagdGa(Agn)gagccuCfaAfaucucsasg		CTGAGATTTGAGGCTCTTCCTAC	
AD-1640476	gsasgau(Uhd)UfgAfGfGfcucuuccuaaL96		VPusUfsaggAfaGfAfgccuCfaAfaucucsasg		CTGAGATTTGAGGCTCTTCCTAC	
AD-1640477	gsasgau(Uhd)ugAfGfGfcucuuccuaaL96		VPusdTsagdGadAgagcdCuCfaaaucucsasg		CTGAGATTTGAGGCTCTTCCTAC	
AD-1640478	asgsauu(Uhd)GfaGfGfCfucuuccuacaL96		VPusGfsuadGg(Agn)agagccUfcAfaaucuscsa		TGAGATTTGAGGCTCTTCCTACA	
AD-1640479	ususuga(Ghd)GfcUfCfUfuccuacauuaL96		VPusAfsaudGu(Agn)ggaagaGfcCfucaaasusc		GATTTGAGGCTCTTCCTACATTG	
AD-1640480	usgsagg(Chd)UfcUfUfUfCfcuacauugaL96		VPusAfscaaUfgUfAfggaaGfaGfccucasasa		TTTGAGGCTCTTCCTACATTGTC	
AD-1640481	usgsagg(Chd)ucUfUfUfCfcuacauuguaL96		VPusdAscadAudGuaggdAaGfagccucasasa		TTTGAGGCTCTTCCTACATTGTC	
AD-1640482	gsasggc(Uhd)CfuUfCfCfCfuacauuguca L96		VPusGfsacaAfuGfUfaggaAfgAfgccucsasa		TTGAGGCTCTTCCTACATTGTCA	
AD-1640483	gsasggc(Uhd)cuUfCfCfCfuacauugucaL96		VPusdGsacdAadTguagdGaAfgagccucsasa		TTGAGGCTCTTCCTACATTGTCA	
AD-1640484	asgsgcu(Chd)UfuCfCfCfUfacauugucaa L96		VPusUfsgadCa(Agn)uguaggAfaGfagccuscsa		TGAGGCTCTTCCTACATTGTCAG	
AD-1640485	asgsgcu(Chd)UfuCfCfCfUfacauugucaa L96		VPusUfsgacAfaUfGfuaggAfaGfagccuscsa		TGAGGCTCTTCCTACATTGTCAG	
AD-1640486	asgsgcu(Chd)uuCfCfCfUfacauugucaaL96		VPusdTsgadCadAuguadGgAfagagccuscsa		TGAGGCTCTTCCTACATTGTCAG	
AD-1640487	gsgscuc(Uhd)UfcCfUfUfAfcauugucaga L96		VPusCfsugaCfaAfUfguagGfaAfgagccsusc		GAGGCTCTTCCTACATTGTCAGG	
AD-1640488	gsgscuc(Uhd)ucCfUfAfcauugucagaL96		VPusdCsugdAcdAaugudAgGfaagagccsusc		GAGGCTCTTCCTACATTGTCAGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640489	gscsucu(Uhd)CfcUfAfCfauugucagga L96		VPusCfscugAfcAfAfuguaGfgAfagag cscsu		AGGCTCTTCCTACATTGTCA GGA	
AD-1640490	gscsucu(Uhd)ccUfAfCfauugucaggaL 96		VPusdCscudGadCaaugdTaGfgaagagc scsu		AGGCTCTTCCTACATTGTCA GGA	
AD-1640491	csuscuu(Chd)CfuAfCfAfuugucaggaa L96		VPusUfsccdTg(Agn)caauguAfgGfaa gagscsc		GGCTCTTCCTACATTGTCAG GAC	
AD-1640492	csusucc(Uhd)AfcAfUfUfgucaggacaa L96		VPusUfsgudCc(Tgn)gacaauGfuAfgg aagsasg		CTCTTCCTACATTGTCAGGA CAT	
AD-1640493	usascau(Uhd)GfuCfAfGfgacauuucaa L96		VPusUfsgadAa(Tgn)guccugAfcAfau guasgsg		CCTACATTGTCAGGACATTT CAT	
AD-1640494	usascau(Uhd)GfuCfAfGfgacauuucaa L96		VPusUfsgaaAfuGfUfccugAfcAfaugu asgsg		CCTACATTGTCAGGACATTT CAT	
AD-1640495	usascau(Uhd)guCfAfGfgacauuucaaL 96		VPusdTsgadAadTguccdTgAfcaaugua sgsg		CCTACATTGTCAGGACATTT CAT	
AD-1640496	ascsauu(Ghd)UfcAfGfGfacauuucaua L96		VPusAfsugaAfaUfGfuccuGfaCfaaug usasg		CTACATTGTCAGGACATTTC ATT	
AD-1640497	ascsauu(Ghd)ucAfGfGfacauuucauaL 96		VPusdAsugdAadAugucdCuGfacaaug usasg		CTACATTGTCAGGACATTTC ATT	
AD-1640498	csasuug(Uhd)CfaGfGfAfcauuucauua L96		VPusAfsaugAfaAfUfguccUfgAfcaau gsusa		TACATTGTCAGGACATTTCA TTT	
AD-1640499	csasuug(Uhd)caGfGfAfcauuucauuaL 96		VPusdAsaudGadAaugudCcUfgacaau gsusa		TACATTGTCAGGACATTTCA TTT	
AD-1640500	ususguc(Ahd)GfgAfCfAfuuucauuuaa L96		VPusUfsaaaUfgAfAfauguCfcUfgaca asusg		CATTGTCAGGACATTTCATT TAG	
AD-1640501	ususguc(Ahd)ggAfCfAfuuucauuuaaL 96		VPusdTsaadAudGaaaudGuCfcugacaa susg		CATTGTCAGGACATTTCATT TAG	
AD-1640502	uscsagg(Ahd)CfaUfUfUfcauuuaguua L96		VPusAfsacuAfaAfUfgaaaUfgUfccug ascsa		TGTCAGGACATTTCATTTAG TTC	
AD-1640503	uscsagg(Ahd)caUfUfUfcauuuaguuaL 96		VPusdAsacdTadAaugadAaUfguccug ascsa		TGTCAGGACATTTCATTTAG TTC	
AD-	csasgga(Chd)AfuUfUfCfauuuaguuca		VPusGfsaacUfaAfAfugaaAfuGfuccu		GTCAGGACATTTCATTTAGT	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640504	L96		gsasc		TCA	
AD-1640505	csasgga(Chd)auUfUfCfauuuaguucaL96		VPusdGsaadCudAaaugdAaAfuguccugsasc		GTCAGGACATTTCATTTAGTTCA	
AD-1640506	asgsgac(Ahd)UfuUfCfAfuuuaguucaaL96		VPusUfsgadAc(Tgn)aaaugaAfaUfgucusgsa		TCAGGACATTTCATTTAGTTCAT	
AD-1640507	gsgsaca(Uhd)UfuCfAfUfuuaguucauaL96		VPusAfsugaAfcUfAfaaugAfaAfugucsusg		CAGGACATTTCATTTAGTTCATG	
AD-1640508	gsgsaca(Uhd)uuCfAfUfuuaguucauaL96		VPusdAsugdAadCuaaadTgAfaaugucsusg		CAGGACATTTCATTTAGTTCATG	
AD-1640509	ascsauu(Uhd)CfaUfUfUfUfagucaugaaL96		VPusUfscadTg(Agn)acuaaaaUfgAfaaugscscsc		GGACATTTCATTTAGTTCATGAT	
AD-1640510	ascsauu(Uhd)CfaUfUfUfUfagucaugaaL96		VPusUfscauGfaAfCfuaaaUfgAfaaugusccsc		GGACATTTCATTTAGTTCATGAT	
AD-1640511	ususuca(Uhd)UfuAfGfUfucaugaucaaL96		VPusUfsgadTc(Agn)ugaacuAfaAfugaaasusg		CATTTCATTTAGTTCATGATCAC	
AD-1640512	uscsauu(Uhd)AfgUfUfCfaugaucacgaL96		VPusCfsgudGa(Tgn)caugaaCfuAfaaugasasa		TTTCATTTAGTTCATGATCACGG	
AD-1640513	uscsauu(Uhd)AfgUfUfCfaugaucacgaL96		VPusCfsgugAfuCfAfugaaCfuAfaaugasasa		TTTCATTTAGTTCATGATCACGG	
AD-1640514	csasuuu(Ahd)GfuUfCfAfugaucacggaL96		VPusCfscgdTg(Agn)ucaugaAfcUfaaaugsasa		TTCATTTAGTTCATGATCACGGT	
AD-1640515	csasuuu(Ahd)GfuUfCfAfugaucacggaL96		VPusCfscguGfaUfCfaugaAfcUfaaaugsasa		TTCATTTAGTTCATGATCACGGT	
AD-1640516	csasuuu(Ahd)guUfCfAfugaucacggaL96		VPusdCscgdTgdAucaudGaAfcuaaaugsasa		TTCATTTAGTTCATGATCACGGT	
AD-1640517	asusuua(Ghd)UfuCfAfUfgaucacgguaL96		VPusAfsccgUfgAfUfcaugAfaCfuaaausgsa		TCATTTAGTTCATGATCACGGTG	
AD-1640518	asusuua(Ghd)uuCfAfUfgaucacgguaL96		VPusdAsccdGudGaucadTgAfacuaaausgsa		TCATTTAGTTCATGATCACGGTG	
AD-1640519	ususuag(Uhd)UfcAfUfGfaucacgguga L96		VPusCfsaccGfuGfAfucauGfaAfcuaaasusg		CATTTAGTTCATGATCACGGTGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640520	ususuag(Uhd)ucAfUfGfaucacggugaL96		VPusdCsacdCgdTgaucdAuGfaacuaaasusg		CATTTAGTTCATGATCACGGTGG	
AD-1640521	ususagu(Uhd)CfaUfGfAfucacggugga L96		VPusCfscacCfgUfGfaucaUfgAfacuaasasu		ATTTAGTTCATGATCACGGTGGT	
AD-1640522	ususagu(Uhd)caUfGfAfucacgguggaL96		VPusdCscadCcdGugaudCaUfgaacuaasasu		ATTTAGTTCATGATCACGGTGGT	
AD-1640523	usasguu(Chd)AfuGfAfUfcacgguggua L96		VPusAfsccaCfcGfUfgaucAfuGfaacuasasa		TTTAGTTCATGATCACGGTGGTA	
AD-1640524	usasguu(Chd)auGfAfUfcacggugguaL96		VPusdAsccdAcdCgugadTcAfugaacuasasa		TTTAGTTCATGATCACGGTGGTA	
AD-1640525	asgsuuc(Ahd)UfgAfUfCfacgguggguaa L96		VPusUfsaccAfcCfGfugauCfaUfgaacuasasa		TTAGTTCATGATCACGGTGGTAG	
AD-1640526	gsusuca(Uhd)GfaUfCfAfcgguggguaga L96		VPusCfsuacCfaCfCfgugaUfcAfugaacsusa		TAGTTCATGATCACGGTGGTAGT	
AD-1640527	gsusuca(Uhd)gaUfCfAfcgguggguagaL96		VPusdCsuadCcdAccgudGaUfcaugaacsusa		TAGTTCATGATCACGGTGGTAGT	
AD-1640528	csasuga(Uhd)CfaCfGfGfuggguaguaaa L96		VPusUfsuadCu(Agn)ccaccgUfgAfucaugsasa		TTCATGATCACGGTGGTAGTAAC	
AD-1640529	asusgau(Chd)AfcGfGfUfgguaguaaca L96		VPusGfsuudAc(Tgn)accaccGfuGfaucausgsa		TCATGATCACGGTGGTAGTAACA	
AD-1640530	gsasuca(Chd)GfgUfGfGfuaguaacaca L96		VPusGfsugdTu(Agn)cuaccaCfcGfugaucsasu		ATGATCACGGTGGTAGTAACACG	
AD-1640531	gsasuca(Chd)GfgUfGfGfuaguaacaca L96		VPusGfsuguUfaCfUfaccaCfcGfugausasu		ATGATCACGGTGGTAGTAACACG	
AD-1640532	gsasuca(Chd)ggUfGfGfuaguaacacaL96		VPusdGsugdTudAcuacdCaCfcgugausasu		ATGATCACGGTGGTAGTAACACG	
AD-1640533	asuscac(Ghd)GfuGfGfUfaguaacacga L96		VPusCfsgudGu(Tgn)acuaccAfcCfgugauscsa		TGATCACGGTGGTAGTAACACGA	
AD-1640534	asuscac(Ghd)GfuGfGfUfaguaacacga L96		VPusCfsgugUfuAfCfuaccAfcCfgugauscsa		TGATCACGGTGGTAGTAACACGA	
AD-	asuscac(Ghd)guGfGfUfaguaacacgaL		VPusdCsgudGudTacuadCcAfccguga		TGATCACGGTGGTAGTAAC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640535	96		uscsa		ACGA	
AD-1640536	uscsacg(Ghd)UfgGfUfAfguaacacgaaL96		VPusUfscgdTg(Tgn)uacuacCfaCfcgugasusc		GATCACGGTGGTAGTAACACGAT	
AD-1640537	csascgg(Uhd)GfgUfAfGfuaacacgauaL96		VPusAfsucgUfgUfUfacuaCfcAfccgugsasu		ATCACGGTGGTAGTAACACGATT	
AD-1640538	ascsggu(Ghd)GfuAfGfUfaacacgauuaL96		VPusAfsaucGfuGfUfuacuAfcCfaccgusgsa		TCACGGTGGTAGTAACACGATTT	
AD-1640539	ascsggu(Ghd)guAfGfUfaacacgauuaL96		VPusdAsaudCgdTguuadCuAfccaccgusgsa		TCACGGTGGTAGTAACACGATTT	
AD-1640540	gscsacc(Ahd)CfcUfAfAfgagaucugcaL96		VPusGfscadGa(Tgn)cucuuaGfgUfggugcsusu		AAGCACCACCTAAGAGATCTGCT	
AD-1640541	csascca(Chd)CfuAfAfGfagaucugcuaL96		VPusAfsgcdAg(Agn)ucucuuAfgGfuggugscsu		AGCACCACCTAAGAGATCTGCTC	
AD-1640542	cscsacc(Uhd)AfaGfAfGfaucugcucaaL96		VPusUfsgadGc(Agn)gaucucUfuAfggugggusg		CACCACCTAAGAGATCTGCTCAT	
AD-1640543	cscsuaa(Ghd)AfgAfUfCfugcucaucuaL96		VPusAfsgadTg(Agn)gcagauCfuCfuuaggsusg		CACCTAAGAGATCTGCTCATCTA	
AD-1640544	usasaga(Ghd)AfuCfUfGfcucaucuaaaL96		VPusUfsuadGa(Tgn)gagcagAfuCfucuuasgsg		CCTAAGAGATCTGCTCATCTAAG	
AD-1640545	asasgag(Ahd)UfcUfGfCfucaucuaagaL96		VPusCfsuudAg(Agn)ugagcaGfaUfcucuusasg		CTAAGAGATCTGCTCATCTAAGC	
AD-1640546	asasgag(Ahd)UfcUfGfCfucaucuaagaL96		VPusCfsuuaGfaUfGfagcaGfaUfcucuusasg		CTAAGAGATCTGCTCATCTAAGC	
AD-1640547	asasgag(Ahd)ucUfGfCfucaucuaagaL96		VPusdCsuudAgdAugagdCaGfaucucusasg		CTAAGAGATCTGCTCATCTAAGC	
AD-1640548	asgsaga(Uhd)CfuGfCfUfcaucuaagcaL96		VPusGfscuuAfgAfUfgagcAfgAfucucususa		TAAGAGATCTGCTCATCTAAGCC	
AD-1640549	asgsaga(Uhd)cuGfCfUfcaucuaagcaL96		VPusdGscudTadGaugadGcAfgaucucususa		TAAGAGATCTGCTCATCTAAGCC	
AD-1640550	gsasgau(Chd)UfgCfUfCfaucuaagccaL96		VPusGfsgcdTu(Agn)gaugagCfaGfaucucsusu		AAGAGATCTGCTCATCTAAGCCT	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640551	gsasgau(Chd)UfgCfUfCfaucuaagcca L96		VPusGfsgcuUfaGfAfugagCfaGfaucu csusu		AAGAGATCTGCTCATCTAA GCCT	
AD-1640552	asgsauc(Uhd)GfcUfCfAfucuaagccua L96		VPusAfsggdCu(Tgn)agaugaGfcAfga ucuscsu		AGAGATCTGCTCATCTAAG CCTA	
AD-1640553	gsasucu(Ghd)CfuCfAfUfcuaagccuaa L96		VPusUfsagdGc(Tgn)uagaugAfgCfag aucsusc		GAGATCTGCTCATCTAAGCC TAA	
AD-1640554	csusgcu(Chd)AfuCfUfAfagccuaagua L96		VPusAfscuuAfgGfCfuuagAfuGfagca gsasu		ATCTGCTCATCTAAGCCTAA GTT	
AD-1640555	csusgcu(Chd)auCfUfAfagccuaaguaL 96		VPusdAscudTadGgcuudAgAfugagca gsasu		ATCTGCTCATCTAAGCCTAA GTT	
AD-1640556	usgscuc(Ahd)UfcUfAfAfgccuaaguua L96		VPusAfsacdTu(Agn)ggcuuaGfaUfga gcasgsa		TCTGCTCATCTAAGCCTAAG TTG	
AD-1640557	usgscuc(Ahd)UfcUfAfAfgccuaaguua L96		VPusAfsacuUfaGfGfcuuaGfaUfgagc asgsa		TCTGCTCATCTAAGCCTAAG TTG	
AD-1640558	usgscuc(Ahd)ucUfAfAfgccuaaguuaL 96		VPusdAsacdTudAggcudTaGfaugagc asgsa		TCTGCTCATCTAAGCCTAAG TTG	
AD-1640559	gscsuca(Uhd)CfuAfAfGfccuaaguuga L96		VPusCfsaacUfuAfGfgcuuAfgAfugag csasg		CTGCTCATCTAAGCCTAAGT TGG	
AD-1640560	gscsuca(Uhd)cuAfAfGfccuaaguugaL 96		VPusdCsaadCudTaggcdTuAfgaugagc sasg		CTGCTCATCTAAGCCTAAGT TGG	
AD-1640561	csuscau(Chd)UfaAfGfCfcuaaguugga L96		VPusCfscaaCfuUfAfggcuUfaGfauga gscsa		TGCTCATCTAAGCCTAAGTT GGT	
AD-1640562	csuscau(Chd)uaAfGfCfcuaaguuggaL 96		VPusdCscadAcdTuaggdCuUfagauga gscsa		TGCTCATCTAAGCCTAAGTT GGT	
AD-1640563	uscsauc(Uhd)AfaGfCfCfcuaaguuggua L96		VPusAfsccaAfcUfUfUfaggcUfuAfgaug asgsc		GCTCATCTAAGCCTAAGTTG GTC	
AD-1640564	uscsauc(Uhd)aaGfCfCfcuaaguugguaL 96		VPusdAsccdAadCuuagdGcUfuagaug asgsc		GCTCATCTAAGCCTAAGTTG GTC	
AD-1640565	csasucu(Ahd)AfgCfCfUfaaguugguca L96		VPusGfsacdCa(Agn)cuuaggCfuUfag augsasg		CTCATCTAAGCCTAAGTTGG TCT	
AD-	csasucu(Ahd)AfgCfCfUfaaguugguca		VPusGfsaccAfaCfUfuaggCfuUfagau		CTCATCTAAGCCTAAGTTGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640566	L96		gsasg		TCT	
AD-1640567	csasucu(Ahd)agCfCfUfaaguuggucaL96		VPusdGsacdCadAcuuadGgCfuuagausgsasg		CTCATCTAAGCCTAAGTTGGTCT	
AD-1640568	asuscua(Ahd)GfcCfUfAfaguuggucuaL96		VPusAfsgacCfaAfCfuuagGfcUfuagausgsa		TCATCTAAGCCTAAGTTGGTCTG	
AD-1640569	asuscua(Ahd)gcCfUfAfaguuggucuaL96		VPusdAsgadCcdAacuudAgGfcuuagausgsa		TCATCTAAGCCTAAGTTGGTCTG	
AD-1640570	uscsuaa(Ghd)CfcUfAfAfguuggucugaL96		VPusCfsagaCfcAfAfcuuaGfgCfuuagasusg		CATCTAAGCCTAAGTTGGTCTGC	
AD-1640571	uscsuaa(Ghd)ccUfAfAfguuggucugaL96		VPusdCsagdAcdCaacudTaGfgcuuagasusg		CATCTAAGCCTAAGTTGGTCTGC	
AD-1640572	csusaag(Chd)CfuAfAfGfuuggucugcaL96		VPusGfscagAfcCfAfacuuAfgGfcuuagsasu		ATCTAAGCCTAAGTTGGTCTGCA	
AD-1640573	usasagc(Chd)UfaAfGfUfuggucugcaaL96		VPusUfsgcdAg(Agm)ccaacuUfaGfgcuuasgsa		TCTAAGCCTAAGTTGGTCTGCAG	
AD-1640574	asgsccu(Ahd)AfgUfUfGfgucugcaggaL96		VPusCfscudGc(Agm)gaccaaCfuUfaggcususa		TAAGCCTAAGTTGGTCTGCAGGC	
AD-1640575	cscsuaa(Ghd)UfuGfGfUfcugcaggcgaL96		VPusCfsgccUfgCfAfgaccAfaCfuuaggscsu		AGCCTAAGTTGGTCTGCAGGCGT	
AD-1640576	csusaag(Uhd)UfgGfUfCfugcaggcguaL96		VPusAfscgdCc(Tgn)gcagacCfaAfcuuagsgsc		GCCTAAGTTGGTCTGCAGGCGTT	
AD-1640577	usasagu(Uhd)GfgUfCfUfgcaggcguuaL96		VPusAfsacgCfcUfGfcagaCfcAfacuuasgsg		CCTAAGTTGGTCTGCAGGCGTTT	
AD-1640578	usasagu(Uhd)ggUfCfUfgcaggcguuaL96		VPusdAsacdGcdCugcadGaCfcaacuuasgsg		CCTAAGTTGGTCTGCAGGCGTTT	
AD-1640579	asgsuug(Ghd)UfcUfGfCfaggcguuugaL96		VPusCfsaaaCfgCfCfugcaGfaCfcaacususa		TAAGTTGGTCTGCAGGCGTTTGA	
AD-1640580	asgsuug(Ghd)ucUfGfCfaggcguuugaL96		VPusdCsaadAcdGccugdCaGfaccaacususa		TAAGTTGGTCTGCAGGCGTTTGA	
AD-1640581	usgsguc(Uhd)GfcAfGfGfcguuugaaaL96		VPusAfsuucAfaAfCfgccuGfcAfgaccasasc		GTTGGTCTGCAGGCGTTTGAATG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640582	usgsguc(Uhd)gcAfGfGfcguuugaauaL96		VPusdAsuudCadAacgcdCuGfcagacc asasc		GTTGGTCTGCAGGCGTTTGAATG	
AD-1640583	gsgsucu(Ghd)CfaGfGfCfguuugaauga L96		VPusCfsaudTc(Agn)aacgccUfgCfaga ccsasa		TTGGTCTGCAGGCGTTTGAATGA	
AD-1640584	gsgsucu(Ghd)CfaGfGfCfguuugaauga L96		VPusCfsauuCfaAfAfcgccUfgCfagacc sasa		TTGGTCTGCAGGCGTTTGAATGA	
AD-1640585	gsgsucu(Ghd)caGfGfCfguuugaaugaL96		VPusdCsaudTcdAaacgdCcUfgcagacc sasa		TTGGTCTGCAGGCGTTTGAATGA	
AD-1640586	uscsugc(Ahd)GfgCfGfUfuugaaugaga scsc		VPusCfsucaUfuCfAfaacgCfcUfgcaga scsc		GGTCTGCAGGCGTTTGAATGAGT	
AD-1640587	uscsugc(Ahd)ggCfGfUfuugaaugagaL96		VPusdCsucdAudTcaaadCgCfcugcaga scsc		GGTCTGCAGGCGTTTGAATGAGT	
AD-1640588	csusgca(Ghd)GfcGfUfUfUfugaaugagua L96		VPusAfscudCa(Tgn)ucaaacGfcCfugc agsasc		GTCTGCAGGCGTTTGAATGAGTT	
AD-1640589	csusgca(Ghd)GfcGfUfUfUfugaaugagua L96		VPusAfscucAfuUfCfaaacGfcCfugcag sasc		GTCTGCAGGCGTTTGAATGAGTT	
AD-1640590	csusgca(Ghd)gcGfUfUfUfugaaugaguaL96		VPusdAscudCadTucaadAcGfccugcag sasc		GTCTGCAGGCGTTTGAATGAGTT	
AD-1640591	usgscag(Ghd)CfgUfUfUfUfgaaugaguua casgsa		VPusAfsacdTc(Agn)uucaaaCfgCfcug		TCTGCAGGCGTTTGAATGAGTTG	
AD-1640592	gscsagg(Chd)GfuUfUfUfGfaaugaguuga L96		VPusCfsaacUfcAfUfucaaAfcGfccugc sasg		CTGCAGGCGTTTGAATGAGTTGT	
AD-1640593	gscsagg(Chd)guUfUfUfGfaaugaguugaL96		VPusdCsaadCudCauucdAaAfcgccug csasg		CTGCAGGCGTTTGAATGAGTTGT	
AD-1640594	csasggc(Ghd)UfuUfGfAfaugaguugua L96		VPusAfscadAc(Tgn)cauucaAfaCfgcc ugscsa		TGCAGGCGTTTGAATGAGTTGTG	
AD-1640595	csasggc(Ghd)UfuUfGfAfaugaguugua L96		VPusAfscaaCfuCfAfuucaAfaCfgccug scsa		TGCAGGCGTTTGAATGAGTTGTG	
AD-1640596	csasggc(Ghd)uuUfGfAfaugaguuguaL96		VPusdAscadAcdTcauudCaAfacgccug scsa		TGCAGGCGTTTGAATGAGTTGTG	
AD-	asgsgcg(Uhd)UfuGfAfAfugaguuguga		VPusCfsacaAfcUfCfauucAfaAfcgccu		GCAGGCGTTTGAATGAGTT	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640597	L96		sgsc		GTGG	
AD-1640598	asgsgcg(Uhd)uuGfAfAfugaguugugaL96		VPusdCsacdAadCucaudTcAfaacgccusgsc		GCAGGCGTTTGAATGAGTTGTGG	
AD-1640599	gscsguu(Uhd)GfaAfUfGfaguuguggua L96		VPusAfsccaCfaAfCfucauUfcAfaacgcscsu		AGGCGTTTGAATGAGTTGTGGTT	
AD-1640600	gscsguu(Uhd)gaAfUfGfaguuguggua L96		VPusdAsccdAcdAacucdAuUfcaaacgcscsu		AGGCGTTTGAATGAGTTGTGGTT	
AD-1640601	gsusuug(Ahd)AfuGfAfGfuugugguug aL96		VPusCfsaacCfaCfAfacucAfuUfcaaacsgsc		GCGTTTGAATGAGTTGTGGTTGC	
AD-1640602	gsusuug(Ahd)auGfAfGfuuguggauga L96		VPusdCsaadCcdAcaacdTcAfuucaaacsgsc		GCGTTTGAATGAGTTGTGGTTGC	
AD-1640603	ususuga(Ahd)UfgAfGfUfuguggauugca L96		VPusGfscaaCfcAfCfaacuCfaUfucaaascsg		CGTTTGAATGAGTTGTGGTTGCC	
AD-1640604	ususuga(Ahd)ugAfGfUfuguggauugcaL96		VPusdGscadAcdCacaadCuCfauucaaascsg		CGTTTGAATGAGTTGTGGTTGCC	
AD-1640605	ususgaa(Uhd)GfaGfUfUfguggauugcca L96		VPusGfsgcaAfcCfAfcaacUfcAfuucaasasc		GTTTGAATGAGTTGTGGTTGCCA	
AD-1640606	ususgaa(Uhd)gaGfUfUfguggauugccaL96		VPusdGsgcdAadCcacdAcUfcauucaasasc		GTTTGAATGAGTTGTGGTTGCCA	
AD-1640607	usgsaau(Ghd)AfgUfUfGfuggauugccaa L96		VPusUfsggdCa(Agn)ccacaaCfuCfauucasasa		TTTGAATGAGTTGTGGTTGCCAA	
AD-1640608	gsasguu(Ghd)UfgGfUfUfUfgccaaguaaa L96		VPusUfsuadCu(Tgn)ggcaacCfaCfaacucsasu		ATGAGTTGTGGTTGCCAAGTAAA	
AD-1640609	asgsuug(Uhd)GfgUfUfUfGfccaaguaaaa L96		VPusUfsuudAc(Tgn)uggcaaCfcAfcaacuscsa		TGAGTTGTGGTTGCCAAGTAAAG	
AD-1640610	gsusugu(Ghd)GfuUfGfCfCfcaaguaaaga L96		VPusCfsuuuAfcUfUfUfggcaAfcCfacaacsusc		GAGTTGTGGTTGCCAAGTAAAGT	
AD-1640611	gsusugu(Ghd)guUfGfCfCfcaaguaaagaL96		VPusdCsuudTadCuuggdCaAfccacaacsusc		GAGTTGTGGTTGCCAAGTAAAGT	
AD-1640612	ususgug(Ghd)UfuGfCfCfCfaaguaaagua L96		VPusAfscuuUfaCfUfuggcAfaCfcacascsu		AGTTGTGGTTGCCAAGTAAAGTG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640613	ususgug(Ghd)uuGfCfCfaaguaaaguaL96		VPusdAscudTudAcuugdGcAfaccaca ascsu		AGTTGTGGTTGCCAAGTAA AGTG	
AD-1640614	usgsguu(Ghd)CfcAfAfGfuaaaguggua L96		VPusAfsccdAc(Tgn)uuacuuGfgCfaac cascsa		TGTGGTTGCCAAGTAAAGT GGTG	
AD-1640615	usgsguu(Ghd)CfcAfAfGfuaaaguggua L96		VPusAfsccaCfuUfUfacuuGfgCfaacca scsa		TGTGGTTGCCAAGTAAAGT GGTG	
AD-1640616	usgsguu(Ghd)ccAfAfGfuaaagugguaL96		VPusdAsccdAcdTuuacdTuGfgcaacca scsa		TGTGGTTGCCAAGTAAAGT GGTG	
AD-1640617	gsgsuug(Chd)CfaAfGfUfaaagugguga L96		VPusCfsaccAfcUfUfuacuUfgGfcaacc sasc		GTGGTTGCCAAGTAAAGTG GTGA	
AD-1640618	gsgsuug(Chd)caAfGfUfaaagugguga L96		VPusdCsacdCadCuuuadCuUfggcaacc sasc		GTGGTTGCCAAGTAAAGTG GTGA	
AD-1640619	gscscaa(Ghd)UfaAfAfGfuggugaacua L96		VPusAfsgudTc(Agn)ccacuuUfaCfuu ggcsasa		TTGCCAAGTAAAGTGGTGA ACTT	
AD-1640620	csasagu(Ahd)AfaGfUfGfgugaacuuaa L96		VPusUfsaadGu(Tgn)caccacUfuUfacu ugsgsc		GCCAAGTAAAGTGGTGAAC TTAC	
AD-1640621	asasgua(Ahd)AfgUfGfGfugaacuuaca L96		VPusGfsuadAg(Tgn)ucaccaCfuUfuac uusgsg		CCAAGTAAAGTGGTGAACT TACG	
AD-1640622	asgsuaa(Ahd)GfuGfGfUfgaacuuacga L96		VPusCfsguaAfgUfUfcaccAfcUfuuac ususg		CAAGTAAAGTGGTGAACTT ACGT	
AD-1640623	asgsuaa(Ahd)guGfGfUfgaacuuacgaL96		VPusdCsgudAadGuucadCcAfcuuuac ususg		CAAGTAAAGTGGTGAACTT ACGT	
AD-1640624	gsusaaa(Ghd)UfgGfUfGfaacuuacgua L96		VPusAfscguAfaGfUfucacCfaCfuuua csusu		AAGTAAAGTGGTGAACTTA CGTG	
AD-1640625	gsusaaa(Ghd)ugGfUfGfaacuuacguaL96		VPusdAscgdTadAguucdAcCfacuuua csusu		AAGTAAAGTGGTGAACTTA CGTG	
AD-1640626	usasaag(Uhd)GfgUfGfAfacuuacguga L96		VPusCfsacgUfaAfGfuucaCfcAfcuuu ascsu		AGTAAAGTGGTGAACTTAC GTGG	
AD-1640627	usasaag(Uhd)ggUfGfAfacuuacgugaL96		VPusdCsacdGudAaguudCaCfcacuuu ascsu		AGTAAAGTGGTGAACTTAC GTGG	
AD-	asasagu(Ghd)GfuGfAfAfcuuacgugga		VPusCfscacGfuAfAfguucAfcCfacuu		GTAAAGTGGTGAACTTACG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640628	L96		usasc		TGGT	
AD-1640629	asasagu(Ghd)guGfAfAfcuuacguggaL96		VPusdCscadCgdTaagudTcAfccacuuusasc		GTAAAGTGGTGAACTTACGTGGT	
AD-1640630	asasgug(Ghd)UfgAfAfCfuuacguggua		VPusAfsccaCfgUfAfaguuCfaCfcacuususa		TAAAGTGGTGAACTTACGTGGTG	
AD-1640631	asasgug(Ghd)ugAfAfCfuuacgugguaL96		VPusdAsccdAcdGuaagdTuCfaccacuususa		TAAAGTGGTGAACTTACGTGGTG	
AD-1640632	asgsugg(Uhd)GfaAfCfUfuacgugguga		VPusCfsaccAfcGfUfaaguUfcAfccacususu		AAAGTGGTGAACTTACGTGGTGA	
AD-1640633	asgsugg(Uhd)gaAfCfUfuacgguggugaL96		VPusdCsacdCadCguaadGuUfcaccacususu		AAAGTGGTGAACTTACGTGGTGA	
AD-1640634	gsusggu(Ghd)AfaCfUfUfacgugguguaa		VPusUfscadCc(Agn)cguaagUfuCfaccacsusu		AAGTGGTGAACTTACGTGGTGAT	
AD-1640635	gsusggu(Ghd)AfaCfUfUfacgugguguaa		VPusUfscacCfaCfGfuaagUfuCfaccacsusu		AAGTGGTGAACTTACGTGGTGAT	
AD-1640636	gsusggu(Ghd)aaCfUfUfacgugguguaaL96		VPusdTscadCcdAcguadAgUfucaccacsusu		AAGTGGTGAACTTACGTGGTGAT	
AD-1640637	gsusgaa(Chd)UfuAfCfGfuggugauuaa		VPusUfsaadTc(Agn)ccacguAfaGfuucacscsa		TGGTGAACTTACGTGGTGATTAA	
AD-1640638	gsasacu(Uhd)AfcGfUfGfgugauuaaua		VPusAfsuudAa(Tgn)caccacGfuAfaguucsasc		GTGAACTTACGTGGTGATTAATG	
AD-1640639	gsasacu(Uhd)AfcGfUfGfgugauuaaua		VPusAfsuuaAfuCfAfccacGfuAfaguucsasc		GTGAACTTACGTGGTGATTAATG	
AD-1640640	gsasacu(Uhd)acGfUfGfgugauuaauaL96		VPusdAsuudAadTcaccdAcGfuaaguucsasc		GTGAACTTACGTGGTGATTAATG	
AD-1640641	asascuu(Ahd)CfgUfGfGfugauuaauga		VPusCfsauuAfaUfCfaccaCfgUfaaguuscsa		TGAACTTACGTGGTGATTAATGA	
AD-1640642	asascuu(Ahd)cgUfGfGfugauuaaugaL96		VPusdCsaudTadAucacdCaCfguaaguuscsa		TGAACTTACGTGGTGATTAATGA	
AD-1640643	ascsuua(Chd)GfuGfGfUfgauuaaugaa		VPusUfscauUfaAfUfcaccAfcGfuaagususc		GAACTTACGTGGTGATTAATGAA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640644	ascsuua(Chd)guGfGfUfgauuaaugaaL96		VPusdTscadTudAaucadCcAfcguaagusc		GAACTTACGTGGTGATTAATGAA	
AD-1640645	csusuac(Ghd)UfgGfUfGfauuaaugaaaL96		VPusUfsucdAu(Tgn)aaucacCfaCfguaagsusu		AACTTACGTGGTGATTAATGAAA	
AD-1640646	csusuac(Ghd)UfgGfUfGfauuaaugaaaL96		VPusUfsucaUfuAfAfucacCfaCfguaagsusu		AACTTACGTGGTGATTAATGAAA	
AD-1640647	csusuac(Ghd)ugGfUfGfauuaaugaaaL96		VPusdTsucdAudTaaucdAcCfacguaagsusu		AACTTACGTGGTGATTAATGAAA	
AD-1640648	ususacg(Uhd)GfgUfGfAfuuaaugaaaaL96		VPusUfsuudCa(Tgn)uaaucaCfcAfcguaasgsu		ACTTACGTGGTGATTAATGAAAT	
AD-1640649	usascgu(Ghd)GfuGfAfUfuaaugaaauaL96		VPusAfsuudTc(Agn)uuaaucAfcCfacguasasg		CTTACGTGGTGATTAATGAAATT	
AD-1640650	usgsgug(Ahd)UfuAfAfUfgaaauuaucaL96		VPusGfsaudAa(Tgn)uucauuAfaUfcaccascsg		CGTGGTGATTAATGAAATTATCT	
AD-1640651	usgsgug(Ahd)UfuAfAfUfgaaauuaucaL96		VPusGfsauaAfuUfUfcauuAfaUfcaccascsg		CGTGGTGATTAATGAAATTATCT	
AD-1640652	usgsgug(Ahd)uuAfAfUfgaaauuaucaL96		VPusdGsaudAadTuucadTuAfaucaccascsg		CGTGGTGATTAATGAAATTATCT	
AD-1640653	asgsuuu(Ghd)GfgCfCfCfgcugcagcuaL96		VPusAfsgcdTg(C2p)agcgggCfcCfaaacuscsa		TGAGTTTGGGCCCGCTGCAGCTC	
AD-1640654	usgsgcg(Ghd)UfaAfCfCfcugcagccuaL96		VPusAfsggdCu(G2p)caggguUfaCfcgccasusc		GATGGCGGTAACCCTGCAGCCTG	
AD-1640655	csasgag(Ahd)CfaGfAfGfugacccagcaL96		VPusGfscudGg(G2p)ucacucUfgUfcucugscsg		CGCAGAGACAGAGTGACCCAGCA	
AD-1640656	asgsaga(Chd)AfgAfGfUfgacccagcaaL96		VPusUfsgcdTg(G2p)gucacuCfuGfucucusgsc		GCAGAGACAGAGTGACCCAGCAA	
AD-1640657	gsasgac(Ahd)GfaGfUfGfacccagcaaaL96		VPusUfsugdCu(G2p)ggucacUfcUfgucucsusg		CAGAGACAGAGTGACCCAGCAAC	
AD-1640658	gsascag(Ahd)GfuGfAfCfccagcaaccaL96		VPusGfsgudTg(C2p)ugggucAfcUfcugucsusc		GAGACAGAGTGACCCAGCAACCC	
AD-	ascsaga(Ghd)UfgAfCfCfcagcaacccaL		VPusGfsggdTu(G2p)cuggguCfaCfuc		AGACAGAGTGACCCAGCAA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640659	96		uguscsu		CCCA	
AD-1640660	gsasgug(Ahd)CfcCfAfGfcaacccagaaL96		VPusUfscudGg(G2p)uugcugGfgUfcacucsusg		CAGAGTGACCCAGCAACCCAGAG	
AD-1640661	asgsuga(Chd)CfcAfGfCfaacccagagaL96		VPusCfsucdTg(G2p)guugcuGfgGfucacuscsu		AGAGTGACCCAGCAACCCAGAGC	
AD-1640662	asgscaa(Chd)CfcAfGfAfgcccaugagaL96		VPusCfsucdAu(G2p)ggcucuGfgGfuugcusgsg		CCAGCAACCCAGAGGCCCATGAGG	
AD-1640663	asascccc(Ahd)GfaGfCfCfcaugagggaaL96		VPusUfsccdCu(C2p)augggcUfcUfggguusgsc		GCAACCCAGAGCCCATGAGGGAC	
AD-1640664	cscscag(Ahd)GfcCfCfAfugagggacaaL96		VPusUfsgudCc(C2p)ucauggGfcUfcugggsusu		AACCCAGAGCCCATGAGGGACAC	
AD-1640665	cscsaga(Ghd)CfcCfAfUfgagggacacaL96		VPusGfsugdTc(C2p)cucaugGfgCfucuggsgsu		ACCCAGAGCCCATGAGGGACACC	
AD-1640666	csgscuc(Chd)CfuCfAfCfuugggucuuaL96		VPusAfsagdAc(C2p)caagugAfgGfgagcgsgsg		CCCGCTCCCTCACTTGGGTCTTC	
AD-1640667	gscsucc(Chd)UfcAfCfUfugggucucaL96		VPusGfsaadGa(C2p)ccaaguGfaGfggagcsgsg		CCGCTCCCTCACTTGGGTCTTCC	
AD-1640668	uscsccu(Chd)AfcUfUfGfggucucccaL96		VPusGfsggdAa(G2p)acccaaGfuGfaggasgsc		GCTCCCTCACTTGGGTCTTCCCT	
AD-1640669	uscsacu(Uhd)GfgGfUfCfuucccuugua L96		VPusAfscadAg(G2p)gaagacCfcAfagugasgsg		CCTCACTTGGGTCTTCCCTTGTC	
AD-1640670	csascuu(Ghd)GfgUfCfUfucccuuguca L96		VPusGfsacdAa(G2p)ggaagaCfcCfaagugsasg		CTCACTTGGGTCTTCCCTTGTCC	
AD-1640671	ususggg(Uhd)CfuUfCfCfcuuguccuca L96		VPusGfsagdGa(C2p)aagggaAfgAfcccaasgsu		ACTTGGGTCTTCCCTTGTCCTCT	
AD-1640672	gsgsguc(Uhd)UfcCfCfUfuguccucuca L96		VPusGfsagdAg(G2p)acaaggGfaAfgacccsasa		TTGGGTCTTCCCTTGTCCTCTCG	
AD-1640673	gsgsucu(Uhd)CfcCfUfUfgucccucga L96		VPusCfsgadGa(G2p)gacaagGfgAfagaccscsa		TGGGTCTTCCCTTGTCCTCTCGC	
AD-1640674	cscscuu(Ghd)UfcCfUfCfucgcgaggga L96		VPusCfsccdTc(G2p)cgagagGfaCfaaggsasa		TTCCCTTGTCCTCTCGCGAGGGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640675	gscscug(Uhd)CfcUfGfAfauucaccgaa L96		VPusUfscgdGu(G2p)aauucaGfgAfca ggcscsc		GGGCCTGTCCTGAATTCACC GAG	
AD-1640676	csusguc(Chd)UfgAfAfUfucaccgagga L96		VPusCfscudCg(G2p)ugaauuCfaGfga cagsgsc		GCCTGTCCTGAATTCACCGA GGG	
AD-1640677	gscsccu(Uhd)CfgCfAfGfgaugcgaaga L96		VPusCfsuudCg(C2p)auccugCfgAfag ggcsgsa		TCGCCCTTCGCAGGATGCG AAGA	
AD-1640678	cscscuu(Chd)GfcAfGfGfaugcgaagaa L96		VPusUfscudTc(G2p)cauccuGfcGfaag ggscsg		CGCCCTTCGCAGGATGCGA AGAG	
AD-1640679	cscsuuc(Ghd)CfaGfGfAfugcgaagaga L96		VPusCfsucdTu(C2p)gcauccUfgCfgaa ggsgsc		GCCCTTCGCAGGATGCGAA GAGT	
AD-1640680	uscsgca(Ghd)GfaUfGfCfgaagauuga L96		VPusCfsaadCu(C2p)uucgcaUfcCfugc gasasg		CTTCGCAGGATGCGAAGAG TTGG	
AD-1640681	usasuuu(Ghd)CfgAfGfAfaaccagggca L96		VPusGfsccdCu(G2p)guuucuCfgCfaa auasasa		TTTATTTGCGAGAAACCAG GGCG	
AD-1640682	asascug(Chd)GfuUfGfUfgaagagaaca L96		VPusGfsuudCu(C2p)uucacaAfcGfca guusasa		TTAACTGCGTTGTGAAGAG AACT	
AD-1640683	csusgcg(Uhd)UfgUfGfAfagagaacuua L96		VPusAfsagdTu(C2p)ucuucaCfaAfcgc agsusu		AACTGCGTTGTGAAGAGAA CTTG	
AD-1640684	csgsuug(Uhd)GfaAfGfAfgaacuuggaa L96		VPusUfsccdAa(G2p)uucucuUfcAfca acgscsa		TGCGTTGTGAAGAGAACTT GGAG	
AD-1640685	gsusgaa(Ghd)AfgAfAfCfuuggaggaga L96		VPusCfsucdCu(C2p)caaguuCfuCfuuc acsasa		TTGTGAAGAGAACTTGGAG GAGC	
AD-1640686	gsasaga(Ghd)AfaCfUfUfgaggagcca L96		VPusGfsgcdTc(C2p)uccaagUfuCfucu ucsasc		GTGAAGAGAACTTGGAGGA GCCG	
AD-1640687	asasgag(Ahd)AfcUfUfGfgaggagccga L96		VPusCfsggdCu(C2p)cuccaaGfuUfcuc uuscsa		TGAAGAGAACTTGGAGGAG CCGA	
AD-1640688	gsasgaa(Chd)UfuGfGfAfggagccgaga L96		VPusCfsucdGg(C2p)uccucccAfaGfuu cucsusu		AAGAGAACTTGGAGGAGCC GAGA	
AD-1640689	asgsaac(Uhd)UfgGfAfGfgagccgagaa L96		VPusUfscudCg(G2p)cuccucCfaAfgu ucuscsu		AGAGAACTTGGAGGAGCCG AGAT	
AD-	gsasacu(Uhd)GfgAfGfGfagccgagaua		VPusAfsucdTc(G2p)gcuccuCfcAfagu		GAGAACTTGGAGGAGCCGA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640690	L96		ucsusc		GATT	
AD-1640691	asascuu(Ghd)GfaGfGfAfgccgagauua L96		VPusAfsaudCu(C2p)ggcuccUfcCfaag uuscsu		AGAACTTGGAGGAGCCGAG ATTT	
AD-1640692	asgsgag(Chd)CfgAfGfAfuuugcucaga L96		VPusCfsugdAg(C2p)aaaucuCfgGfcu ccuscsc		GGAGGAGCCGAGATTTGCT CAGT	
AD-1640693	gsgsagc(Chd)GfaGfAfUfuugcucagua L96		VPusAfscudGa(G2p)caaaucUfcGfgc uccsusc		GAGGAGCCGAGATTTGCTC AGTG	
AD-1640694	asgsccg(Ahd)GfaUfUfUfgcucagugca L96		VPusGfscadCu(G2p)agcaaaUfcUfcgg cuscsc		GGAGCCGAGATTTGCTCAG TGCC	
AD-1640695	cscsgag(Ahd)UfuUfGfCfucagugccaa L96		VPusUfsggdCa(C2p)ugagcaAfaUfcu cggscsu		AGCCGAGATTTGCTCAGTG CCAC	
AD-1640696	gsasgau(Uhd)UfgCfUfCfagugccacua L96		VPusAfsgudGg(C2p)acugagCfaAfau cucsgsg		CCGAGATTTGCTCAGTGCCA CTT	
AD-1640697	asgsauu(Uhd)GfcUfCfAfgugccacuua L96		VPusAfsagdTg(G2p)cacugaGfcAfaau cuscsg		CGAGATTTGCTCAGTGCCAC TTC	
AD-1640698	gsasuuu(Ghd)CfuCfAfGfugccacuuca L96		VPusGfsaadGu(G2p)gcacugAfgCfaa aucsusc		GAGATTTGCTCAGTGCCACT TCC	
AD-1640699	ususugc(Uhd)CfaGfUfGfccacuuccca L96		VPusGfsggdAa(G2p)uggcacUfgAfgc aaasusc		GATTTGCTCAGTGCCACTTC CCT	
AD-1640700	gscsuca(Ghd)UfgCfCfAfcuucccucua L96		VPusAfsgadGg(G2p)aaguggCfaCfug agcsasa		TTGCTCAGTGCCACTTCCCT CTT	
AD-1640701	csuscag(Uhd)GfcCfAfCfuucccucuua L96		VPusAfsagdAg(G2p)gaagugGfcAfcu gagscsa		TGCTCAGTGCCACTTCCCTC TTC	
AD-1640702	asgsugc(Chd)AfcUfUfCfccucuucuaa L96		VPusUfsagdAa(G2p)agggaaGfuGfgc acusgsa		TCAGTGCCACTTCCCTCTTC TAG	
AD-1640703	gscscac(Uhd)UfcCfCfUfcuucuaguca L96		VPusGfsacdTa(G2p)aagaggGfaAfgu ggcsasc		GTGCCACTTCCCTCTTCTAG TCT	
AD-1640704	ascsuuc(Chd)CfuCfUfUfcuagucugaa L96		VPusUfscadGa(C2p)uagaagAfgGfga agusgsg		CCACTTCCCTCTTCTAGTCT GAG	
AD-1640705	ususccc(Uhd)CfuUfCfUfagucugagaa L96		VPusUfscudCa(G2p)acuagaAfgAfgg gaasgsu		ACTTCCCTCTTCTAGTCTGA GAG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640706	cscscuc(Uhd)UfcUfAfGfucugagagga L96		VPusCfscudCu(C2p)agacuaGfaAfgag ggsasa		TTCCCTCTTCTAGTCTGAGA GGG	
AD-1640707	csuscuu(Chd)UfaGfUfCfugagagggaa L96		VPusUfsccdCu(C2p)ucagacUfaGfaag agsgsg		CCCTCTTCTAGTCTGAGAGG GAA	
AD-1640708	csusucu(Ahd)GfuCfUfGfagagggaaga L96		VPusCfsuudCc(C2p)ucucagAfcUfaga agsasg		CTCTTCTAGTCTGAGAGGGA AGA	
AD-1640709	ususcua(Ghd)UfcUfGfAfgagggaagaa L96		VPusUfscudTc(C2p)cucucaGfaCfuag aasgsa		TCTTCTAGTCTGAGAGGGA AGAG	
AD-1640711	asgsucu(Ghd)AfgAfGfCfgaagagggca L96		VPusGfsccdCu(C2p)uucccuCfuCfaga cusasg		CTAGTCTGAGAGGGAAGAG GGCT	
AD-1640712	uscsuga(Ghd)AfgGfGfAfagagggcuga L96		VPusCfsagdCc(C2p)ucuuccCfuCfuca gascsu		AGTCTGAGAGGGAAGAGGG CTGG	
AD-1640713	csusgag(Ahd)GfgGfAfAfgagggcugga L96		VPusCfscadGc(C2p)cucuucCfcUfcuc agsasc		GTCTGAGAGGGAAGAGGGC TGGG	
AD-1640714	ususugg(Ahd)GfcUfGfGfagagauguga L96		VPusCfsacdAu(C2p)ucuccaGfcUfcca aascsc		GGTTTGGAGCTGGAGAGAT GTGG	
AD-1640715	usasgga(Chd)GfcCfUfCfggcgggagua L96		VPusAfscudCc(C2p)gccgagGfcGfucc uasasa		TTTAGGACGCCTCGGCGGG AGTG	
AD-1640716	asgsggc(Ghd)CfgUfCfCfaaugggagaa L96		VPusUfscudCc(C2p)auuggaCfgCfgcc cuscsa		TGAGGGCGCGTCCAATGGG AGAT	
AD-1640717	gsgsgcg(Chd)GfuCfCfAfaugggagaua L96		VPusAfsucdTc(C2p)cauuggAfcGfcgc ccsusc		GAGGGCGCGTCCAATGGGA GATT	
AD-1640718	gsgscgc(Ghd)UfcCfAfAfugggagauua L96		VPusAfsaudCu(C2p)ccauugGfaCfgc gccscsu		AGGGCGCGTCCAATGGGAG ATTT	
AD-1640719	csgscgu(Chd)CfaAfUfGfggagauuuca L96		VPusGfsaadAu(C2p)ucccauUfgGfac gcgscsc		GGCGCGTCCAATGGGAGAT TTCT	
AD-1640720	ascsagc(Chd)UfgAfGfAfuuugaggcua L96		VPusAfsgcdCu(C2p)aaaucuCfaGfgcu gususu		AAACAGCCTGAGATTTGAG GCTC	
AD-1640721	asgsccu(Ghd)AfgAfUfUfugaggcucua L96		VPusAfsgadGc(C2p)ucaaauCfuCfagg cusgsu		ACAGCCTGAGATTTGAGGC TCTT	
AD-	gscscug(Ahd)GfaUfUfUfgaggcucuua		VPusAfsagdAg(C2p)cucaaaUfcUfcag		CAGCCTGAGATTTGAGGCT	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640722	L96		gcsusg		CTTC	
AD-1640723	cscsuga(Ghd)AfuUfUfGfaggcucuuca L96		VPusGfsaadGa(G2p)ccucaaAfuCfuca ggscsu		AGCCTGAGATTTGAGGCTCT TCC	
AD-1640724	usgsaga(Uhd)UfuGfAfGfgcucuuccua L96		VPusAfsggdAa(G2p)agccucAfaAfuc ucasgsg		CCTGAGATTTGAGGCTCTTC CTA	
AD-1640725	gsasuuu(Ghd)AfgGfCfUfcuuccuacaa L96		VPusUfsgudAg(G2p)aagagcCfuCfaa aucsusc		GAGATTTGAGGCTCTTCCTA CAT	
AD-1640726	asusuug(Ahd)GfgCfUfCfuuccuacaua L96		VPusAfsugdTa(G2p)gaagagCfcUfcaa auscsu		AGATTTGAGGCTCTTCCTAC ATT	
AD-1640727	usgsagg(Chd)UfcUfUfUfCfcuacauugua L96		VPusAfscadAu(G2p)uaggaaGfaGfcc ucasasa		TTTGAGGCTCTTCCTACATT GTC	
AD-1640728	gscsucu(Uhd)CfcUfAfCfauugucagga L96		VPusCfscudGa(C2p)aauguaGfgAfag agcscsu		AGGCTCTTCCTACATTGTCA GGA	
AD-1640729	uscsuuc(Chd)UfaCfAfUfugucaggaca L96		VPusGfsucdCu(G2p)acaaugUfaGfga agasgsc		GCTCTTCCTACATTGTCAGG ACA	
AD-1640730	ususccu(Ahd)CfaUfUfGfucaggacaua L96		VPusAfsugdTc(C2p)ugacaaUfgUfag gaasgsa		TCTTCCTACATTGTCAGGAC ATT	
AD-1640731	uscscua(Chd)AfuUfGfUfcaggacauua L96		VPusAfsaudGu(C2p)cugacaAfuGfua ggasasg		CTTCCTACATTGTCAGGACA TTT	
AD-1640732	csusaca(Uhd)UfgUfCfAfggacauuuca L96		VPusGfsaadAu(G2p)uccugaCfaAfug uagsgsa		TCCTACATTGTCAGGACATT TCA	
AD-1640733	ususguc(Ahd)GfgAfCfAfuuucauuuaa L96		VPusUfsaadAu(G2p)aaauguCfcUfga caasusg		CATTGTCAGGACATTTCATT TAG	
AD-1640734	gsgsaca(Uhd)UfuCfAfUfuuaguucaua L96		VPusAfsugdAa(C2p)uaaaugAfaAfug uccsusg		CAGGACATTTCATTTAGTTC ATG	
AD-1640735	ususcau(Uhd)UfaGfUfUfcaugaucaca L96		VPusGfsugdAu(C2p)augaacUfaAfau gaasasu		ATTTCATTTAGTTCATGATC ACG	
AD-1640736	asgsuuc(Ahd)UfgAfUfCfacgguggguaa L96		VPusUfsacdCa(C2p)cgugauCfaUfgaa cusasa		TTAGTTCATGATCACGGTGG TAG	
AD-1640737	ususcau(Ghd)AfuCfAfCfgguggguagua L96		VPusAfscudAc(C2p)accgugAfuCfau gaascsu		AGTTCATGATCACGGTGGT AGTA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1640738	uscsaug(Ahd)UfcAfCfGfgugguaguaa L96		VPusUfsacdTa(C2p)caccguGfaUfcaugasasc		GTTCATGATCACGGTGGTAGTAA	
AD-1640739	usgsauc(Ahd)CfgGfUfGfguaguaacaa L96		VPusUfsgudTa(C2p)uaccacCfgUfgaucasusg		CATGATCACGGTGGTAGTAACAC	
AD-1640740	csascgg(Uhd)GfgUfAfGfuaacacgaua L96		VPusAfsucdGu(G2p)uuacuaCfcAfccgugsasu		ATCACGGTGGTAGTAACACGATT	
AD-1640741	usasagc(Ahd)CfcAfCfCfuaagagaucaL96		VPusGfsaudCu(C2p)uuagguGfgUfgcuuasasa		TTTAAGCACCACCTAAGAGATCT	
AD-1640742	ascscac(Chd)UfaAfGfAfgaucugcuca L96		VPusGfsagdCa(G2p)aucucuUfaGfguggusgsc		GCACCACCTAAGAGATCTGCTCA	
AD-1640743	csasccu(Ahd)AfgAfGfAfucugcucaua L96		VPusAfsugdAg(C2p)agaucuCfuUfaggugsgsu		ACCACCTAAGAGATCTGCTCATC	
AD-1640744	ascscua(Ahd)GfaGfAfUfcugcucauca L96		VPusGfsaudGa(G2p)cagaucUfcUfuaggusgsg		CCACCTAAGAGATCTGCTCATCT	
AD-1640745	csusaag(Ahd)GfaUfCfUfgcucaucuaa L96		VPusUfsagdAu(G2p)agcagaUfcUfcuuagsgsu		ACCTAAGAGATCTGCTCATCTAA	
AD-1640746	asgsaga(Uhd)CfuGfCfUfcaucuaagca L96		VPusGfscudTa(G2p)augagcAfgAfucucususa		TAAGAGATCTGCTCATCTAAGCC	
AD-1640747	asuscug(Chd)UfcAfUfCfuaagccuaaa L96		VPusUfsuadGg(C2p)uuagauGfaGfcagauscsu		AGATCTGCTCATCTAAGCCTAAG	
AD-1640748	csusgcu(Chd)AfuCfUfAfagccuaagua L96		VPusAfscudTa(G2p)gcuuagAfuGfagcagsasu		ATCTGCTCATCTAAGCCTAAGTT	
AD-1640749	uscsuaa(Ghd)CfcUfAfAfguuggucuga L96		VPusCfsagdAc(C2p)aacuuaGfgCfuuagasusg		CATCTAAGCCTAAGTTGGTCTGC	
AD-1640750	csusaag(Chd)CfuAfAfGfuuggucugca L96		VPusGfscadGa(C2p)caacuuAfgGfcuuagsasu		ATCTAAGCCTAAGTTGGTCTGCA	
AD-1640751	asasgcc(Uhd)AfaGfUfUfggucugcaga L96		VPusCfsugdCa(G2p)accaacUfuAfggcuusasg		CTAAGCCTAAGTTGGTCTGCAGG	
AD-1640752	gscscua(Ahd)GfuUfGfGfucugcaggca L96		VPusGfsccdTg(C2p)agaccaAfcUfuaggcsusu		AAGCCTAAGTTGGTCTGCAGGCG	
AD-	cscsuaa(Ghd)UfuGfGfUfcugcaggcga		VPusCfsgcdCu(G2p)cagaccAfaCfuua		AGCCTAAGTTGGTCTGCAG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1640753	L96		ggscsu		GCGT	
AD-1640754	usasagu(Uhd)GfgUfCfUfgcaggcguua L96		VPusAfsacdGc(C2p)ugcagaCfcAfacu uasgsg		CCTAAGTTGGTCTGCAGGC GTTT	
AD-1640755	gsuscug(Chd)AfgGfCfGfuuugaaugaa L96		VPusUfscadTu(C2p)aaacgcCfuGfcag acscsa		TGGTCTGCAGGCGTTTGAAT GAG	
AD-1640756	gscsagg(Chd)GfuUfUfGfaaugaguuga L96		VPusCfsaadCu(C2p)auucaaAfcGfccu gcsasg		CTGCAGGCGTTTGAATGAG TTGT	
AD-1640757	ususuga(Ahd)UfgAfGfUfuggguugca L96		VPusGfscadAc(C2p)acaacuCfaUfuca aascsg		CGTTTGAATGAGTTGTGGTT GCC	
AD-1640758	ususgaa(Uhd)GfaGfUfUfgguguugcca L96		VPusGfsgcdAa(C2p)cacaacUfcAfuuc aasasc		GTTTGAATGAGTTGTGGTTG CCA	
AD-1640759	asasuga(Ghd)UfuGfUfGfguugccaaga L96		VPusCfsuudGg(C2p)aaccacAfaCfuca uuscsa		TGAATGAGTTGTGGTTGCCA AGT	
AD-1640760	asusgag(Uhd)UfgUfGfGfuugccaagua L96		VPusAfscudTg(G2p)caaccaCfaAfcuc aususc		GAATGAGTTGTGGTTGCCA AGTA	
AD-1640761	usgsagu(Uhd)GfuGfGfUfugccaaguaa L96		VPusUfsacdTu(G2p)gcaaccAfcAfacu casusu		AATGAGTTGTGGTTGCCAA GTAA	
AD-1640762	ususgcc(Ahd)AfgUfAfAfaguggugaaa L96		VPusUfsucdAc(C2p)acuuuaCfuUfgg caascsc		GGTTGCCAAGTAAAGTGGT GAAC	
AD-1640763	usgscca(Ahd)GfuAfAfAfguggugaaca L96		VPusGfsuudCa(C2p)cacuuuAfcUfug gcasasc		GTTGCCAAGTAAAGTGGTG AACT	
AD-1640764	cscsaag(Uhd)AfaAfGfUfggugaacuua L96		VPusAfsagdTu(C2p)accacuUfuAfcuu ggscsa		TGCCAAGTAAAGTGGTGAA CTTA	
AD-1640765	asgsuaa(Ahd)GfuGfGfUfgaacuuacga L96		VPusCfsgudAa(G2p)uucaccAfcUfuu acususg		CAAGTAAAGTGGTGAACTT ACGT	
AD-1640766	usgsgug(Ahd)AfcUfUfAfcguggugaua L96		VPusAfsucdAc(C2p)acguaaGfuUfcac cascsu		AGTGGTGAACTTACGTGGT GATT	
AD-1640767	usgsaac(Uhd)UfaCfGfUfggugauuaaa L96		VPusUfsuadAu(C2p)accacgUfaAfgu ucascsc		GGTGAACTTACGTGGTGATT AAT	
AD-1640768	ascsgug(Ghd)UfgAfUfUfUfaaugaaauua L96		VPusAfsaudTu(C2p)auuaauCfaCfcac gusasa		TTACGTGGTGATTAATGAA ATTA	

Table 4. Results of Dual-Luciferase Assays

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640653.1	367	88	10	101	2
AD-1640654.1	421	49	11	58	2
AD-1640313.1	422	73	10	77	12
AD-1640314.1	470	42	3	44	10
AD-1640655.1	471	72	18	69	0
AD-1640656.1	472	43	9	51	0
AD-1640657.1	473	28	9	38	5
AD-1640315.1	474	52	8	60	8
AD-1640658.1	475	81	13	79	9
AD-1640659.1	476	54	9	68	6
AD-1640316.1	477	48	12	49	8
AD-1640317.1	478	92	19	82	8
AD-1640660.1	479	74	9	63	3
AD-1640661.1	480	36	5	46	1
AD-1640662.1	488	66	11	67	2
AD-1640319.1	488	82	15	72	2
AD-1640318.1	488	91	10	95	1
AD-1640321.1	489	69	10	76	0
AD-1640320.1	489	86	20	85	7
AD-1640324.1	490	65	8	70	5
AD-1640322.1	490	68	11	83	3
AD-1640323.1	490	82	12	87	6
AD-1640663.1	491	59	12	71	1
AD-1640325.1	492	61	6	56	15
AD-1640664.1	493	58	10	67	1
AD-1640665.1	494	77	6	75	3
AD-1640327.1	554	71	9	68	6
AD-1640326.1	554	62	7	72	4
AD-1640666.1	554	77	12	74	4
AD-1640667.1	555	47	4	53	0
AD-1640328.1	556	94	10	96	10
AD-1640668.1	557	80	12	96	3
AD-1640329.1	558	83	6	91	8
AD-1640330.1	559	52	4	59	6
AD-1640331.1	559	71	18	69	4
AD-1640332.1	559	71	11	70	15
AD-1640669.1	561	23	2	32	5
AD-1640333.1	562	35	8	32	0
AD-1640334.1	562	39	6	36	5
AD-1640670.1	562	40	5	42	1
AD-1640337.1	563	37	7	41	3
AD-1640336.1	563	51	7	52	4
AD-1640335.1	563	80	20	95	18
AD-1640339.1	564	65	22	65	4
AD-1640338.1	564	79	13	82	11
AD-1640671.1	565	70	8	74	2

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640340.1	566	62	5	66	1
AD-1640672.1	567	75	17	80	3
AD-1640673.1	568	90	9	97	4
AD-1640341.1	569	47	8	53	4
AD-1640343.1	570	52	2	49	7
AD-1640342.1	570	55	11	57	5
AD-1640345.1	571	80	14	67	7
AD-1640344.1	571	73	12	69	3
AD-1640346.1	572	55	7	54	7
AD-1640347.1	572	60	6	59	3
AD-1640349.1	573	56	12	64	4
AD-1640348.1	573	56	7	66	1
AD-1640351.1	574	49	15	62	7
AD-1640674.1	574	65	18	81	2
AD-1640350.1	574	62	16	83	1
AD-1640675.1	613	31	6	53	1
AD-1640352.1	614	38	3	45	4
AD-1640353.1	614	44	6	46	3
AD-1640355.1	615	47	9	45	3
AD-1640354.1	615	46	2	49	2
AD-1640676.1	615	41	7	54	4
AD-1640357.1	616	41	2	43	3
AD-1640356.1	616	53	6	72	14
AD-1640358.1	656	69	12	85	6
AD-1640359.1	657	86	4	92	5
AD-1640361.1	658	79	12	76	5
AD-1640360.1	658	82	6	84	2
AD-1640677.1	658	98	11	107	5
AD-1640678.1	659	62	5	82	14
AD-1640363.1	660	46	13	50	6
AD-1640362.1	660	65	13	64	3
AD-1640679.2	660	74	9	88	35
AD-1640364.1	661	62	9	71	6
AD-1640365.1	662	66	13	77	12
AD-1640367.1	663	26	4	42	1
AD-1640366.1	663	47	9	46	2
AD-1640680.2	663	46	6	46	18
AD-1640368.1	664	37	7	48	2
AD-1640369.1	664	56	13	58	5
AD-1640370.1	665	57	11	54	5
AD-1640371.1	665	46	7	56	10
AD-1640681.2	704	65	20	65	26
AD-1640372.1	705	19	2	28	4
AD-1640374.1	705	31	4	34	1
AD-1640373.1	705	33	4	38	4
AD-1640376.1	706	46	7	58	6
AD-1640375.1	706	61	21	63	4
AD-1640378.1	707	30	4	45	6

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640377.1	707	52	16	73	8
AD-1640379.1	735	22	4	31	8
AD-1640682.2	736	41	5	33	16
AD-1640380.1	737	38	8	42	6
AD-1640683.2	738	32	7	25	12
AD-1640383.1	739	14	2	14	3
AD-1640382.1	739	11	2	16	3
AD-1640381.1	739	18	2	22	6
AD-1640384.1	740	14	2	17	3
AD-1640385.1	740	18	4	20	8
AD-1640684.2	741	36	4	33	15
AD-1640386.1	742	21	2	24	2
AD-1640387.1	742	19	2	27	7
AD-1640389.1	745	20	4	25	4
AD-1640685.2	745	27	4	28	11
AD-1640388.1	745	19	3	29	4
AD-1640390.1	746	19	1	25	7
AD-1640686.2	747	38	8	44	17
AD-1640687.2	748	67	25	58	19
AD-1640391.1	749	12	2	20	3
AD-1640393.1	750	29	7	48	13
AD-1640392.1	750	36	3	51	9
AD-1640688.2	750	85	18	73	28
AD-1640689.2	751	65	11	47	15
AD-1640690.2	752	30	3	36	16
AD-1640691.2	753	51	8	50	18
AD-1640395.1	755	26	6	31	7
AD-1640394.1	755	27	5	40	8
AD-1640397.1	756	22	3	26	3
AD-1640396.1	756	34	4	50	4
AD-1640399.1	757	35	3	43	12
AD-1640398.1	757	46	3	62	19
AD-1640402.1	758	42	9	50	12
AD-1640400.1	758	45	7	56	12
AD-1640401.1	758	50	18	57	20
AD-1640403.1	759	89	11	85	5
AD-1640692.2	760	52	4	56	23
AD-1640693.2	761	48	5	49	16
AD-1640404.1	762	32	2	42	3
AD-1640694.2	763	39	7	40	19
AD-1640405.1	764	32	7	34	2
AD-1640695.2	765	55	11	63	29
AD-1640406.1	766	37	8	46	9
AD-1640696.2	767	46	9	40	13
AD-1640697.2	768	39	7	37	15
AD-1640698.2	769	46	2	36	14
AD-1640407.1	770	77	14	85	4
AD-1640699.2	771	109	7	94	35

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640410.1	772	44	4	66	8
AD-1640409.1	772	56	15	67	7
AD-1640408.1	772	87	13	102	6
AD-1640412.1	773	63	5	75	6
AD-1640413.1	773	64	8	79	6
AD-1640411.1	773	91	16	98	8
AD-1640700.2	774	131	11	102	38
AD-1640701.2	775	105	10	81	21
AD-1640414.1	778	78	11	92	4
AD-1640415.1	778	83	18	97	7
AD-1640702.2	778	143	23	134	50
AD-1640417.1	781	82	23	71	3
AD-1640416.1	781	81	11	75	1
AD-1640703.2	781	100	7	79	30
AD-1640420.1	782	45	5	52	3
AD-1640419.1	782	46	9	56	2
AD-1640418.1	782	77	8	85	7
AD-1640421.1	783	62	10	74	3
AD-1640422.1	783	64	10	74	6
AD-1640429.1	783	52	6	76	4
AD-1640430.1	784	38	10	50	5
AD-1640704.2	784	95	7	74	33
AD-1640433.1	785	38	3	53	3
AD-1640432.1	785	44	7	58	1
AD-1640431.1	785	78	5	71	2
AD-1640705.2	786	76	5	71	26
AD-1640434.1	787	93	16	87	4
AD-1640706.2	788	159	13	120	38
AD-1640435.1	789	85	8	86	10
AD-1640437.1	789	75	11	88	4
AD-1640436.1	789	75	18	89	10
AD-1640707.2	790	104	27	99	47
AD-1640438.1	791	48	12	58	7
AD-1640440.1	792	74	22	71	2
AD-1640439.1	792	77	19	82	7
AD-1640708.2	792	102	21	82	21
AD-1640709.2	793	107	13	112	38
AD-1640442.1	794	44	6	64	2
AD-1640710.1	794	95	18	90	25
AD-1640441.1	794	81	11	90	7
AD-1640444.1	795	46	6	68	5
AD-1640443.1	795	68	6	87	12
AD-1640445.1	795	90	21	92	11
AD-1640446.1	796	94	13	97	6
AD-1640447.1	796	93	7	108	4
AD-1640711.2	797	84	11	75	29
AD-1640448.1	798	69	9	80	3
AD-1640449.1	799	68	9	80	9

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640450.1	799	75	8	83	10
AD-1640712.2	799	115	9	103	29
AD-1640452.1	800	72	6	79	7
AD-1640451.1	800	78	8	90	12
AD-1640713.2	800	118	13	106	31
AD-1640454.1	850	27	3	32	2
AD-1640453.1	850	28	6	34	3
AD-1640714.2	850	40	5	40	15
AD-1640456.1	851	16	1	25	5
AD-1640455.1	851	35	7	38	8
AD-1640458.1	873	13	2	15	5
AD-1640457.1	873	17	2	17	5
AD-1640461.1	874	13	1	19	6
AD-1640459.1	874	22	2	30	7
AD-1640460.1	874	34	14	34	4
AD-1640715.2	895	107	14	87	22
AD-1640462.1	895	83	14	95	5
AD-1640464.1	940	30	3	39	4
AD-1640463.1	940	55	10	50	5
AD-1640465.1	940	52	6	61	17
AD-1640716.2	942	66	8	49	10
AD-1640717.2	943	41	1	42	14
AD-1640718.2	944	37	4	31	8
AD-1640719.2	946	30	6	26	8
AD-1640467.1	947	12	3	19	3
AD-1640468.1	947	18	8	21	8
AD-1640466.1	947	17	1	25	6
AD-1640469.1	948	14	1	21	8
AD-1640470.1	948	22	7	23	7
AD-1640720.2	986	45	8	42	12
AD-1640471.1	987	14	1	17	5
AD-1640721.2	988	22	4	21	8
AD-1640722.2	989	27	6	22	10
AD-1640723.2	990	25	3	20	7
AD-1640472.1	991	17	6	24	8
AD-1640474.1	992	16	3	19	6
AD-1640724.2	992	49	6	28	6
AD-1640473.1	992	41	8	43	14
AD-1640477.1	993	13	9	14	4
AD-1640476.1	993	13	2	15	3
AD-1640475.1	993	11	1	15	7
AD-1640478.1	994	9	5	13	7
AD-1640725.2	995	22	4	21	8
AD-1640726.2	996	28	4	25	10
AD-1640479.1	997	18	1	26	6
AD-1640481.1	999	18	2	23	10
AD-1640727.2	999	41	6	31	10
AD-1640480.1	999	28	7	38	8

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640482.1	1000	19	3	21	3
AD-1640483.1	1000	13	2	21	8
AD-1640485.1	1001	17	1	21	10
AD-1640486.1	1001	16	1	21	4
AD-1640484.1	1001	23	3	26	5
AD-1640488.1	1002	17	3	32	13
AD-1640487.1	1002	43	12	61	11
AD-1640490.1	1003	28	6	36	9
AD-1640489.1	1003	27	8	44	8
AD-1640728.2	1003	72	12	61	24
AD-1640491.1	1004	17	5	20	5
AD-1640729.2	1005	27	5	21	10
AD-1640492.1	1006	29	5	38	5
AD-1640730.2	1007	30	5	21	10
AD-1640731.2	1008	16	4	20	9
AD-1640732.2	1010	22	4	16	7
AD-1640495.1	1011	27	4	20	6
AD-1640494.1	1011	19	5	22	6
AD-1640493.1	1011	50	6	36	5
AD-1640497.1	1012	9	2	14	5
AD-1640496.1	1012	16	6	17	6
AD-1640498.1	1013	8	2	13	5
AD-1640499.1	1013	14	3	18	11
AD-1640500.1	1015	17	5	20	9
AD-1640733.2	1015	26	3	21	9
AD-1640501.1	1015	18	4	24	11
AD-1640503.1	1018	16	4	20	10
AD-1640502.1	1018	16	2	22	12
AD-1640505.1	1019	15	3	16	5
AD-1640504.1	1019	15	1	19	10
AD-1640506.1	1020	19	5	22	8
AD-1640734.2	1021	22	3	14	6
AD-1640507.1	1021	14	3	15	7
AD-1640508.1	1021	14	2	16	8
AD-1640510.1	1023	20	5	18	6
AD-1640509.1	1023	24	4	23	11
AD-1640511.1	1026	16	6	19	8
AD-1640735.2	1027	25	1	15	7
AD-1640513.1	1028	17	2	19	10
AD-1640512.1	1028	27	8	45	4
AD-1640516.1	1029	12	0	14	7
AD-1640515.1	1029	12	3	15	6
AD-1640514.1	1029	20	3	30	3
AD-1640518.1	1030	13	3	15	4
AD-1640517.1	1030	19	3	16	4
AD-1640520.1	1031	24	4	21	6
AD-1640519.1	1031	29	3	28	4
AD-1640522.1	1032	19	4	17	5

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640521.1	1032	17	2	18	3
AD-1640524.1	1033	16	3	17	6
AD-1640523.1	1033	22	5	23	7
AD-1640736.2	1034	33	4	27	8
AD-1640525.1	1034	30	4	27	4
AD-1640526.1	1035	16	3	17	6
AD-1640527.1	1035	16	3	19	6
AD-1640737.2	1036	38	5	27	9
AD-1640738.2	1037	27	4	21	8
AD-1640528.1	1038	18	5	17	7
AD-1640529.1	1039	52	10	49	5
AD-1640739.2	1040	37	5	27	11
AD-1640530.1	1041	26	6	23	6
AD-1640531.1	1041	19	3	24	5
AD-1640532.1	1041	22	4	26	3
AD-1640535.1	1042	17	1	20	3
AD-1640534.1	1042	20	3	26	5
AD-1640533.1	1042	34	3	34	3
AD-1640536.1	1043	41	2	41	3
AD-1640740.2	1044	24	8	20	6
AD-1640537.1	1044	18	2	22	5
AD-1640539.1	1045	21	3	19	3
AD-1640538.1	1045	23	6	22	1
AD-1640741.2	1066	77	23	64	22
AD-1640540.1	1069	39	4	41	7
AD-1640541.1	1070	40	4	37	1
AD-1640742.2	1071	24	4	27	12
AD-1640542.1	1072	32	2	30	3
AD-1640743.2	1073	28	5	25	9
AD-1640744.2	1074	32	5	30	11
AD-1640543.1	1075	20	3	20	5
AD-1640745.2	1076	27	5	22	9
AD-1640544.1	1077	77	21	47	8
AD-1640547.1	1078	22	7	21	5
AD-1640546.1	1078	22	9	24	6
AD-1640545.1	1078	24	3	26	4
AD-1640746.2	1079	25	8	19	9
AD-1640549.1	1079	18	3	21	4
AD-1640548.1	1079	25	5	25	2
AD-1640551.1	1080	21	5	24	5
AD-1640550.1	1080	29	6	27	4
AD-1640552.1	1081	21	4	19	4
AD-1640553.1	1082	14	3	17	5
AD-1640747.2	1083	28	9	20	7
AD-1640555.1	1085	20	5	20	4
AD-1640748.2	1085	25	5	26	11
AD-1640554.1	1085	30	6	27	4
AD-1640558.1	1086	28	5	27	7

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640557.1	1086	41	7	36	4
AD-1640556.1	1086	63	15	61	2
AD-1640559.1	1087	36	4	27	4
AD-1640560.1	1087	32	9	28	9
AD-1640561.1	1088	29	3	31	4
AD-1640562.1	1088	31	5	35	1
AD-1640564.1	1089	19	2	20	5
AD-1640563.1	1089	17	4	22	5
AD-1640567.1	1090	21	2	20	5
AD-1640565.1	1090	22	2	25	8
AD-1640566.1	1090	28	10	26	3
AD-1640569.1	1091	14	1	16	5
AD-1640568.1	1091	16	1	17	6
AD-1640571.1	1092	11	2	17	11
AD-1640749.2	1092	22	2	19	11
AD-1640570.1	1092	21	1	23	5
AD-1640750.2	1093	12	2	12	7
AD-1640572.1	1093	14	5	20	15
AD-1640573.1	1094	37	4	28	2
AD-1640751.2	1095	33	7	28	9
AD-1640574.1	1096	68	17	71	21
AD-1640752.2	1097	57	12	37	10
AD-1640753.2	1098	49	15	31	13
AD-1640575.1	1098	48	10	53	8
AD-1640576.1	1099	24	4	27	4
AD-1640578.1	1100	22	5	32	5
AD-1640754.2	1100	46	13	35	9
AD-1640577.1	1100	30	8	37	10
AD-1640580.1	1102	27	4	23	3
AD-1640579.1	1102	37	11	35	5
AD-1640582.1	1105	29	9	25	8
AD-1640581.1	1105	20	3	27	5
AD-1640583.1	1106	32	11	33	5
AD-1640584.1	1106	24	5	34	11
AD-1640585.1	1106	27	10	35	6
AD-1640755.2	1107	56	17	40	14
AD-1640586.1	1108	24	2	29	2
AD-1640587.1	1108	23	3	30	5
AD-1640590.1	1109	13	2	20	5
AD-1640589.1	1109	16	3	25	6
AD-1640588.1	1109	34	2	50	15
AD-1640591.1	1110	28	3	35	6
AD-1640756.2	1111	24	7	18	7
AD-1640593.1	1111	20	2	22	6
AD-1640592.1	1111	17	2	23	5
AD-1640595.1	1112	13	3	20	6
AD-1640594.1	1112	14	3	21	6
AD-1640596.1	1112	15	2	22	7

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640597.1	1113	11	1	20	4
AD-1640598.1	1113	15	2	22	5
AD-1640599.1	1115	16	1	25	5
AD-1640600.1	1115	23	2	29	6
AD-1640601.1	1117	15	3	18	4
AD-1640602.1	1117	13	1	18	5
AD-1640757.2	1118	23	3	17	9
AD-1640603.1	1118	13	3	20	6
AD-1640604.1	1118	14	1	20	9
AD-1640606.1	1119	11	2	15	6
AD-1640605.1	1119	11	3	16	5
AD-1640758.2	1119	22	3	17	8
AD-1640607.1	1120	29	7	28	6
AD-1640759.2	1122	70	4	46	20
AD-1640760.2	1123	54	20	34	17
AD-1640761.2	1124	47	24	29	18
AD-1640608.1	1125	30	2	33	6
AD-1640609.1	1126	35	3	29	8
AD-1640611.1	1127	18	2	22	5
AD-1640610.1	1127	17	3	23	4
AD-1640612.1	1128	23	3	23	3
AD-1640613.1	1128	25	2	25	4
AD-1640616.1	1131	19	3	19	4
AD-1640615.1	1131	16	3	21	8
AD-1640614.1	1131	25	3	27	5
AD-1640617.1	1132	36	7	38	3
AD-1640618.1	1132	44	5	41	5
AD-1640762.2	1134	35	20	29	18
AD-1640763.2	1135	21	9	20	13
AD-1640619.1	1136	15	2	14	5
AD-1640764.2	1137	14	11	16	10
AD-1640620.1	1138	17	1	22	4
AD-1640621.1	1139	14	2	15	3
AD-1640623.1	1140	15	1	17	6
AD-1640765.2	1140	29	9	19	9
AD-1640622.1	1140	19	4	33	3
AD-1640625.1	1141	16	0	17	3
AD-1640624.1	1141	29	3	39	4
AD-1640626.1	1142	14	2	17	4
AD-1640627.1	1142	15	3	18	5
AD-1640629.1	1143	9	1	12	6
AD-1640628.1	1143	11	1	16	3
AD-1640631.1	1144	10	1	14	4
AD-1640630.1	1144	14	3	17	4
AD-1640632.1	1145	27	3	29	5
AD-1640633.1	1145	34	4	30	3
AD-1640636.1	1146	12	3	14	3
AD-1640634.1	1146	15	3	18	3

Duplex ID	Position in Dual-Luc Vector (HTT_ex_plus_int_1_full)	% Message Remaining-50nM	std dev.	% Avg Message Remaining-10nM	std dev.
AD-1640635.1	1146	20	2	28	3
AD-1640766.2	1147	29	10	19	9
AD-1640637.1	1149	9	2	13	4
AD-1640767.2	1150	41	9	24	10
AD-1640640.1	1151	28	4	31	4
AD-1640639.1	1151	27	6	39	7
AD-1640638.1	1151	58	3	73	5
AD-1640641.1	1152	11	2	15	5
AD-1640642.1	1152	15	2	16	4
AD-1640644.1	1153	9	1	14	3
AD-1640643.1	1153	18	2	20	3
AD-1640647.1	1154	18	2	26	0
AD-1640646.1	1154	24	5	26	3
AD-1640645.1	1154	40	12	48	2
AD-1640648.1	1155	18	3	18	3
AD-1640649.1	1156	17	2	20	6
AD-1640768.2	1157	41	10	27	14
AD-1640651.1	1160	11	2	13	4
AD-1640652.1	1160	12	1	16	1
AD-1640650.1	1160	15	1	17	4

Example 2. Design, and Synthesis of Additional dsRNA Duplexes

Additional siRNAs were designed, synthesized, and prepared using methods known in the art and described above in Example 1.

A detailed list of the unmodified HTT sense and antisense strand nucleotide sequences is shown in Table 5. A detailed list of the modified HTT sense and antisense strand nucleotide sequences is shown in Table 6.

Table 5. Unmodified Sense and Antisense Strand Sequences of Intron 1 Targeting HTT dsRNA Agents

Duplex Name	Sense strand sequence 5' to 3'	SEQ ID NO.	Range in NG_009378.1	Antisense strand sequence 5' to 3'	SEQ ID NO.	Range in NG_009378.1
AD-1718647	UAAAGUGGUGAACUUACGUGA		6193-6213	UCACGUAAGUUCACCACUUUACU		6191-6213
AD-1718648	UAAAGUGGUGAACUUACGUGA		6193-6213	UCACGUAAGUUCACCACUUUACU		6191-6213
AD-1718649	AAAGUGGUGAACUUACGUGGA		6194-6214	UCCACGTAAGUTCACCACUUUAC		6192-6214
AD-1718653	AACUUACGUGGUGAUUAAUGA		6203-6223	UCAUUAAUCACCACGUAAGUUCA		6201-6223
AD-1718654	AACUUACGUGGUGAUUAAUGA		6203-6223	UCAUTAAUCACCACGUAAGUUCA		6201-6223
AD-1718655	CAGGACAUUUCAUUUAGUUCA		6070-6090	UGAACUAAAUGAAAUGUCCUGAC		6068-6090
AD-1718656	CAGGACAUUUCAUUUAGUUCA		6070-6090	UGAACUAAAUGAAAUGUCCUGAC		6068-6090
AD-1718660	CAUUGUCAGGACAUUUCAUUA		6064-6084	UAAUGAAAUGUCCUGACAAUGUA		6062-6084
AD-1718662	ACUUACGUGGUGAUUAAUGAA		6204-6224	UTCATUAAUCACCACGUAAGUUC		6202-6224
AD-1718663	AAGUGGUGAACUUACGUGGUA		6195-6215	UACCACGUAAGTUCACCACUUUA		6193-6215
AD-1718669	GCAGUGGAUGACAUAAUGCUA		5924-5944	UAGCAUTAUGUCAUCCACUGCCC		5922-5944
AD-1718670	GCAGUGGAUGACAUAAUGCUA		5924-5944	UAGCAUUAUGUCAUCCACUGCCC		5922-5944
AD-1718673	AUUUAGUUCAUGAUCACGGUA		6081-6101	UACCGUGAUCATGAACUAAAUGA		6079-6101
AD-1718674	AUUUAGUUCAUGAUCACGGUA		6081-6101	UACCGUGAUCAUGAACUAAAUGA		6079-6101
AD-1718676	UAGUUCAUGAUCACGGUGGUA		6084-6104	UACCACCGUGATCAUGAACUAAA		6082-6104
AD-1718677	GUUCAUGAUCACGGUGGUAGA		6086-6106	UCUACCACCGUGAUCAUGAACUA		6084-6106
AD-1718678	UGGUGAUUAAUGAAAUUAUCA		6211-6231	UGAUAAUUUCAUUAAUCACCACG		6209-6231
AD-1718679	UGGUGAUUAAUGAAAUUAUCA		6211-6231	UGAUAATUUCATUAAUCACCACG		6209-6231
AD-1718680	UGGUGAUUAAUGAAAUUAUCA		6211-6231	UGAUAATUUCAUUAAUCACCACG		6209-6231
AD-1718682	GGACAUUUCAUUUAGUUCAUA		6072-6092	UAUGAACUAAAUGAAAUGUCCUG		6070-6092
AD-1718683	GGACAUUUCAUUUAGUUCAUA		6072-6092	UAUGAACUAAATGAAAUGUCCUG		6070-6092
AD-1718702	CAUUUAGUUCAUGAUCACGGA		6080-6100	UCCGTGAUCAUGAACUAAAUGAA		6078-6100
AD-1718715	CUACAUUGUCAGGACAUUUCA		6061-6081	UGAAAUGUCCUGACAAUGUAGGA		6059-6081
AD-1718717	UUCAUUUAGUUCAUGAUCACA		6078-6098	UGUGAUCAUGAACUAAAUGAAAU		6076-6098
AD-1718721	GUGAACUUACGUGGUGAUUAA		6200-6220	UUAATCACCACGUAAGUUCACCA		6198-6220

Table 6. Modified Sense and Antisense Strand Sequences of Intron 1 Targeting HTT dsRNA Agents

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	mRNA target sequence	SEQ ID NO.
AD-1718647	usasaag(Uhd)GfgUfGfAfacuuacgusgsa		VPusCfsacgUfaAfGfuucaCfcAfcuuuascsu		AGTAAAGTGGTGAACTTACGTGG	
AD-1718648	usasaag(Uhd)ggUfGfAfacuuacgusgsa		VPusdCsacdGudAaguudCaCfcacuuuascsu		AGTAAAGTGGTGAACTTACGTGG	
AD-1718649	asasagu(Ghd)guGfAfAfcuuacgugsgsa		VPusdCscadCgdTaagudTcAfccacuuusasc		GTAAAGTGGTGAACTTACGTGGT	
AD-1718653	asascuu(Ahd)CfgUfGfGfugauuaausgsa		VPusCfsauuAfaUfCfaccaCfgUfaaguuscsa		TGAACTTACGTGGTGATTAATGA	
AD-1718654	asascuu(Ahd)cgUfGfGfugauuaausgsa		VPusdCsaudTadAucacdCaCfguaaguuscsa		TGAACTTACGTGGTGATTAATGA	
AD-1718655	csasgga(Chd)auUfUfCfauuuaguuscsa		VPusdGsaadCudAaaugdAaAfuguccugsasc		GTCAGGACATTTCATTTAGTTCA	
AD-1718656	csasgga(Chd)AfuUfUfCfauuuaguuscsa		VPusGfsaacUfaAfAfugaaAfuGfuccugsasc		GTCAGGACATTTCATTTAGTTCA	
AD-1718660	csasuug(Uhd)CfaGfGfAfcauuucaususa		VPusAfsaugAfaAfUfguccUfgAfcaaugsusa		TACATTGTCAGGACATTTCATTT	
AD-1718662	ascsuua(Chd)guGfGfUfgauuaaugsasa		VPusdTscadTudAaucadCcAfcguaagususc		GAACTTACGTGGTGATTAATGAA	
AD-1718663	asasgug(Ghd)ugAfAfCfuuacguggsusa		VPusdAsccdAcdGuaagdTuCfaccacuususa		TAAAGTGGTGAACTTACGTGGTG	
AD-1718669	gscsagu(Ghd)gaUfGfAfcauaaugcsusa		VPusdAsgcdAudTaugudCaUfccacugcscsc		GGGCAGTGGATGACATAATGCTT	
AD-1718670	gscsagu(Ghd)GfaUfGfAfcauaaugcsusa		VPusAfsgcaUfuAfUfgucaUfcCfacugcscsc		GGGCAGTGGATGACATAATGCTT	
AD-1718673	asususua(Ghd)uuCfAfUfgaucacggsusa		VPusdAsccdGudGaucadTgAfacuaaausgsa		TCATTTAGTTCATGATCACGGTG	
AD-1718674	asususua(Ghd)UfuCfAfUfgaucacggsusa		VPusAfsccgUfgAfUfcaugAfaCfuaaausgsa		TCATTTAGTTCATGATCACGGTG	
AD-1718676	usasguu(Chd)auGfAfUfcacgguggsusa		VPusdAsccdAcdCgugadTcAfugaacuasasa		TTTAGTTCATGATCACGGTGGTA	
AD-1718677	gsususca(Uhd)gaUfCfAfcggugguasgsa		VPusdCsuadCcdAccgudGaUfcaugaacsusa		TAGTTCATGATCACGGTGGTAGT	
AD-1718678	usgsgug(Ahd)UfuAfAfUfgaaauuauscsa		VPusGfsauaAfuUfUfcauuAfaUfcaccascsg		CGTGGTGATTAATGAAATTATCT	
AD-1718679	usgsgug(Ahd)uuAfAfUfgaaauuauscsa		VPusdGsaudAadTuucadTuAfaucaccascsg		CGTGGTGATTAATGAAATTATCT	
AD-1718680	usgsgug(Ahd)UfuAfAfUfgaaauuauscsa		VPusGfsaudAa(Tgn)uucauuAfaUfcaccascsg		CGTGGTGATTAATGAAATTATCT	
AD-1718682	gsgsaca(Uhd)UfuCfAfUfuuaguucasusa		VPusAfsugaAfcUfAfaaugAfaAfuguccsusg		CAGGACATTTCATTTAGTTCATG	
AD-1718683	gsgsaca(Uhd)uuCfAfUfuuaguucasusa		VPusdAsugdAadCuaaadTgAfaauguccsusg		CAGGACATTTCATTTAGTTCATG	
AD-1718702	csasuuu(Ahd)guUfCfAfugaucacgsgsa		VPusdCscgdTgdAucaudGaAfcuaaaugsasa		TTCATTTAGTTCATGATCACGGT	
AD-1718715	csusaca(Uhd)UfgUfCfAfggacauuuscsa		VPusGfsaadAu(G2p)uccugaCfaAfuguagsgsa		TCCTACATTGTCAGGACATTTCA	
AD-1718717	ususcau(Uhd)UfaGfUfUfcaugaucascsa		VPusGfsugdAu(C2p)augaacUfaAfaugaasasu		ATTTCATTTAGTTCATGATCACG	
AD-1718721	gsusgaa(Chd)UfuAfCfGfuggugauusasa		VPusUfsaadTc(Agn)ccacguAfaGfuucacscsa		TGGTGAACTTACGTGGTGATTAA	

INFORMAL SEQUENCE LISTING

SEQ ID NO:1

>NM_002111.8 Homo sapiens huntingtin (HTT), mRNA

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SEQ ID NO:7
Reverse Complement of SEQ ID NO:2
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SEQ ID NO:8
Reverse Complement of SEQ ID NO:3
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SEQ ID NO:9
Reverse Complement of SEQ ID NO:4
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SEQ ID NO:10
Reverse Complement of SEQ ID NO:5

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We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Huntingtin (HTT) in a cell, wherein the dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to intron 1 retained in mutant HTT mRNA, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-3 and 5-6.

2. The dsRNA agent of claim 1, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 5790-5810; 5791-5811; 5924-5944; 5925-5945; 5998-6018; 6063-6083; 6064-6084; 6194-6214; 6195-6215; or 6211-6231 of SEQ ID NO:11.

3. The dsRNA agent of claim 2, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of nucleotides 5790-5810; 5791-5811; 5924-5944; 6064-6084; or 6194-6214 of SEQ ID NO:11.

4. The dsRNA agent of any one of claims 1-3, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more that three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1640384; AD-1640458; AD-1640457; AD-1640461; AD-1640628; AD-1640629; AD-1640498; AD-1640651; AD-1640631; AD-1640497; AD-1640382; or AD-1640467.

5. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Huntingtin (HTT) in a cell, wherein the dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more that three nucleotides from any one of the nucleotide sequences of nucleotides 5922-5944, 6059-6106; 6059-6084; 6068-6092; 6076-6106; 6191-6231; 6191-6215; 6191-6214; 6192-6215; 6198-6231; or 6198-6224 of SEQ ID NO:11.

6. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Huntingtin (HTT) in a cell, wherein the dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more that three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-

1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

7. The dsRNA agent of claim 6, wherein the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the sense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721, and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

8. The dsRNA agent of claim 6, wherein the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the sense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721, and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

9. The dsRNA agent of claim 6, wherein the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the sense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-

1718715; AD-1718717; or AD-1718721, and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

10. The dsRNA agent of claim 6, wherein the dsRNA agent comprises a sense strand comprising a nucleotide sequence selected from any one of the sense strand nucleotide sequences of a duplex selected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721, and an antisense strand comprising a nucleotide sequence selected from any one of the antisense strand nucleotide sequences of a duplex elected from the group consisting of AD-1718647; AD-1718648; AD-1718649; AD-1718653; AD-1718654 AD-1718655; AD-1718656; AD-1718660; AD-1718662; AD-1718663; AD-1718669; AD-1718670; AD-1718673; AD-1718674; AD-1718676; AD-1718677; AD-1718678; AD-1718679; AD-1718680; AD-1718682; AD-1718683; AD-1718702; AD-1718715; AD-1718717; or AD-1718721.

11. The dsRNA agent of any one of claims 1-10, wherein the sense strand, the antisense strand, or both the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

12. The dsRNA agent of claim 11, wherein the lipophilic moiety is conjugated to one or more internal positions in the double stranded region of the dsRNA agent.

13. The dsRNA agent of claim 11 or 12, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on the antisense strand.

14. The dsRNA agent of claim 11 or 12, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand *via* a linker or carrier.

15. The dsRNA agent of any one of claims 1-14, wherein lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

16. The dsRNA agent of any one of claims 1-15, wherein the hydrophobicity of the dsRNA agent, measured by the unbound fraction in a plasma protein binding assay of the dsRNA agent, exceeds 0.2.

17. The dsRNA agent of 16, wherein the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

18. The dsRNA agent of any one of claims 12-16, wherein the internal positions include all positions except the terminal two positions from each end of the sense strand or the antisense strand.

19. The dsRNA agent of claim 18, wherein the internal positions include all positions except the terminal three positions from each end of the sense strand or the antisense strand.

20. The dsRNA agent of any one of claims 12-19, wherein the internal positions exclude a cleavage site region of the sense strand.

21. The dsRNA agent of claim 20, wherein the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.

22. The dsRNA agent of claim 20, wherein the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.

23. The dsRNA agent of any one of claims 12-19, wherein the internal positions exclude a cleavage site region of the antisense strand.

24. The dsRNA agent of claim 23, wherein the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.

25. The dsRNA agent of any one of claims 12-24, wherein the internal positions include all positions except positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.

26. The dsRNA agent of any one of claims 11-25, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5'end of each strand.

27. The dsRNA agent of claim 26, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand.

28. The dsRNA agent of claim 12, wherein the positions in the double stranded region exclude a cleavage site region of the sense strand.

29. The dsRNA agent of any one of claims 11-28, wherein the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.

30. The dsRNA agent of any one of claims 11-28, wherein the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.

31. The dsRNA agent of any one of claims 11-30, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

32. The dsRNA agent of claim 31, wherein the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

33. The dsRNA agent of claim 32, wherein the lipophilic moiety contains a saturated or unsaturated C4-C30 hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

34. The dsRNA agent of claim 33, wherein the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

35. The dsRNA agent of claim 34, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

36. The dsRNA agent of claim 35, wherein the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

37. The dsRNA agent of any one of claims 11-36, wherein the lipophilic moiety is conjugated *via* a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region.

38. The dsRNA agent of claim 37, wherein the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

39. The dsRNA agent of any one of claims 11-38, wherein the lipophilic moiety is conjugated to the dsRNA agent *via* a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

40. The double-stranded iRNA agent of any one of claims 1-39, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

41. The dsRNA agent of any one of claims 1-40, wherein the dsRNA agent comprises at least one modified nucleotide.

42. The dsRNA agent of claim 41, wherein no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides

43. The dsRNA agent of claim 41, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

44. The dsRNA agent of any one of claims 41-43, wherein at least one of the modified nucleotides is selected from the group a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a 2'-5'-linked ribonucleotide (3'-RNA), a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified

nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a glycol nucleic acid S-Isomer (S-GNA), a nucleotide comprising 2-hydroxymethyl-tetrahydrofurane-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative, a dodecanoic acid bisdecylamide group; acytidine-2`-phosphate, a guanosine-2`-phosphate, a uridine-2`-phosphate, a adenosine-2`-phosphate, a 2'-O-hexadecyl-adenosine-3'-phosphate, a 2'-O-hexadecyl-cytidine-3'-phosphate, a 2'-O-hexadecyl-guanosine-3'-phosphate, and a 2'-O-hexadecyl-uridine-3'-phosphate, and combinations thereof.

45. The dsRNA agent of claim 44, wherein the modified nucleotide is selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, 3'-terminal deoxy-thymine nucleotides (dT), a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

46. The dsRNA agent of claim 44, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), and, a vinyl-phosphonate nucleotide; and combinations thereof.

47. The dsRNA agent of claim 44, wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification.

48. The dsRNA of claim 47, wherein the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acids (UNA), and a glycerol nucleic acid (GNA).

49. The dsRNA agent of claim 44, wherein the modified nucleotide comprises a short sequence of 3'-terminal deoxy-thymine nucleotides (dT).

50. The dsRNA agent of claim 44, wherein the modifications on the nucleotides are 2'-O-methyl, GNA and 2'fluoro modifications.

51. The dsRNA agent of claim 44, wherein the dsRNA comprises at least one 2'-fluoro nucleotide modification.

52. The dsRNA agent of claim 44, wherein the antisense strand comprises at least one 2'-fluoro nucleotide modification.

53. The dsRNA agent of claim 44, wherein the antisense strand comprises a 2'-fluoro nucleotide modification at positions 2, 14 and 16, counting from the 5'-end of the antisense strand.

54. The dsRNA agent of claim 44, wherein the antisense strand comprises a 2'-fluoro nucleotide modification at positions 2, 6, 14 and 16, counting from the 5'-end of the antisense strand.

55. The dsRNA agent of claim 44, wherein the antisense strand comprises a 2'-fluoro nucleotide modification at positions 2, 6, 9, 14 and 16, counting from the 5'-end of the antisense strand.

56. The dsRNA agent of claim 44, wherein the antisense strand comprises a 2'-fluoro nucleotide modification at positions 2, 6, 8, 9, 14 and 16, counting from the 5'-end of the antisense strand.

57. The dsRNA agent of claim 44, wherein the antisense strand comprises at least one 2'-fluoro nucleotide modification.

58. The dsRNA agent of claim 44, wherein the sense strand comprises a 2'-fluoro nucleotide modification at positions 7, 9 and 11, counting from the 5'-end of the sense strand or at positions 11, 13 and 15, counting from the 3'-end of the sense strand.

59. The dsRNA agent of claim 44, wherein the sense strand comprises a 2'-fluoro nucleotide modification at positions 7, 9, 10 and 11, counting from the 5'-end of the sense strand or at positions 11, 12, 13 and 15, counting from the 3'-end of the sense strand.

60. The dsRNA agent of claim 44, wherein the sense strand comprises a 2'-fluoro nucleotide modification at positions 9, 10, and 11, counting from the 5'-end of the sense strand or at positions 11, 12, and 13 counting from the 3'-end of the sense strand.

61. The dsRNA agent of claim 44, wherein the antisense strand comprises at least one DNA nucleotide modifications.

62. The dsRNA agent of claim 44, wherein the antisense strand comprises a DNA nucleotide modification at positions 2, 5, 7, and 12, counting from the 5'-end of the antisense strand.

63. The dsRNA agent of claim 44, wherein the antisense strand comprises a DNA nucleotide modification at positions 2, 5, 7, 12, and 14 counting from the 5'-end of the antisense strand.

64. The dsRNA agent of claim 44, wherein the antisense strand a DNA nucleotide modification at positions 2, 5, 7, and 12, and a 2'-fluoro nucleotide at position 14 counting from the 5'-end of the antisense strand.

65. The dsRNA agent of claim 44, wherein the antisense strand a DNA nucleotide modification at positions 2, 5, 7, 12, 14 and 16 counting from the 5'-end of the antisense strand.

66. The dsRNA agent of claim 44, wherein the dsRNA comprises at least one thermally destabilizing nucleotide modification.

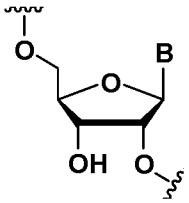
67. The dsRNA agent of claim 44, wherein the antisense strand comprises at least one thermally destabilizing nucleotide modification.

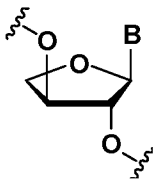
68. The dsRNA agent of claim 44, wherein the antisense strand comprises at least one thermally destabilizing nucleotide modification in the seed region of the antisense strand.

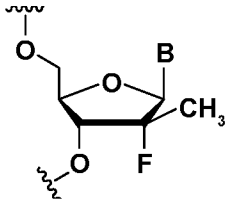
69. The dsRNA agent of claim 44, wherein the antisense strand comprises a thermally destabilizing nucleotide modification at least at one of positions 6, 7 or 8, counting from the 5'-end of the strand.

70. The dsRNA agent of claim 44, wherein the antisense strand comprises a thermally destabilizing nucleotide modification at position 7, counting from the 5'-end of the strand.

71. The dsRNA of claim 44, wherein the thermally destabilizing nucleotide modification is an abasic nucleotide, 2'-deoxy nucleotides, acyclic nucleotide (e.g., unlocked nucleic acid (UNA), glycol nucleic acid (GNA) or (S)-glycol nucleic acid (S-GNA)), a 2'-5' linked nucleotide (3'-RNA), threose nucleotide (TNA), 2' gem Me/F nucleotide or mismatch with an opposing nucleotide in the other strand.

3'RNA: 

TNA: 

2’ gem Me/F nucleotide: 

72. The dsRNA of any one of the preceding claims, wherein any nucleotide not otherwise defined comprises a 2’-OMe nucleotide modification.

73. The dsRNA agent of any one of claims 1-72, further comprising at least one phosphorothioate internucleotide linkage.

74. The dsRNA agent of claim 73, wherein the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

75. The dsRNA agent of any one of claims 1-74, wherein each strand is no more than 30 nucleotides in length.

76. The dsRNA agent of any one of claims 1-75, wherein at least one strand comprises a 3’ overhang of at least 1 nucleotide.

77. The dsRNA agent of any one of claims 1-75, wherein at least one strand comprises a 3’ overhang of at least 2 nucleotides.

78. The dsRNA agent of any one of claims 1-77, wherein the double stranded region is 15-30 nucleotide pairs in length.

79. The dsRNA agent of claim 78, wherein the double stranded region is 17-23 nucleotide pairs in length.

80. The dsRNA agent of claim 78, wherein the double stranded region is 17-25 nucleotide pairs in length.

81. The dsRNA agent of claim 78, wherein the double stranded region is 23-27 nucleotide pairs in length.

82. The dsRNA agent of claim 78, wherein the double stranded region is 19-21 nucleotide pairs in length.

83. The dsRNA agent of claim 78, wherein the double stranded region is 21-23 nucleotide pairs in length.

84. The dsRNA agent of any one of claims 1-83, wherein each strand is 19-30 nucleotides in length.

85. The dsRNA agent of any one of claims 1-83, wherein each strand is 19-23 nucleotides in length.

86. The dsRNA agent of any one of claims 1-83, wherein each strand is 21-23 nucleotides in length.

87. The dsRNA agent of any one of claims 1-86, further comprising a targeting ligand that targets a liver tissue.

88. The dsRNA agent of claim 87, wherein the targeting ligand is a GalNAc conjugate.

89. The dsRNA agent of any one of claims 11-88, wherein the lipophilic moeity or targeting ligand is conjugated *via* a bio-clevable linker selected from the group consisting of DNA, RNA, disulfide, amide, funtionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

90. The dsRNA agent of any one of claims 11-89, wherein the 3' end of the sense strand is protected *via* an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.

91. The dsRNA agent of any one of claims 1-90 further comprising
a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,

a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.

92. The dsRNA agent of any one of claims 1-90 further comprising
a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

93. The dsRNA agent of any one of claims 1-90 further comprising
a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

94. The dsRNA agent of any one of claims 1-90 further comprising
a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

95. The dsRNA agent of any one of claims 1-90 further comprising
a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and

a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

96. The dsRNA agent of any one of claims 1-95, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

97. The dsRNA agent of claim 96, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

98. The dsRNA agent of any one of claims 1-97, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

99. The dsRNA agent of any one of claims 1-98, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

100. A cell containing the dsRNA agent of any one of claims 1-99.

101. A pharmaceutical composition for inhibiting expression of a gene encoding HTT, comprising the dsRNA agent of any one of claims 1-99.

102. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-99 and a lipid formulation.

103. A method of inhibiting expression of a huntingtin (HTT) gene in a cell, the method comprising:
(a) contacting the cell with the dsRNA agent of any one of claims 1-99, or the pharmaceutical composition of claim 101 or 102; and
(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the HTT gene, thereby inhibiting expression of the HTT gene in the cell.

104. The method of claim 103, wherein the cell is within a subject.

105. The method of claim 104, wherein the subject is a human.

106. The method of any one of claims 103-105, wherein the expression of HTT is inhibited by at least 50%.

107. The method of claim 106, wherein the subject has been diagnosed with a HTT-associated disease.

108. The method of claim 107, wherein the nucleotide repeat expansion disease is Huntington's disease.

109. A method of treating a subject diagnosed with an HTT-associated disease, the method comprising administering to the subject a therapeutically effective amount of the the dsRNA agent of any one of claims 1-99, or the pharmaceutical composition of claim 101 or 102, thereby treating the subject.

110. The method of claim 109, wherein treating comprises amelioration of at least on sign or symptom of the disease.

111. The method of claim 109, where treating comprises prevention of progression of the disease.

112. The method of any one of claims 109-111, wherein the HTT-associated disease is Huntington's disease.

113. The method of any one of claims 109-112, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

114. The method of any one of claims 109-113, wherein the dsRNA agent is administered to the subject intrathecally.

115. The method of any one of claims 109-114, further comprising measuring a level of HTT in a sample obtained from the subject.

116. The method of any one of claims 109-115, further comprising administering to the subject an additional agent suitable for treatment or prevention of an HTT-associated disorder.

117. An RNA-induced silencing complex (RISC) comprising an antisense strand of the dsRNA agent of any one of claims 1- 99.