(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
06 May 2021 (06.05.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/087036 A1

(51) International Patent Classification:
C12N 15/113 (2010.01)

(21) International Application Number:
PCT/US2020/057849

(22) International Filing Date:
29 October 2020 (29.10.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/929,174 01 November 2019 (01.11.2019) US

(71) Applicant: **ALNYLAM PHARMACEUTICALS, INC.** [US/US]; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US).

(72) Inventors: **SOUNDARAPANDIAN, Mangala Meenakshi**; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US). **MCININCH, James D.**; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US). **BOSTWICK, Bret Lee**; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US). **SCHLEGEL, Mark K.**; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US). **CASTORENO, Adam**; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US). **ZUBER, Jeffrey**; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US).

(74) Agent: **LACCOTRIPE ZACHARAKIS, Maria** et al.; McCarter & English, LLP, 265 Franklin Street, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

WO 2021/087036 A1

(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, *e.g.*, exon 1 of an 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 APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 62/929,174, filed on November 1, 2019, the entire contents of which are incorporated herein by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 26, 2020, is named 121301_10320_SL.txt and is 1,468,832 bytes in size.

BACKGROUND OF THE INVENTION

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.

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 poyglutamine repeat results in a wild-type transcript, a full-length mutant transcript having the expanded polyglutamine repeat, as well as a truncated mutant transcript having the expanded polyglutamine repeat. 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

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

The present disclosure provides RNAi agent compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a huntingin (HTT) gene. 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.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Huntingtin (HTT), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by no more than 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 1 and the antisense strand comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by no more than 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 6, and wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand.

In some embodiments, the nucleotide sequence of the sense strand comprises any one of the sense strand nucleotide sequences in any one of Tables 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33.

In some embodiments, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 618-640, 1215-1237, 1248-1270, 1403-1425, 4051-4073, 4393-4415, 4398-4420, 4403-4425, 4441-4463, 4518-4540, 4548-4570, 5105-5127, 5215-5237, 5217-5239, 5221-5243, 5222-5244, 5366-5388, 5372-5394, 5450-5472, 5509-5531, 5883-5905, 6009-6031, 6010-6032, 6011-6033, 6012-6034, 6013-6035, 6014-6036, 6015-6037, 6347-6369, 6512-6534, 7523-7545, 7525-7547, 7526-7548, 9127-9149, 9531-9553, or 9538-9560 of SEQ ID NO:1.

In some embodiments, the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than 0, 1, 2, or 3 nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-953769.1, AD-953778.1, AD-953784.1, AD-953786.1, AD-953849.1, AD-953854.1, AD-953855.1, AD-953857.1, AD-953862.1, AD-953866.1, AD-953867.1, AD-953880.1, AD-953883.1, AD-953884.1, AD-953885.1, AD-953886.1, AD-953887.1, AD-953888.1, AD-953889.1, AD-953891.1, AD-953896.1, AD-953898.1, AD-953899.1, AD-953900.1, AD-953901.1, AD-953902.1, AD-953903.1, AD-953904.1, AD-953907.1, AD-953911.1, AD-953921.1, AD-953923.1, AD-953924.1, AD-953932.1, and AD-953933.1, AD-953937.1.

In some embodiments, the lipophilic moiety is conjugated *via* a linker or a carrier.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) 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 an mRNA encoding HTT, and wherein the region of complementarity comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 3, 2, 1, or 0 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33.

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.

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

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.

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.

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.

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.

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.

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.

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

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.

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.

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

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.

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.

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

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.

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.

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.

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

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.

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.

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.

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.

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)

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

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

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.

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

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.

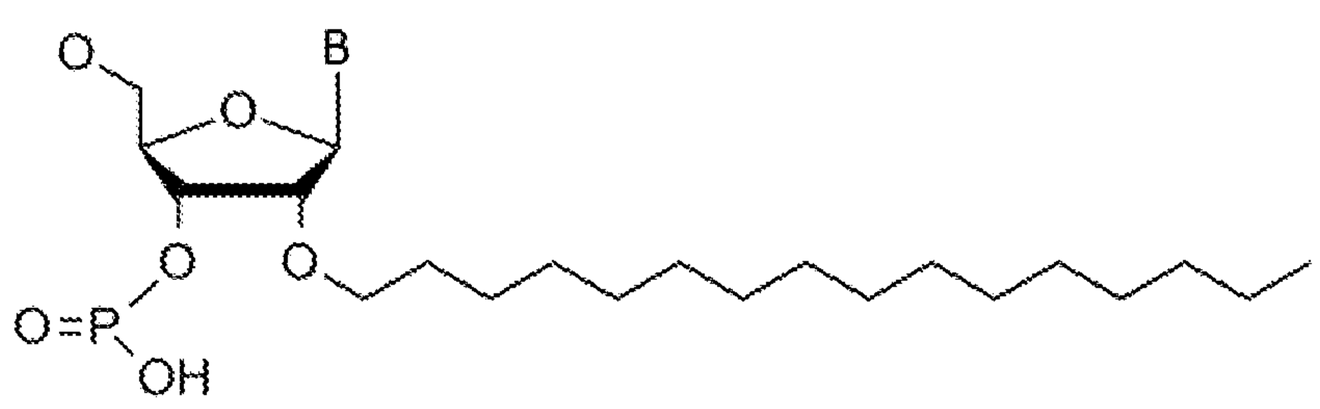
The double stranded region may be 15-30 nucleotide pairs in length; 17-23 nucleotide pairs in length; 17-25 nucleotide pairs in length; 23-27 nucleotide pairs in length; 19-21 nucleotide pairs in length; or 21-23 nucleotide pairs in length.

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

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 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.

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



,

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

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.

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.

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.

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.

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.

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.

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.

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).

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.

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

An additional aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a huntingtin (HTT) gene, where the double stranded RNAi agent targeted to HTT includes a sense strand and an antisense strand forming a double stranded region, where the sense strand includes at least 15, *e.g.,* 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 3 nucleotides (*i.e.,* differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 1-5 and the antisense strand includes at least 15, *e.g.,* 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 3 nucleotides (*i.e.,* differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 6-10; where a substitution of a uracil for any thymine in the sequences provided in the SEQ ID NOs: 1-10 (when comparing aligned sequences) does not count as a difference that contributes to the differing by no more than 3 nucleotides from any one of the nucleotide sequences provided in SEQ ID NOs: 1-10, where substantially all of the nucleotides of the sense strand include a modification that is a 2'-O-methyl modification, a GNA or a 2'-fluoro modification, where the sense strand includes two phosphorothioate internucleotide linkages at the 5'-terminus, where substantially all of the nucleotides of the antisense strand include a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, where the antisense strand includes two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and where the sense strand is conjugated to one or more lipophilic, *e.g.*, C16, ligands.

Another aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a huntingtin (HTT) gene, where the double stranded RNAi agent targeted to HTT includes a sense strand and an antisense strand forming a double stranded region, where the sense strand includes at least 15, *e.g.,* 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 3 nucleotides (*i.e.,* differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 1-5 and the antisense strand includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.,* differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 6-10, where a substitution of a uracil for any thymine in the sequences provided in the SEQ ID NOs: 1-10 (when comparing aligned sequences) does not count as a difference that contributes to the differing by no more than 3 nucleotides from any one of the nucleotide sequences provided in SEQ ID NOs:1-10; where the sense strand includes at least one 3'-terminal deoxy-thymine nucleotide (dT), and where the antisense strand includes at least one 3'-terminal deoxy-thymine nucleotide (dT).

An additional aspect of the instant disclosure provides a double stranded ribonucleic acid (RNAi) agent for inhibiting expression of a huntingtin (HTT) gene, where the RNAi agent possesses a sense strand and an antisense strand, and where the antisense strand includes a region of complementarity which includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.,* differing by 3, 2, 1, or 0 nucleotides), *e.g.*, at least 15 nucleotides (*i.e.,* differing by 3, 2, 1, or 0 nucleotides), at least 19 nucleotides (*i.e.,* differing by 3, 2, 1, or 0 nucleotides), from any one of the antisense strand nucleobase sequences of Tables 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33. In one embodiment, the RNAi agent includes one or more of the following

modifications: a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-C-alkyl-modified nucleotide, a nucleotide comprising a glycol nucleic acid (GNA), a phosphorothioate (PS) and a vinyl phosphonate (VP). Optionally, the RNAi agent includes at least one of each of the following modifications: a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-C-alkyl-modified nucleotide, a nucleotide comprising a glycol nucleic acid (GNA), a phosphorothioate and a vinyl phosphonate (VP).

In another embodiment, the RNAi agent includes four or more PS modifications, optionally six to ten PS modifications, optionally eight PS modifications.

In an additional embodiment, each of the sense strand and the antisense strand of the RNAi agent possesses a 5'-terminus and a 3'-terminus, and the RNAi agent includes eight PS modifications positioned at each of the penultimate and ultimate internucleotide linkages from the respective 3'- and 5'-termini of each of the sense and antisense strands of the RNAi agent.

In another embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes only one nucleotide including a GNA. Optionally, the nucleotide including a GNA is positioned on the antisense strand at the seventh nucleobase residue from the 5'-terminus of the antisense strand.

In an additional embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes one to four 2'-C-alkyl-modified nucleotides. Optionally, the 2'-C-alkyl-modified nucleotide is a 2'-C16-modified nucleotide. Optionally, the RNAi agent includes a single 2'- C-alkyl, *e.g.*, C16-modified nucleotide. Optionally, the single 2'- C-alkyl, *e.g.*, C16-modified nucleotide is located on the sense strand at the sixth nucleobase position from the 5'-terminus of the sense strand.

In another embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes two or more 2'-fluoro modified nucleotides. Optionally, each of the sense strand and the antisense strand of the RNAi agent includes two or more 2'-fluoro modified nucleotides. Optionally, the 2'-fluoro modified nucleotides are located on the sense strand at nucleobase positions 7, 9, 10 and 11 from the 5'-terminus of the sense strand and on the antisense strand at nucleobase positions 2, 14 and 16 from the 5'-terminus of the antisense strand.

In an additional embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes one or more VP modifications. Optionally, the RNAi agent includes a single VP modification at the 5'-terminus of the antisense strand.

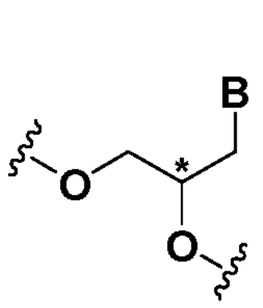
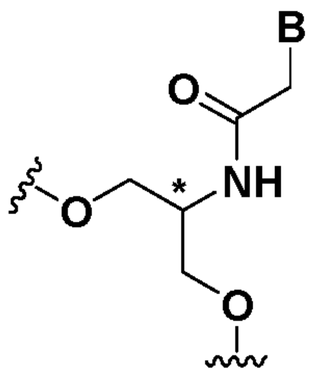
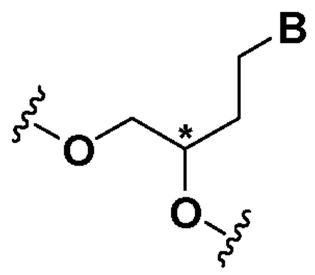
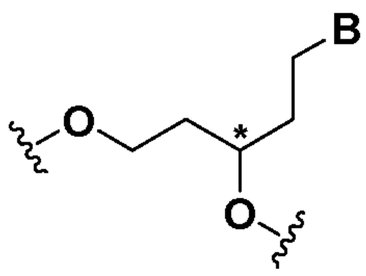
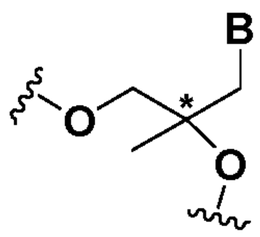
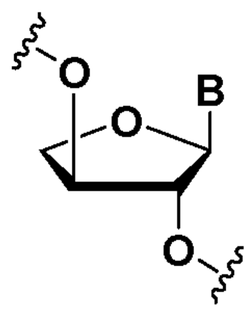
In another embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes two or more 2'-O-methyl modified nucleotides. Optionally, the RNAi agent includes 2'-O-methyl modified nucleotides at all nucleobase locations not modified by a 2'-fluoro, a 2'-C-alkyl or a glycol nucleic acid (GNA). Optionally, the two or more 2'-O-methyl modified nucleotides are located on the sense strand at positions 1, 2, 3, 4, 5, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21 from the 5'-terminus of the sense

strand and on the antisense strand at positions 1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22 and 23 from the 5'-terminus of the antisense strand.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In another embodiment, each strand has 19-30 nucleotides.

In certain embodiments, the antisense strand of the RNAi agent includes at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions of the 5′ region or a precursor thereof. Optionally, the thermally destabilizing modification of the duplex is one or more of


,

,

,

,

, and


where B is nucleobase.

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 ot he invention.

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).

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.

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

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.

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

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.

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.

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.

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.

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

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.

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

BRIEF DESCRIPTIONS OF THE FIGURES

FIG.1 is a graph showing wild-type human HTT mRNA levels in the livers of mice expressing a portion of wild-type human HTT (via AAV). These mice were subcutaneously administered a single 3 mg/kg dose of the indicated dsRNA duplexes targeting exon 1 of the human HTT transcript at Day 14 post AAV dose. Human HTT levels shown are normalized to AAV treated controls 14 days post siRNA dose.

FIG.2 is a graph showing wild-type human HTT mRNA levels in the livers of mice expressing a portion of wild-type human HTT (via AAV). These mice were subcutaneously administered a single 3 mg/kg dose of the indicated dsRNA duplexes targeting exon 1 of the human HTT transcript at Day 14 post AAV dose. Human HTT levels shown are normalized to AAV treated controls 14 days post siRNA dose.

FIG. 3A is a graph showing full length mutant human HTT mRNA levels in the livers of YAC128 mice and subcutaneously administered a single 10 mg/kg dose of the indicated dsRNA duplexes targeting exon 1 of the human HTT transcript at Day 7 post-dose. Human HTT levels shown are normalized to PBS treatment levels.

FIG. 3B is a Western Blot showing mutant human HTT protein and wildtype mouse HTT protein levels in the livers of YAC128 mice, subcutaneously administered a single 10 mg/kg dose of the indicated dsRNA duplexes targeting exon 1 of the human HTT transcript at Day 7 post-dose.

FIG. 3C is a bar graph showing mutant human HTT protein levels in the livers of YAC128 mice subcutaneously administered a single 10 mg/kg dose of the indicated dsRNA duplexes targeting exon 1 of the human HTT transcript at Day 7 post-dose. Mutant human HTT levels shown are normalized to PBS treatment levels.

FIG. 4A is a graph showing full-length mutant HTT mRNA levels in the livers of YAC128 mice subcutaneously administered a single 10 mg/kg dose of the indicated dsRNA duplexes targeting exon 1 of the HTT transcript at Day 7 post-dose. Full-length mutant human HTT levels shown are normalized to PBS treatment levels.

FIG. 4B is a bar graph showing quantification of mutant HTT protein levels in the livers of YAC128 mice subcutaneously administered a single 10 mg/kg dose of the indicated dsRNA duplexes targeting exon 1 of the HTT transcript at Day 7 post-dose. Mutant human HTT levels shown are normalized to PBS treatment levels.

FIG. 5 is a graph showing full-length mutant human HTT mRNA levels in the livers of YAC128 mice subcutaneously administered a single 10 mg/kg dose of the indicated dsRNA duplexes targeting exon 1 of the HTT transcript at Day 7 post-dose. Human HTT levels shown are normalized to PBS treatment levels.

FIG. 6 is a graph showing full-length mutant human HTT mRNA levels in YAC128 mice subcutaneously administered a single 10 mg/kg dose of the indicated dsRNA duplexes at Day 7 post-dose and the corresponding full-length mutant human HTT protein levels in the livers. Mutant human mRNA and protein HTT levels shown are normalized to PBS treatment levels.

FIG. 7 is a graph showing mutant full-length human HTT mRNA levels in YAC128 mice subcutaneously administered a single 10 mg/kg dose of the indicated dsRNA duplexes at Day 7 post-dose. Mutant human HTT levels shown are normalized to PBS treatment levels.

FIGS. 8A and **8B** are graphs showing full-length human HTT mRNA levels in human fibroblasts transfected with 10 nM or 50 nM of the indicated dsRNA duplexes targeting various exons or exon 1 specifically of human HTT. Fibroblasts were obtained from Coriell, adult healthy control patient ("Control", GM02153), an HD patient with adult disease onset ("Adult", GM04478") and an HD patient with juvenile disease onset ("Juvenile", GM09197"). HTT levels shown are normalized to mock transfected controls.

FIGS. 9A and **9B** are graphs showing full-length human HTT mRNA levels in human fibroblasts transfected with 10 nM or 50 nM of the indicated dsRNA duplexes targeting various exons or exon 1 specifically of human HTT. Fibroblasts were obtained from Coriell, adult healthy control patient ("Control", GM02153), an HD patient with adult disease onset ("Adult", GM04478")

and an HD patient with juvenile disease onset ("Juvenile", GM09197"). HTT levels shown are normalized to mock transfected controls.

FIGS. 10A-10D a are graphs showing full-length human HTT mRNA levels in human fibroblasts transfected with 10 nM or 50 nM of the indicated dsRNA duplexes targeting various exons or exon 1 specifically of human HTT. Fibroblasts were obtained from Coriell, adult healthy control patient ("Control", GM02153), an HD patient with adult disease onset ("Adult", GM04478") and an HD patient with juvenile disease onset ("Juvenile", GM09197"). HTT levels shown are normalized to mock transfected controls.

FIGS. 11A-11D are graphs showing full-length HTT mRNA mRNA levels in human fibroblasts transfected with 10 nM or 50 nM of the indicated dsRNA duplexes targeting various exons or exon 1 specifically of human HTT. Fibroblasts were obtained from Coriell, adult healthy control patient ("Control", GM02153), an HD patient with adult disease onset ("Adult", GM04478") and an HD patient with juvenile disease onset ("Juvenile", GM09197"). HTT levels shown are normalized to mock transfected controls.

FIG 12 is a graph showing full-length mutant human HTT mRNA levels in the livers of YAC 128 mice or wildtype mice expressing a portion of human wild-type HTT ("AAV") and subcutaneously administered a single dose of the indicated dsRNA duplexes targeting the full length HTT transcript at the indicated days post dose. HTT levels shown are normalized to PBS treatment levels.

FIGS.13A-D are graphs showing full-length human HTT mRNA levels in the livers of mice expressing a portion of human wild-type HTT via AAV. These mice were subcutaneously administered a single 3 mg/kg dose of the indicated dsRNA duplexes targeting the full length HTT transcript at 14 days post-dose. HTT levels are shown relative to AAV treated control levels 14 days post siRNA dose.

DETAILED DESCRIPTION OF THE INVENTION

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.

The iRNAs of the invention have been designed to target an HTT gene, including portions of the gene that are conserved in the HTT orthologs of other mammalian species. The iRNAs of the invention have also been designed to target a particular portion of an HTT gene, exon 1, *e.g.,* thereby targeting the full-length wild-type transcript, the full-length mutant transcript, as well as the truncated mutant transcript. 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, *e.g.,* exon 1, or the specific modifications in these iRNAs confer to the iRNAs of the invention improved efficacy, stability, potency, durability, and safety.

Accordingly, the present disclosure also provides methods of using the RNAi compositions of the disclosure 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).

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.

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.

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).

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

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.

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.

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.

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.

The term “at least” 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.

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.

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

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.

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

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.

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);

and GenBank Accession No.: XM_028848247.1 (Macaca mulatta HTT, SEQ ID NO: 5, reverse complement, SEQ ID NO: 10).

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

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

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.

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.

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.

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.

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.

"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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

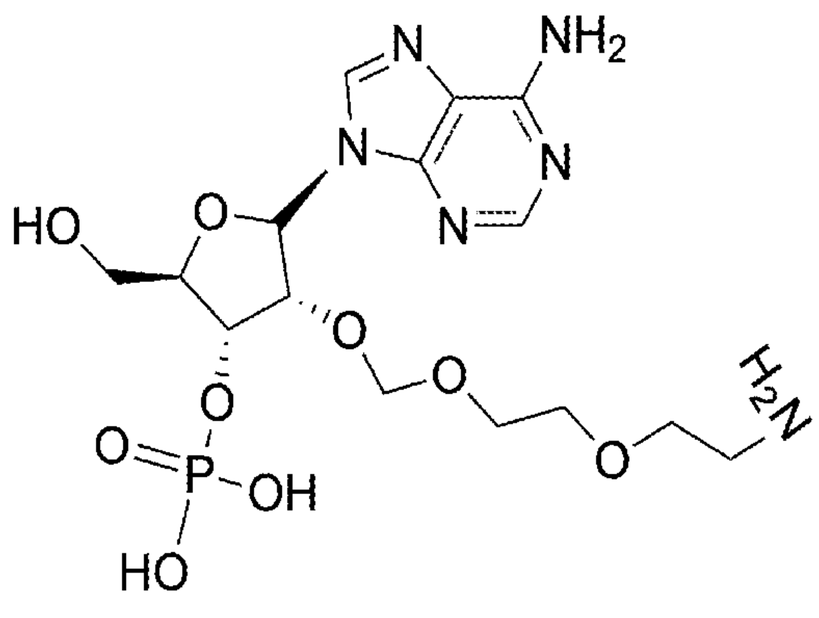
sense strand of the duplex. In certain embodiments, an extended overhang is present on the 3'end of the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 5'end of the sense strand of the duplex. In certain embodiments, an extended overhang is on the antisense 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.

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.

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.

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.

An exemplary 2'adem modified nucleotide is shown below:



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.

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.

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

SUBSTITUTE SHEET (RULE 26)

example, in the 3'-terminal nucleotide of the iRNA agent. In some embodiments, the mismatch(s) is not in the seed region.

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.

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.

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.

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.

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.

"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.

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.

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.

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 complement component 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, or a fragment of any one of SEQ ID NOs:1-5, 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.

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, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33, 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.

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, or a fragment of any one of SEQ ID NOs:6-10, 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.

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, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33, 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

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:

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

"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.

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.

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.

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.

"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.

"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.

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.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, 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.

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.

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

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.

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.

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.

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.

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.

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).

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.

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.

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.

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, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33, 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, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33. 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, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33, and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33.

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.

It will be understood that, although the sequences in Tables 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33 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, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33 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 Tables 3, 9, 12, 15, 17, 27, 29 and 32 are conjugated to a GalNAc ligand, these agents may be conjugated to a moiety that directs delivery to the CNS, *e.g.,* a C16 ligand, as described herein. A lipophilic ligand can be included in any of the positions provided in the instant application.

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.

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

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.

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.

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.

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.

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 CH_2 component parts.

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.

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.

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.

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[$(CH_2)_nO$] $_mCH_3$, O(CH_2).$_nOCH_3$, O$(CH_2)_nNH_2$, O$(CH_2)_nCH_3$, O$(CH_2)_nONH_2$, and O$(CH_2)_nON[(CH_2)_nCH_3)]_2$, 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$(CH_2)_2ON(CH_3)_2$ 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).

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.

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.

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.

An RNAi agent of the disclosure can also be modified to 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. 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).

An RNAi agent of the disclosure can also be modified to include one or more bicyclic sugar moities. A “bicyclic sugar” is a furanosyl ring modified by the bridging of two atoms. A “bicyclic nucleoside” (“BNA”) is a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms 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. Thus, in some embodiments an agent of the disclosure 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'-CH2-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 disclosure 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 disclosure include one or more bicyclic nucleosides comprising a 4′ to 2′ bridge. Examples of such 4′ to 2′ bridged bicyclic nucleosides, include but are not limited to 4′-(CH2)—O-2′ (LNA); 4′-(CH2)—S-2′; 4′-(CH2)2—O-2′ (ENA); 4′-CH(CH3)—O-2′ (also referred to as “constrained ethyl” or “cEt”) and 4′-CH(CH2OCH3)—O-2′ (and analogs thereof; see, *e.g.*, U.S. Pat. No. 7,399,845); 4′-C(CH3)(CH3)—O-2′ (and analogs thereof; see *e.g.*, US Patent No. 8,278,283); 4′-CH2—N(OCH3)-2′ (and analogs thereof; see *e.g.*, US Patent No. 8,278,425); 4′-CH2—O—N(CH3)-2′ (see, *e.g.*,U.S. Patent Publication No. 2004/0171570); 4′-CH2—N(R)—O-2′, wherein R is H, C1-C12 alkyl, or a protecting group (see, *e.g.*, U.S. Pat. No. 7,427,672); 4′-CH2—C(H)(CH3)-2′ (see, *e.g.*, Chattopadhyaya *et al., J. Org. Chem.*, 2009, 74, 118-134); and 4′-CH2—C(=CH2)-2′ (and

analogs thereof; see, *e.g.*, US Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

Additional representative US Patents and US Patent Publications that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: US 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.

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).

An RNAi agent of the disclosure 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)-0-2' bridge. In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as “S-cEt.”

An RNAi agent of the disclosure 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.

Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, US 2013/0190383; and WO 2013/036868, the entire contents of each of which are hereby incorporated herein by reference.

In some embodiments, an RNAi agent of the disclosure 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).

Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

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'-0-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in WO 2011/005861.

Other modifications of an RNAi agent of the disclosure include a 5' phosphate or 5' phosphate mimic, *e.g.*, a 5'-terminal phosphate or phosphate mimic on the antisense strand of an RNAi agent. Suitable phosphate mimics are disclosed in, for example US 2012/0157511, the entire contents of which are incorporated herein by reference.

A. Modified RNAi agents Comprising Motifs of the Disclosure

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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).

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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

wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

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

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

each n_p and n_q independently represent an overhang nucleotide;

wherein Nb and Y do not have the same modification; and

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.

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

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.

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:

$$5'\ n_p\text{-}N_a\text{-}YYY\text{-}N_b\text{-}ZZZ\text{-}N_a\text{-}n_q\ 3' \quad (Ib);$$

$$5'\ n_p\text{-}N_a\text{-}XXX\text{-}N_b\text{-}YYY\text{-}N_a\text{-}n_q\ 3' \quad (Ic); \text{ or}$$

$$5'\ n_p\text{-}N_a\text{-}XXX\text{-}N_b\text{-}YYY\text{-}N_b\text{-}ZZZ\text{-}N_a\text{-}n_q\ 3' \quad (Id).$$

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.

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

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.

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.

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

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

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

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.

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

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)

wherein:

k and l are each independently 0 or 1;

p' and q' are each independently 0-6;

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

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

each n_p' and n_q' independently represent an overhang nucleotide;

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

and

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

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

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 17-23nucleotidein 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.

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

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.

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

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

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

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

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.

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.

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.

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

5' $n_{p'}$-$N_{a'}$-Y'Y'Y'- $N_{a'}$-$n_{q'}$ 3' (Ia).

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.

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

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.

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.

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.

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.

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):

sense: 5' n_p -N_a-(X X X)$_i$ -N_b- Y Y Y -N_b -(Z Z Z)$_j$-N_a-n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'-n_q' 5'

(III)

wherein:

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

p, p', q, and q' are each independently 0-6;

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;

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

wherein

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

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.

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.

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

5' n_p - N_a -Y Y Y -N_a-n_q 3'

3' n_p'-N_a'-Y'Y'Y' -N_a'n_q' 5'

(IIIa)

5' n_p -N_a -Y Y Y -N_b -Z Z Z -N_a-n_q 3'

3' n_p'-N_a'-Y'Y'Y'-N_b'-Z'Z'Z'-N_a'n_q' 5'

(IIIb)

5' n_p-N_a- X X X -N_b -Y Y Y - N_a-n_q 3'

3' n_p'-N_a'-X'X'X'-N_b'-Y'Y'Y'-N_a'-n_q' 5'

(IIIc)

5' n_p -N_a -X X X -N_b-Y Y Y -N_b- Z Z Z -N_a-n_q 3'

3' n_p'-N_a'-X'X'X'-N_b'-Y'Y'Y'-N_b'-Z'Z'Z'-N_a-n_q' 5'

(IIId)

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.

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.

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.

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.

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.

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.

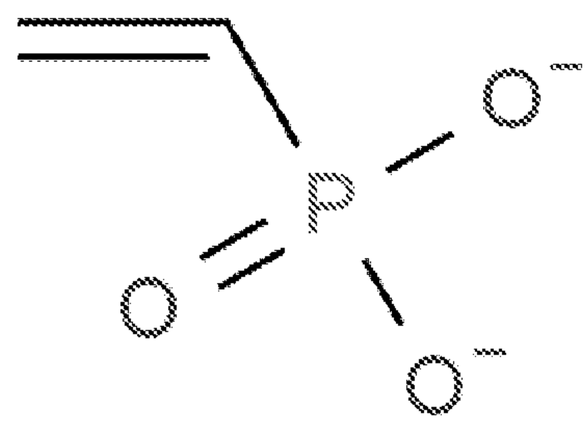
In one embodiment, the RNAi agent is a multimer containing at least two duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of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

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.

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.

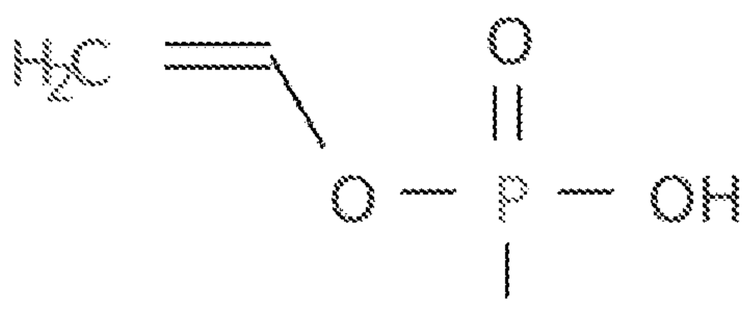
Various publications describe multimeric RNAi agents that can be used in the methods of the disclosure. Such publications include WO2007/091269, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520; and US 7858769, the entire contents of each of which are hereby incorporated herein by reference.

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 vinyl phosphonate of the disclosure has the following structure:



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 preferred 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.

Vinyl phosphate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphate structure is:



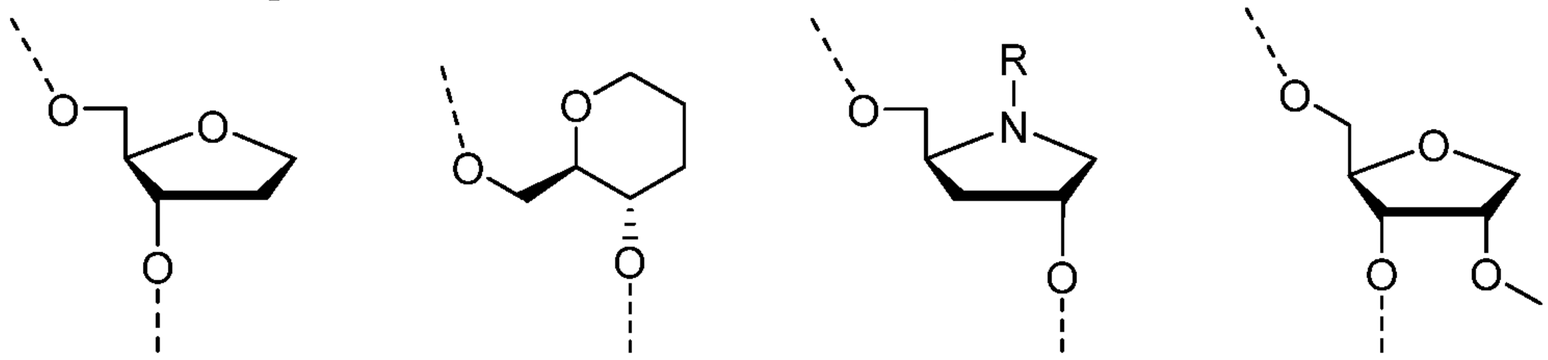
i. Thermally Destabilizing Modifications

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) to reduce or inhibit off-target gene silencing. It has

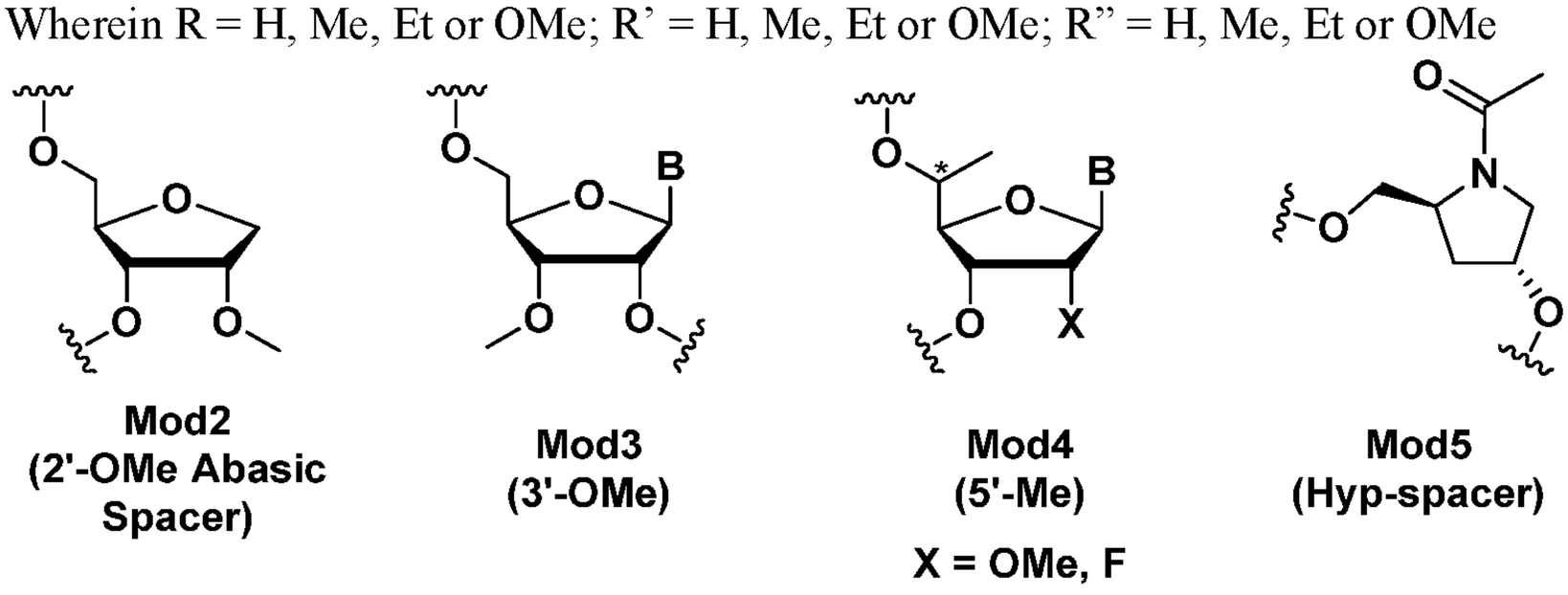
been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, 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.

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) or glycol nucleic acid (GNA).

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



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)

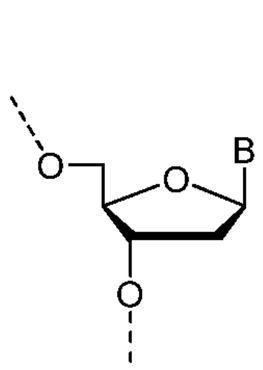
Mod4 (5'-Me)

X = OMe, F

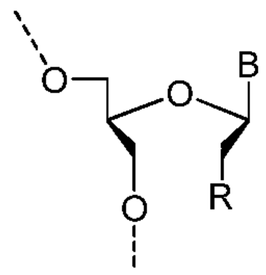
Mod5 (Hyp-spacer)

wherein B is a modified or unmodified nucleobase.

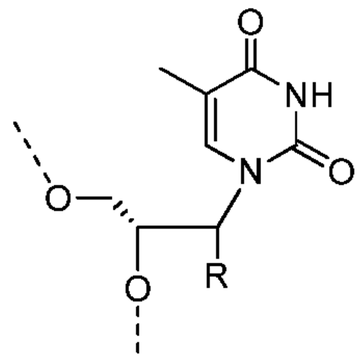
Exemplified sugar modifications include, but are not limited to the following:



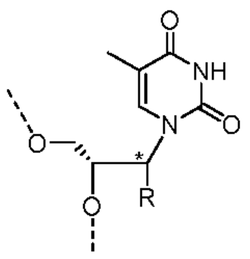
2'-deoxy



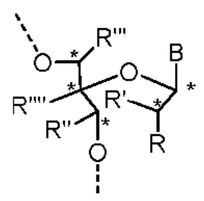
unlocked nucleic acid
R= H, OH, O-alkyl



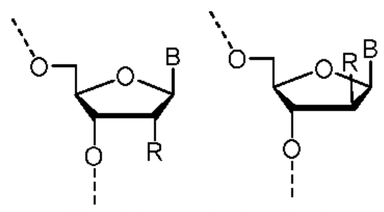
glycol nucleic acid
R= H, OH, O-alkyl



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



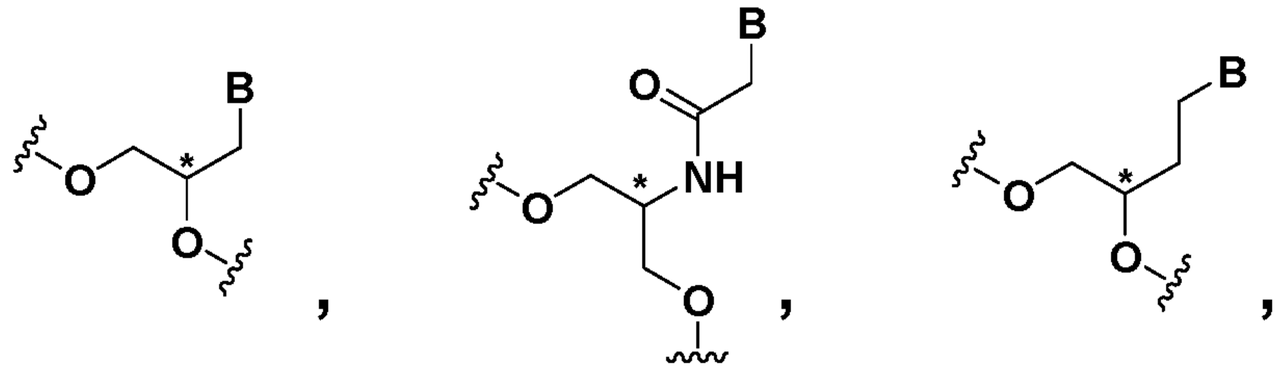
unlocked nucleic acid
R= H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R'' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R''' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R'''' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2

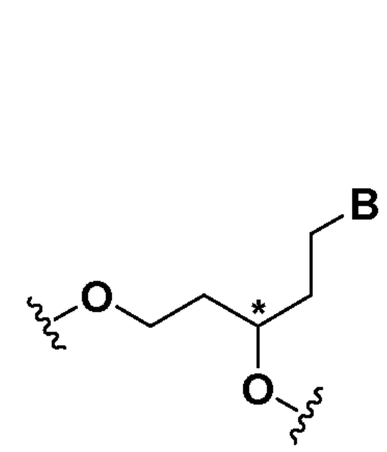


R = H, methyl, ethyl

wherein B is a modified or unmodified nucleobase.

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



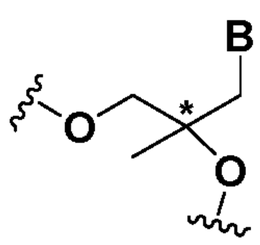


,

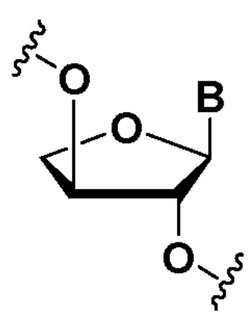
,

,

,

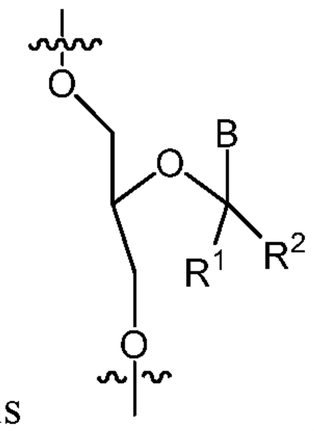
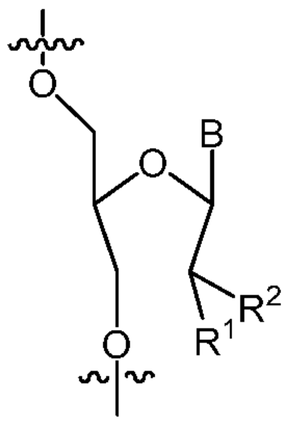
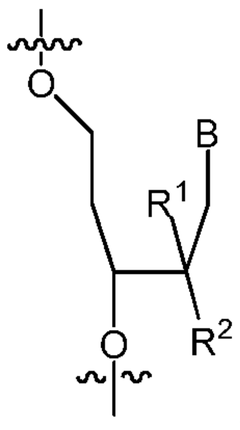
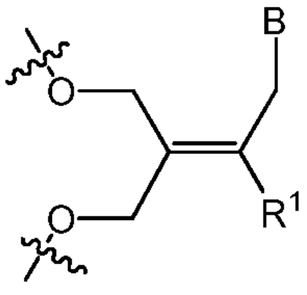
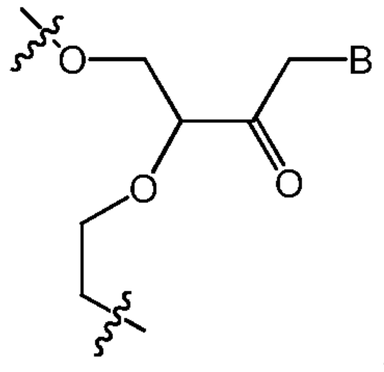


, and

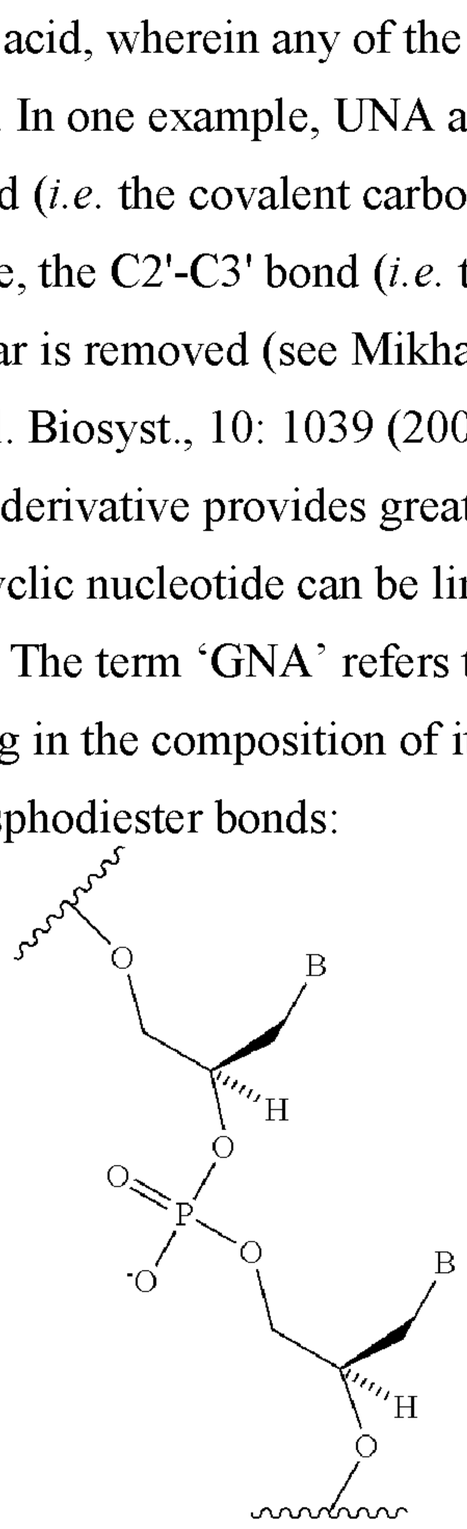


wherein B is a modified or unmodified nucleobase and the asterisk on each structure represents either *R*, *S* or *racemic*.

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  ,  ,  ,  or  , 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.

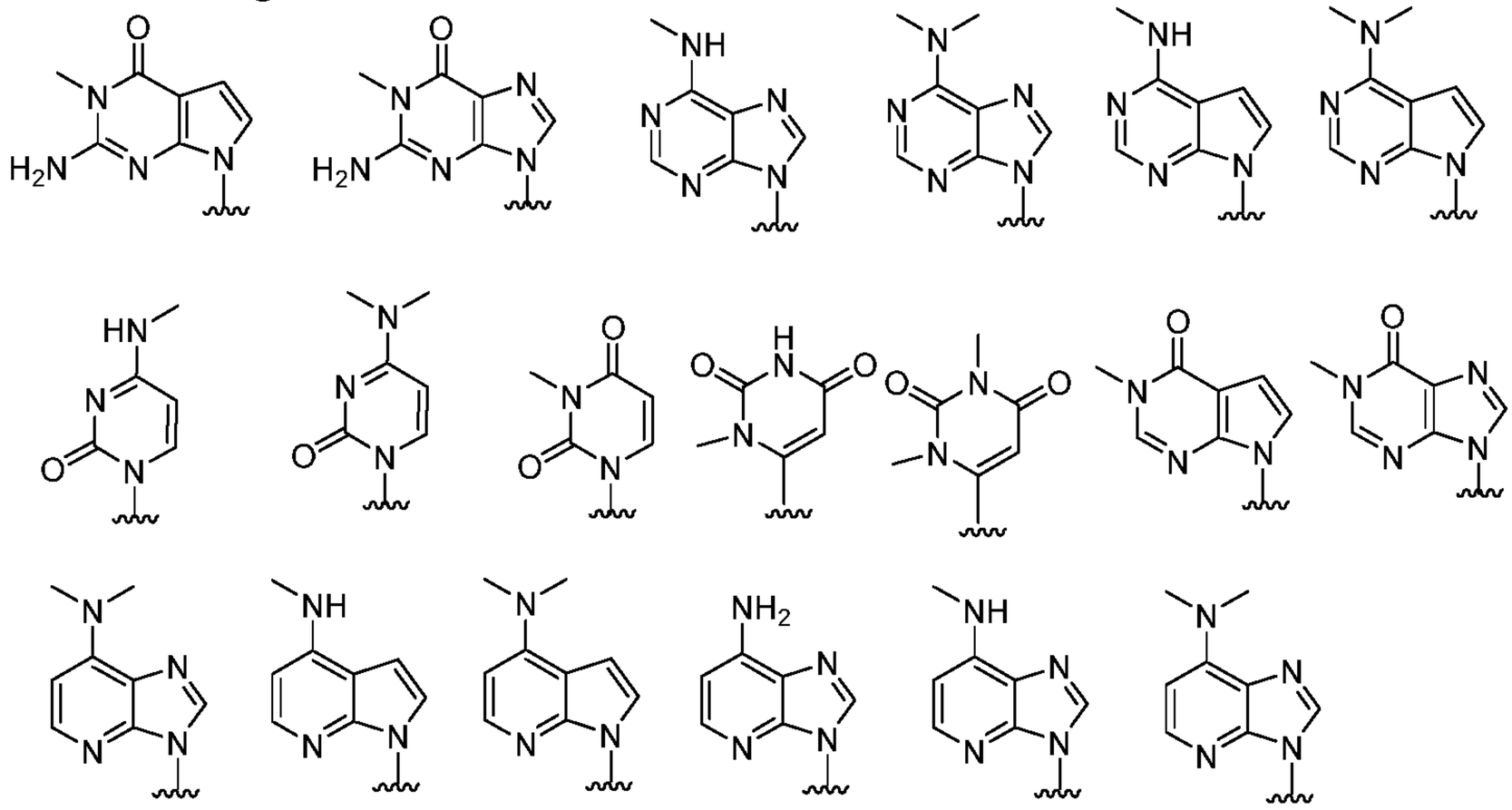
The term 'GNA' refers to glycol nucleic acid which is a polymer similar to DNA or RNA but differing in the composition of its "backbone" in that is composed of repeating glycerol units linked by phosphodiester bonds:



(R)-GNA

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.

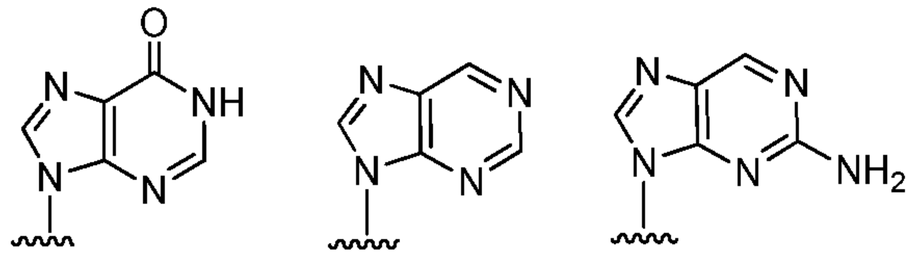
In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes nucleotides with impaired W-C H-bonding to complementary base on the target mRNA, such as:



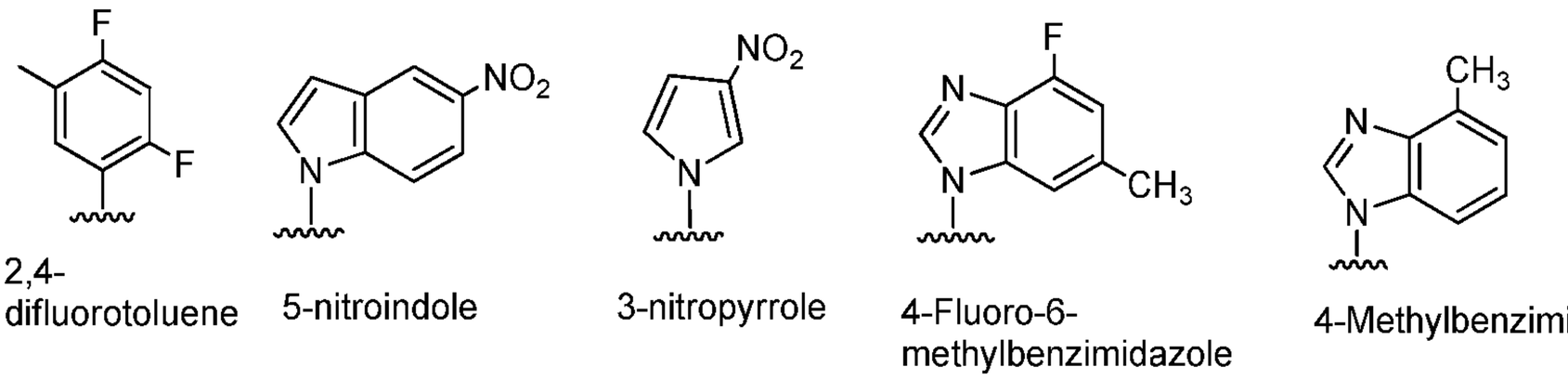
More examples of abasic nucleotide, acyclic nucleotide modifications (including UNA and GNA), and mismatch modifications have been described in detail in WO 2011/133876, which is herein incorporated by reference in its entirety.

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.

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:

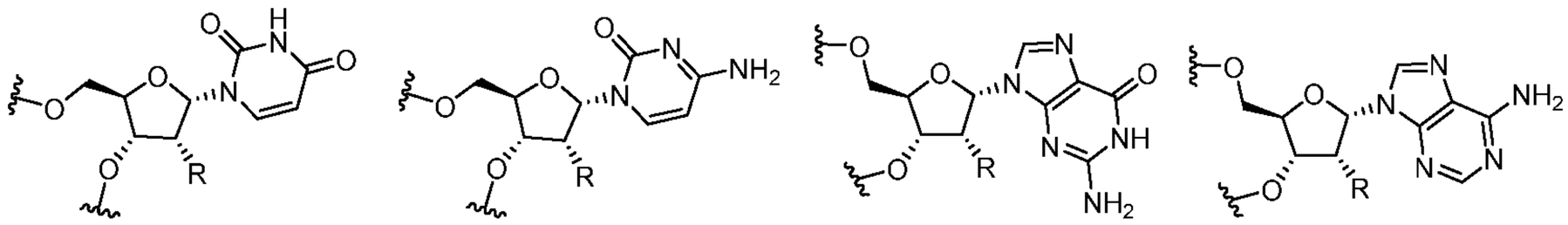


inosine nebularine 2-aminopurine



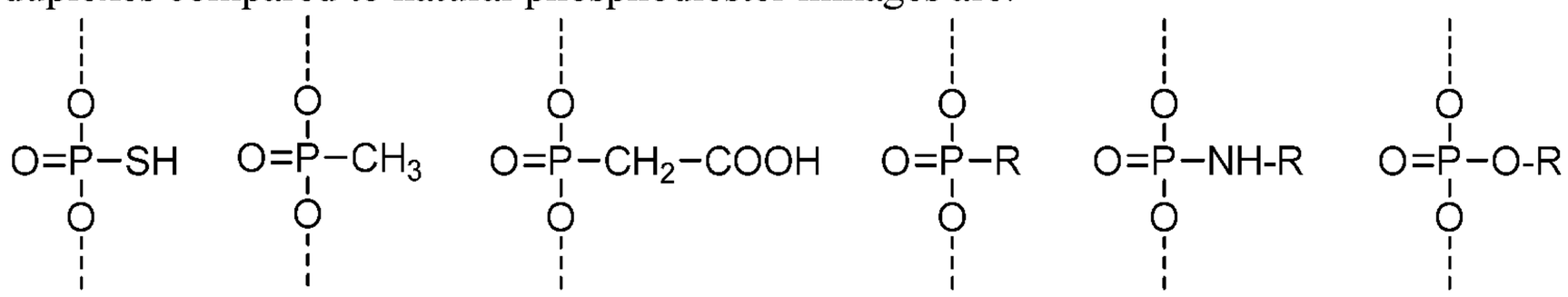
2,4-difluorotoluene 5-nitroindole 3-nitropyrrole 4-Fluoro-6-methylbenzimidazole 4-Methylbenzimidazole

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.

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



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.

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

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.

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), 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.

In some embodiments, the dsRNA molecule of the disclosure comprising 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). 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.

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), 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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).

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).

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).

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).

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).

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).

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).

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).

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).

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).

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).

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).

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).

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).

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 the antisense strand (counting from the 5'-end).

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 positions 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

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 the antisense strand (counting from the 5'-end).

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 positions 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

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 the antisense strand (counting from the 5'-end).

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.

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.

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.

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.

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), 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.

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), 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.

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), 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.

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), 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 and 33. These agents may further comprise a ligand.

IV. iRNAs Conjugated to Ligands

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).

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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

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.

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.

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.

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.

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).

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

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).

In certain embodiments, a carbohydrate conjugate comprises a monosaccharide.

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).

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.

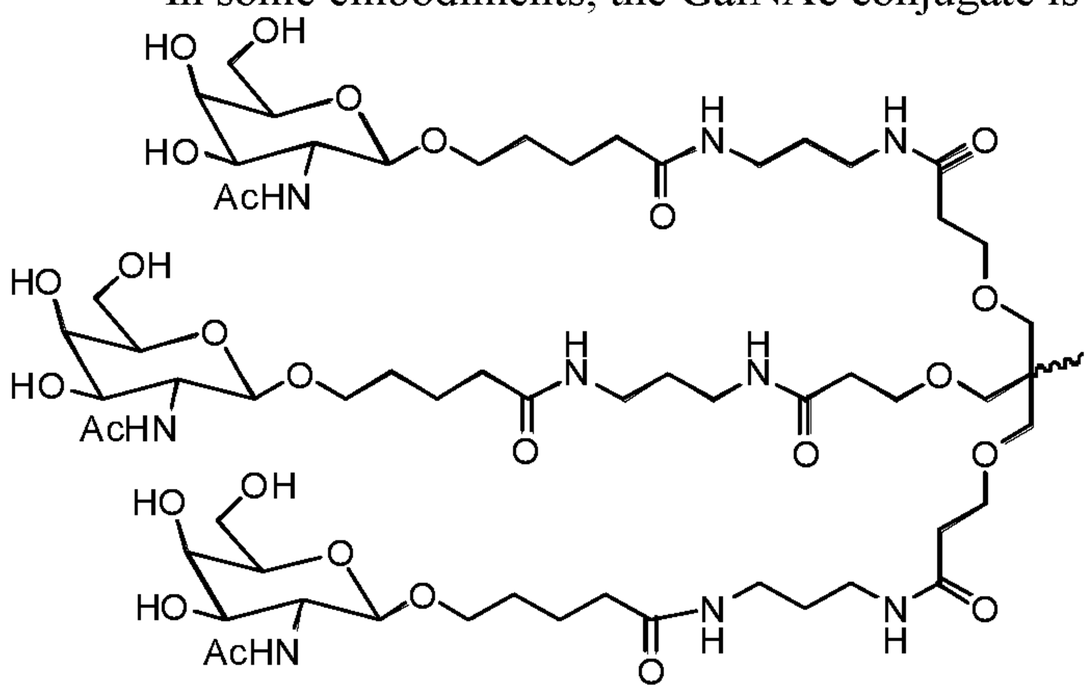
In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other embodiments of the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

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.

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.

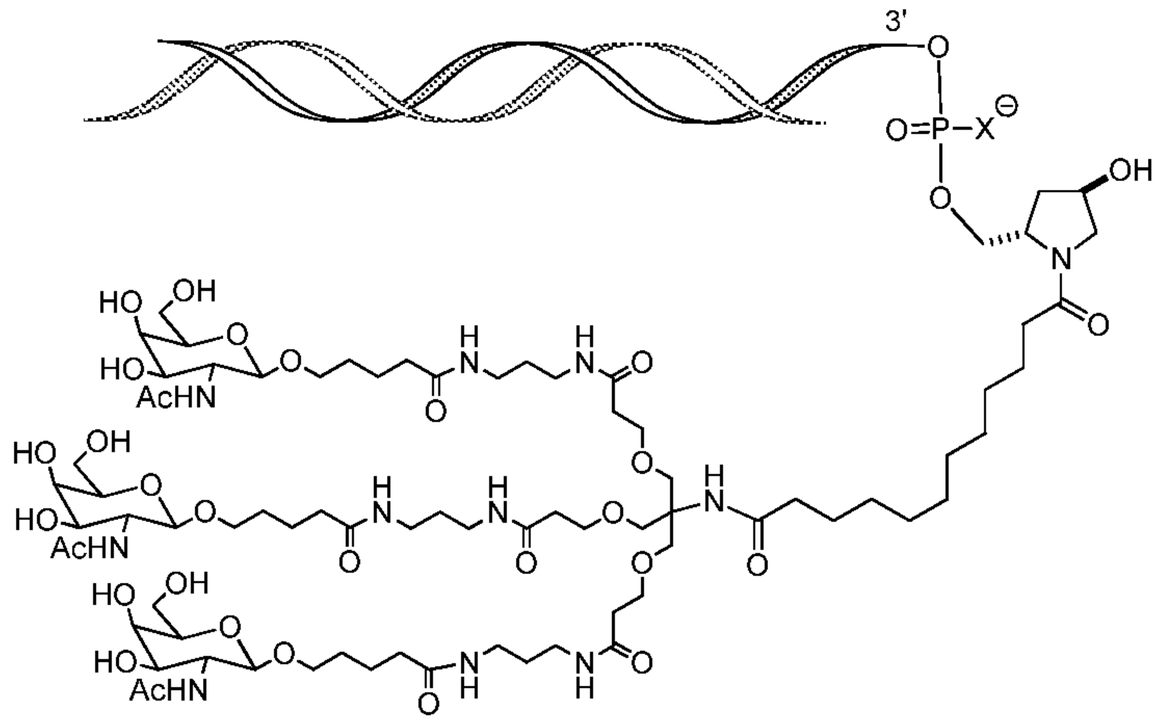
In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of 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.

In some embodiments, the GalNAc conjugate is

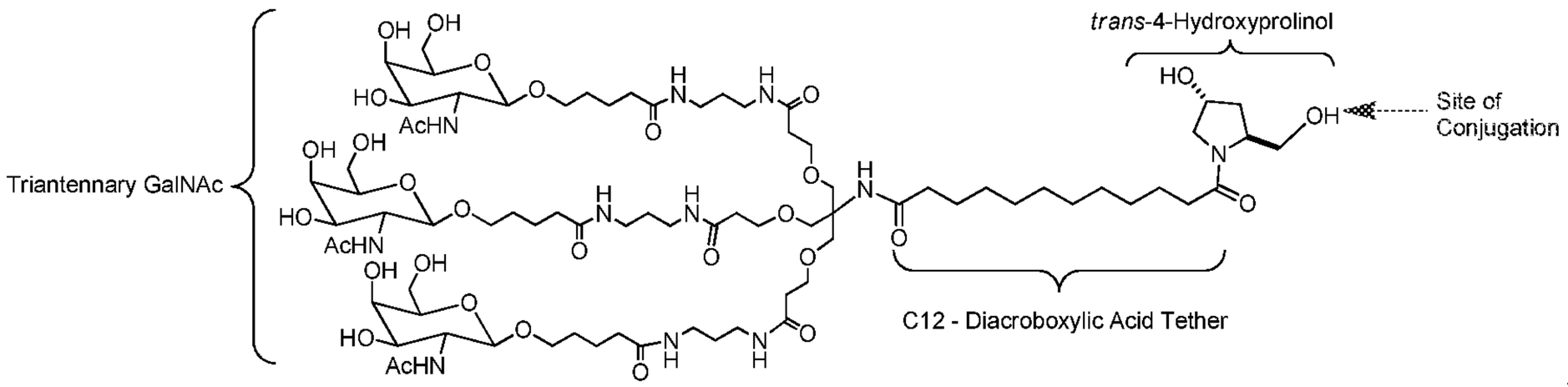


Formula II.

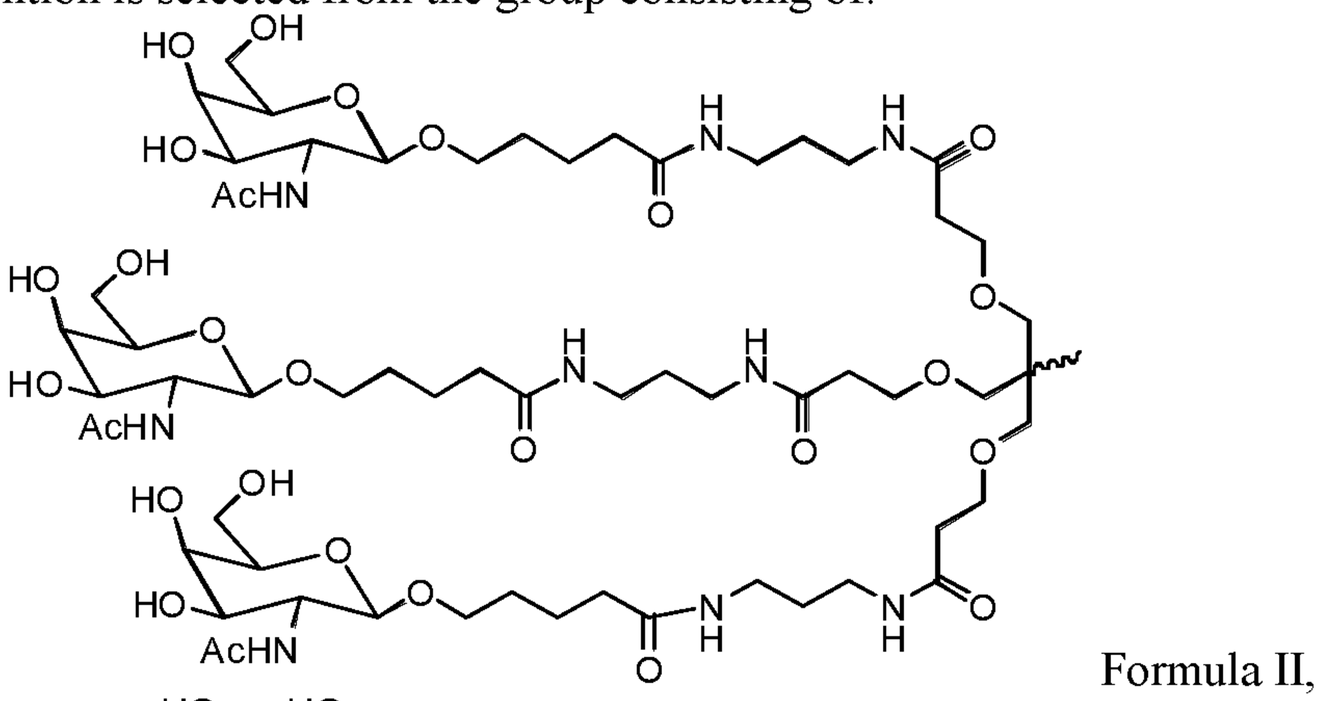
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S



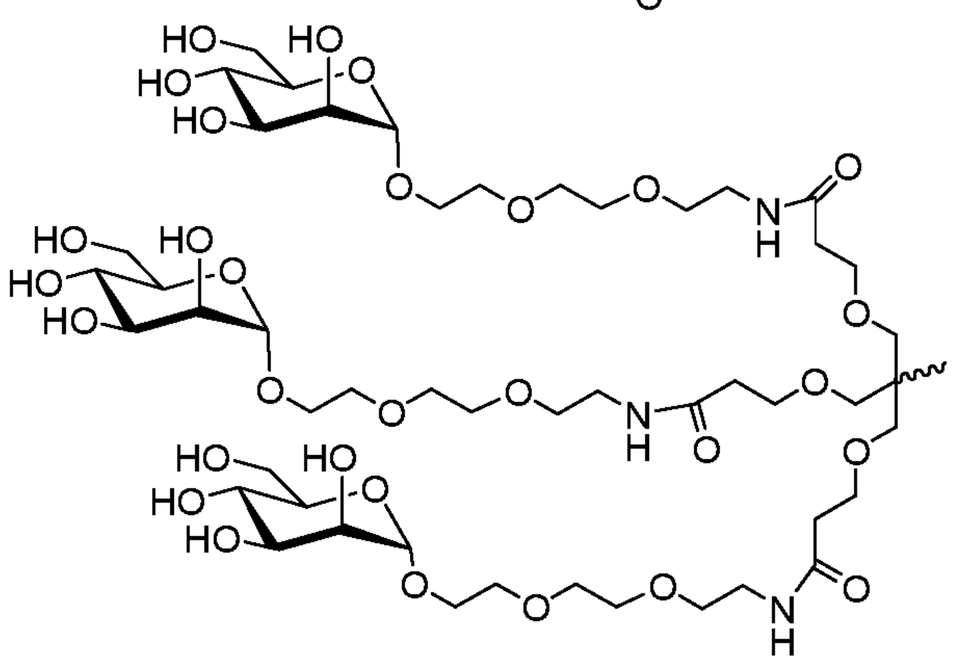
In some embodiments, the RNAi agent is conjugated to L96 as defined in Table 1 and shown below:



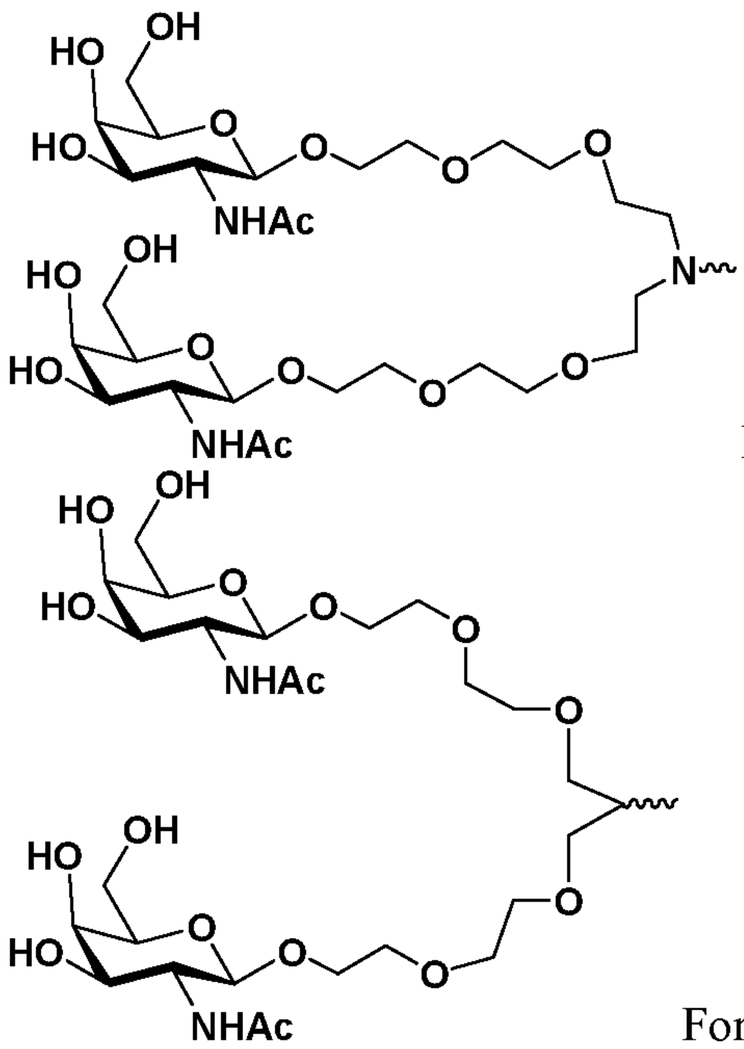
In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



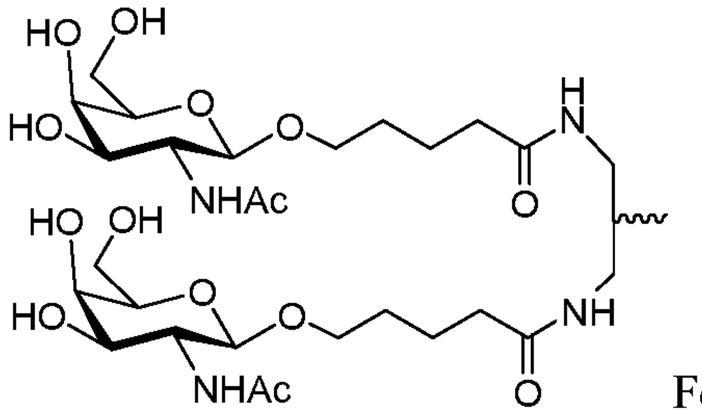
Formula II,



Formula III,

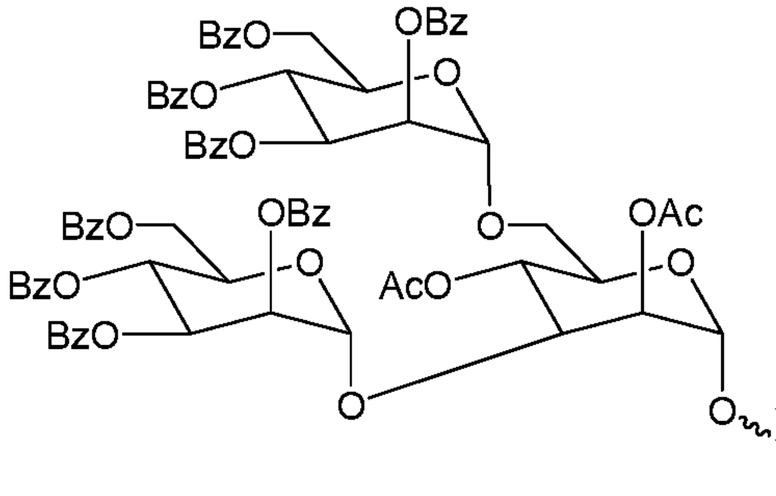


Formula IV,



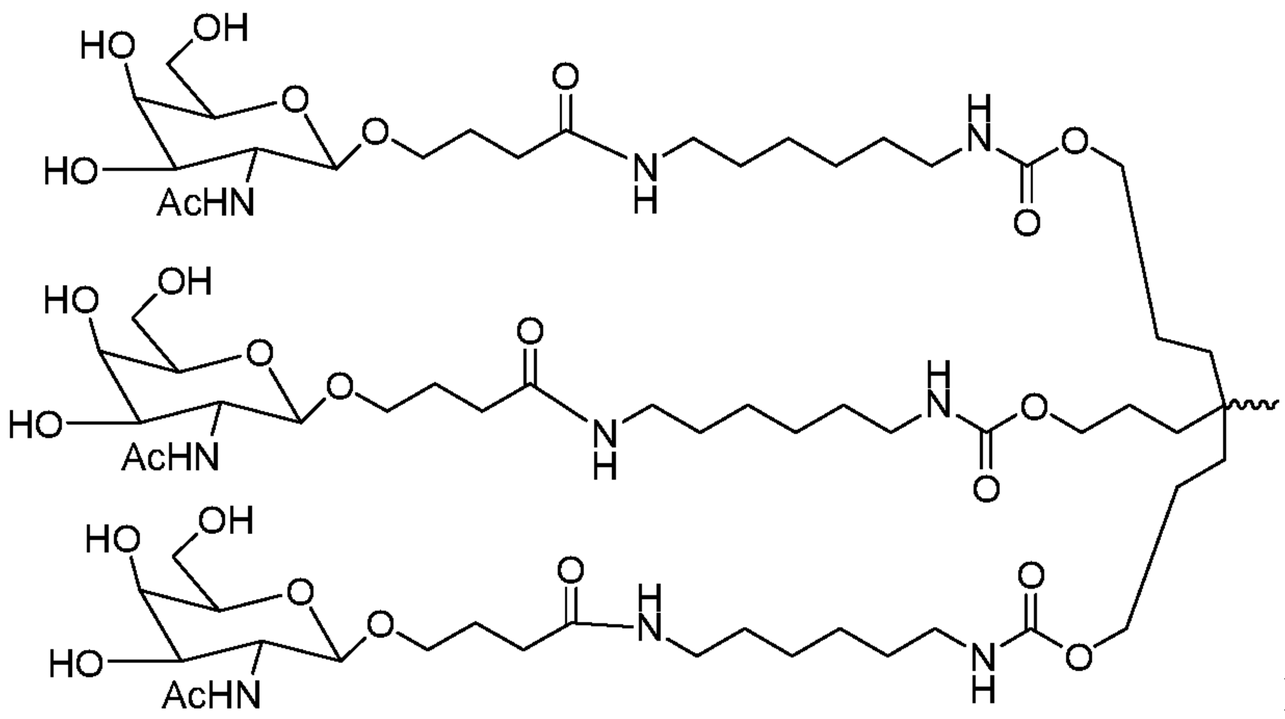
Formula V,

Formula VI,

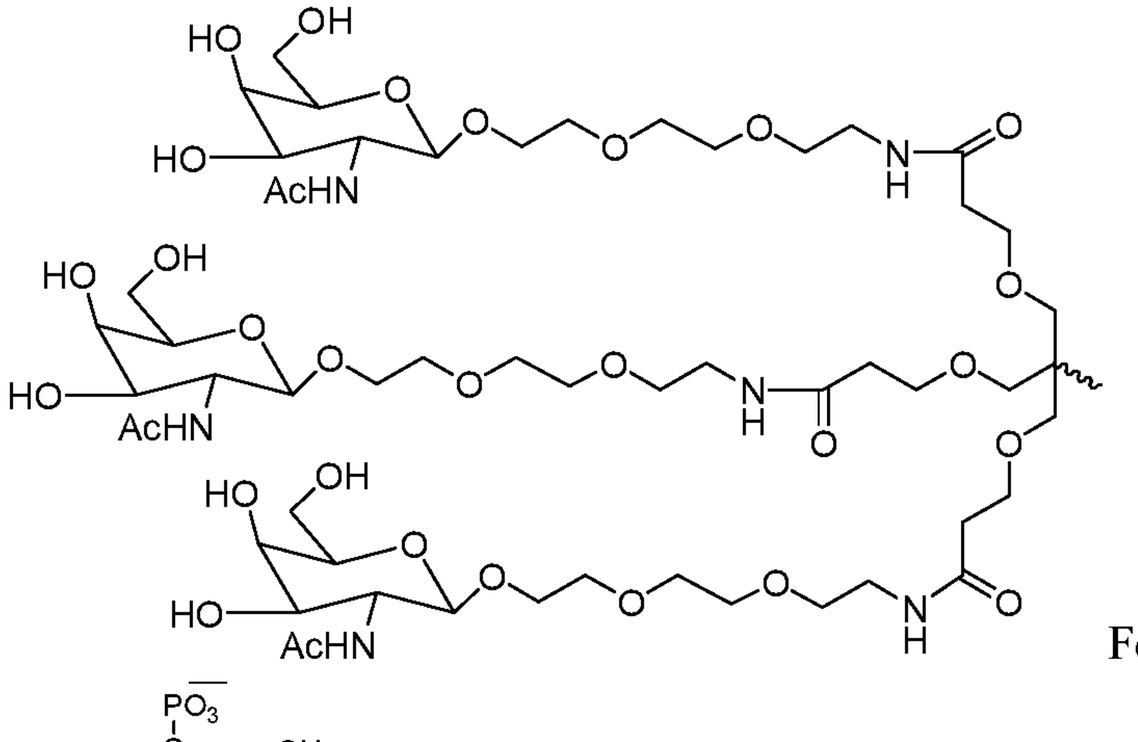


Formula VII,

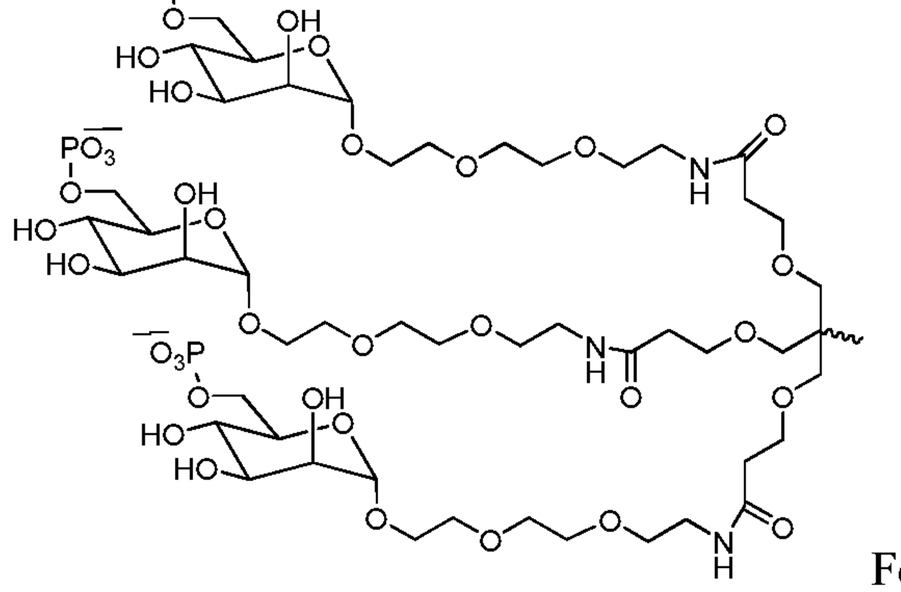
Formula VIII,



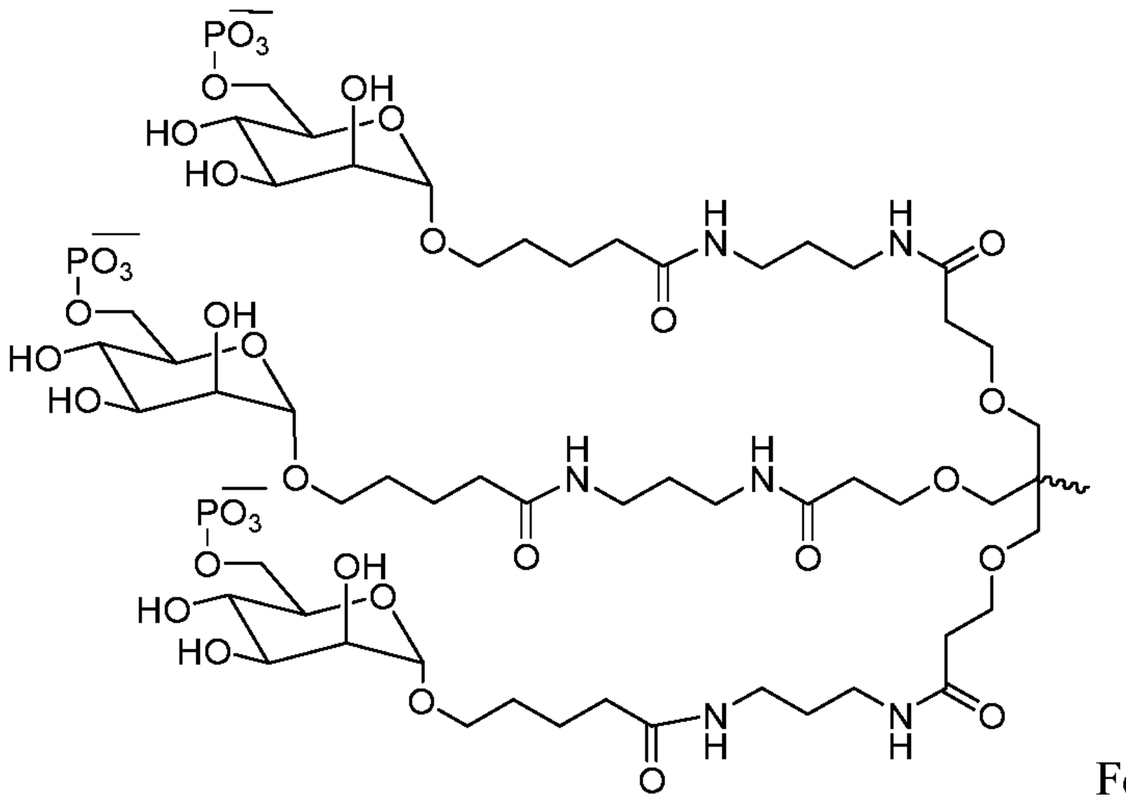
Formula IX,



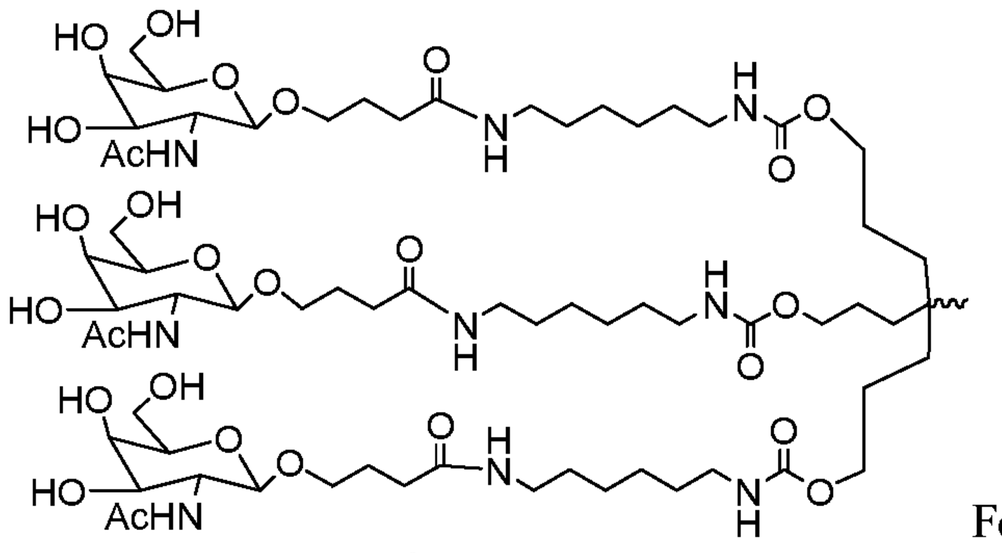
Formula X,



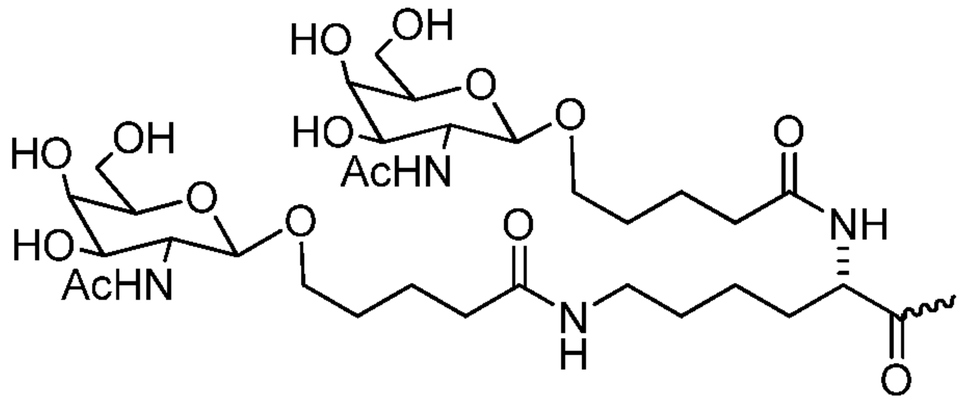
Formula XI,



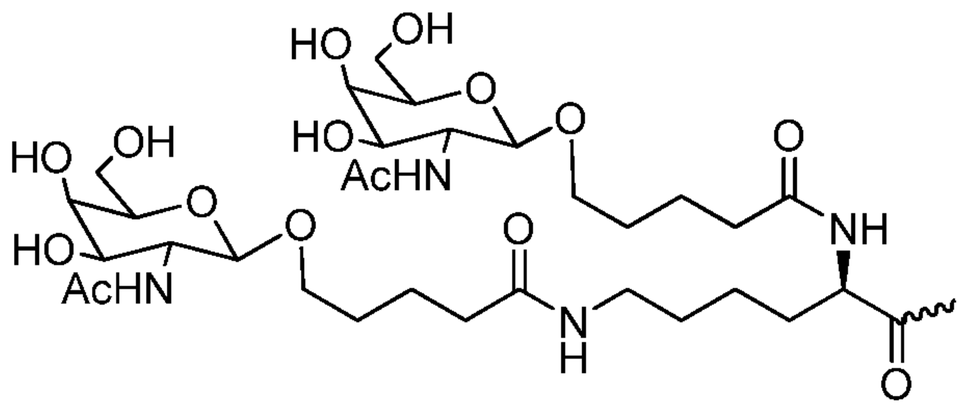
Formula XII,



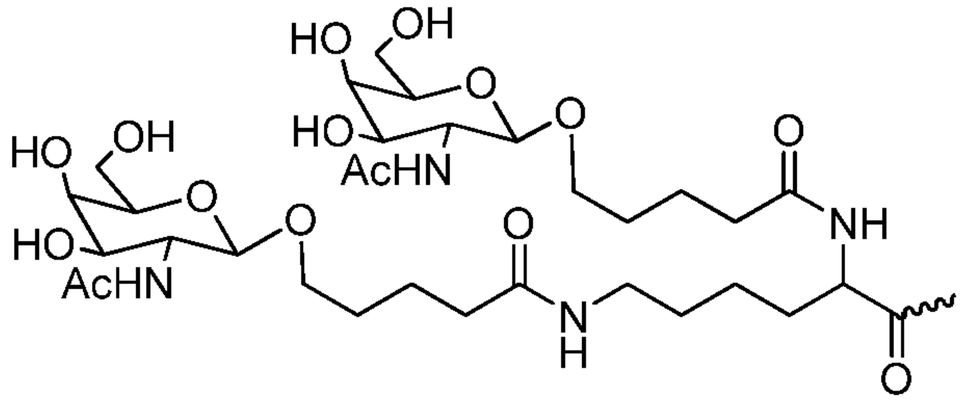
Formula XIII,



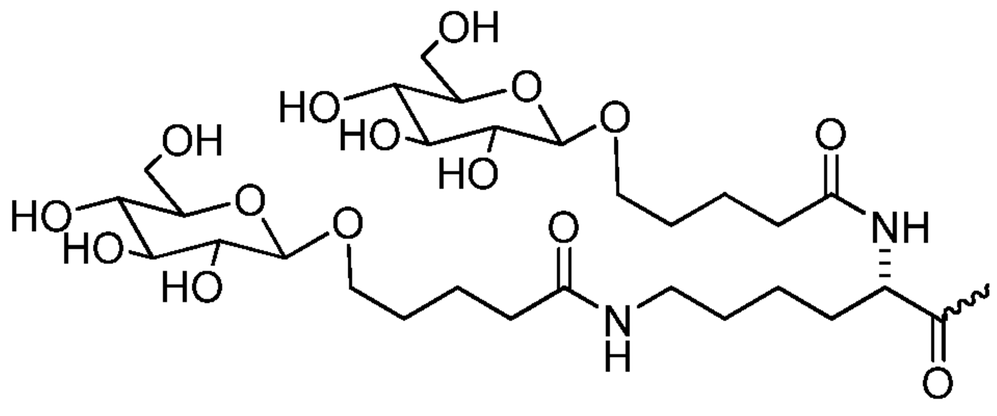
Formula XIV,



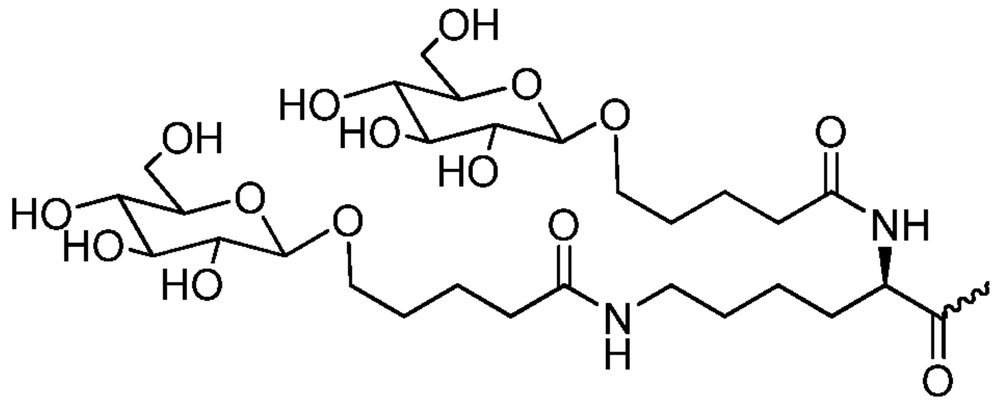
Formula XV,



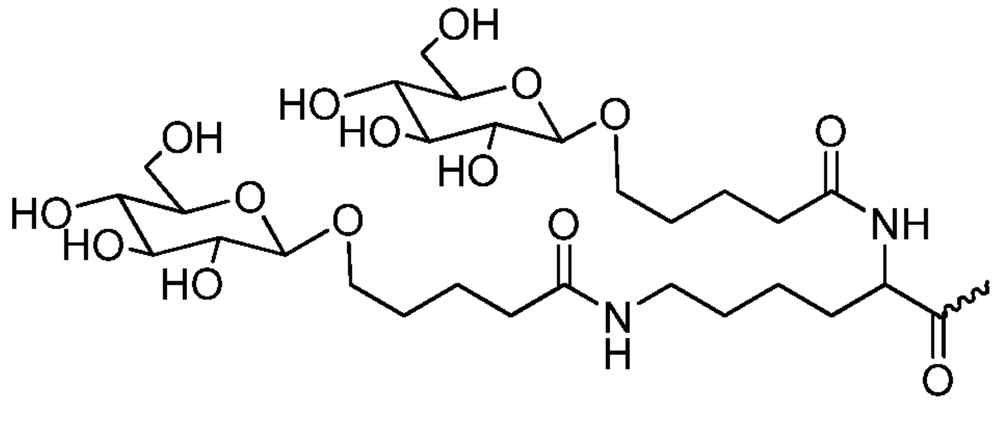
Formula XVI,



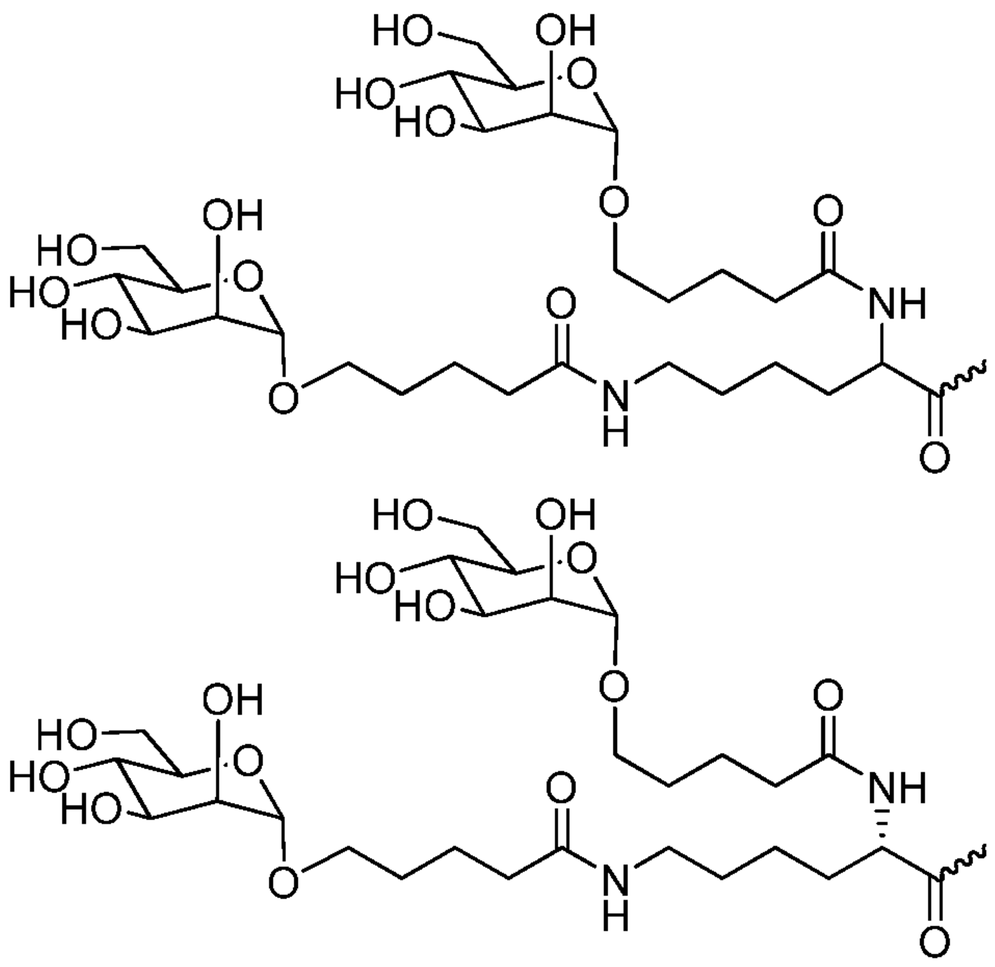
Formula XVII,



Formula XVIII,

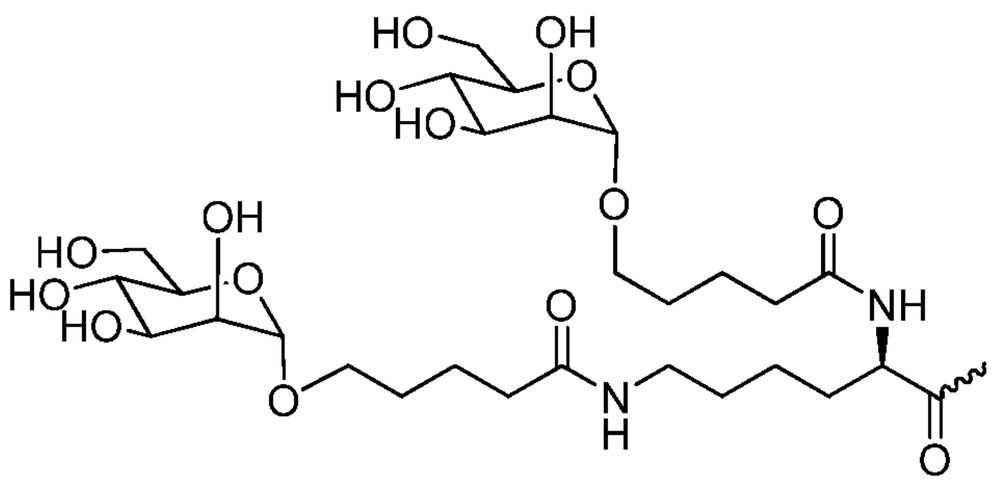


Formula XIX,

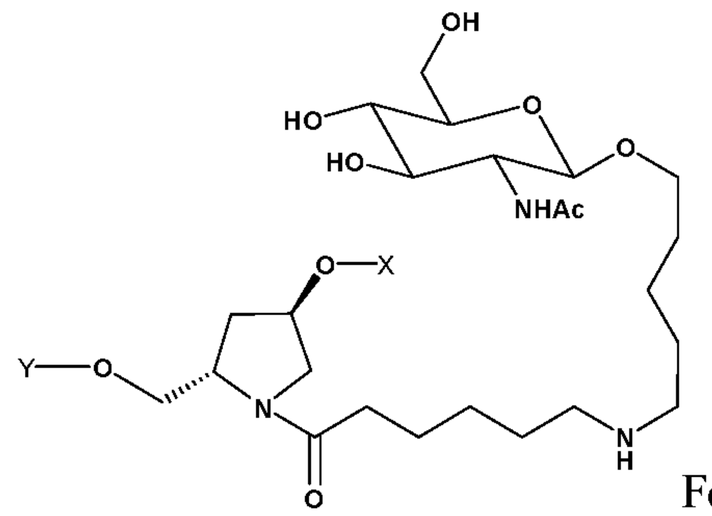


Formula XX,

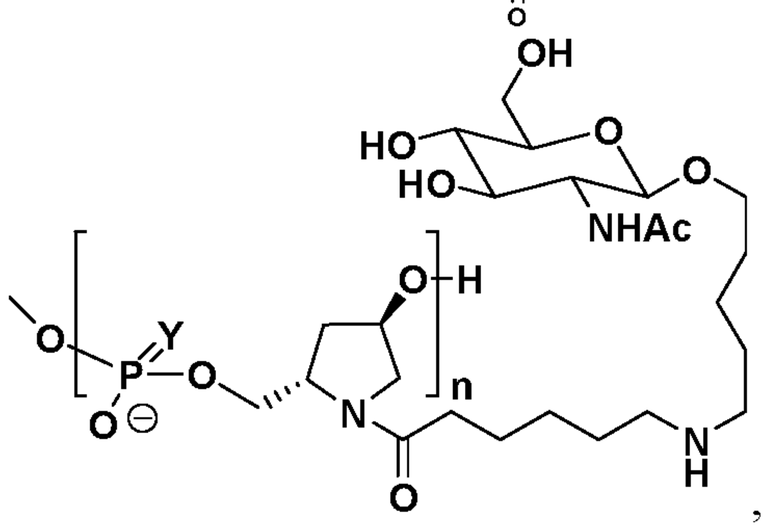
Formula XXI,



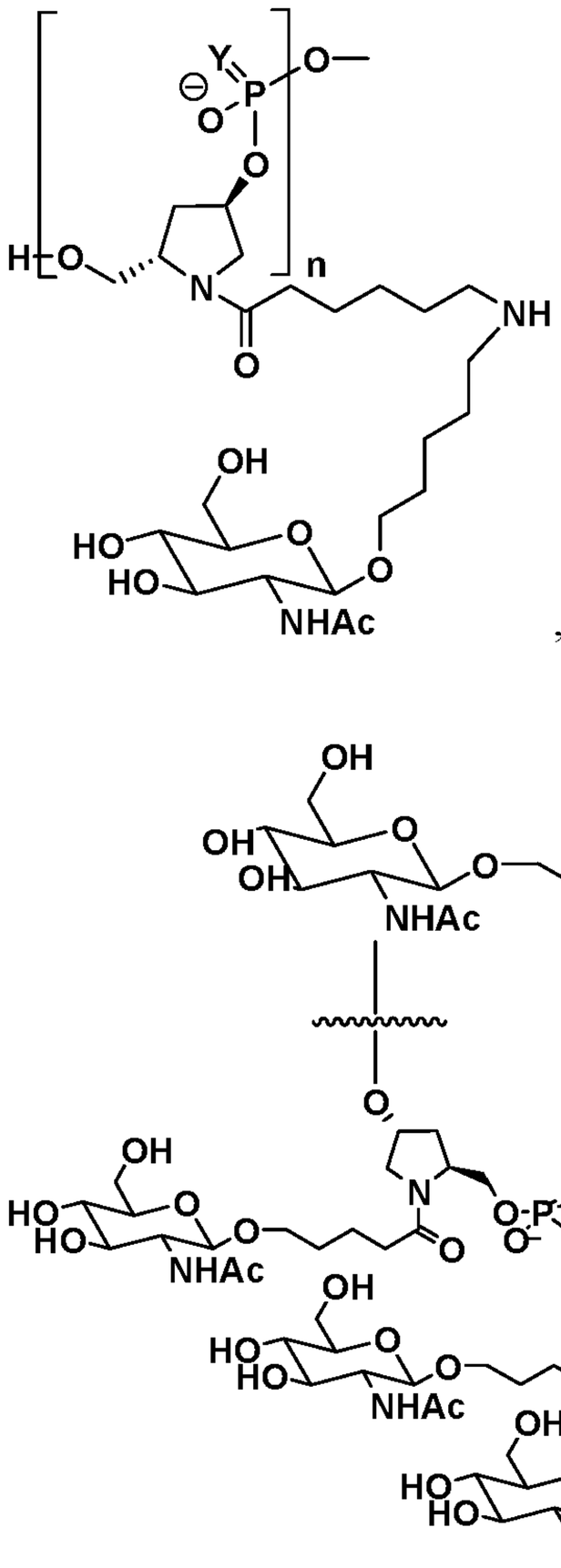
Formula XXII,



Formula XXIII;



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

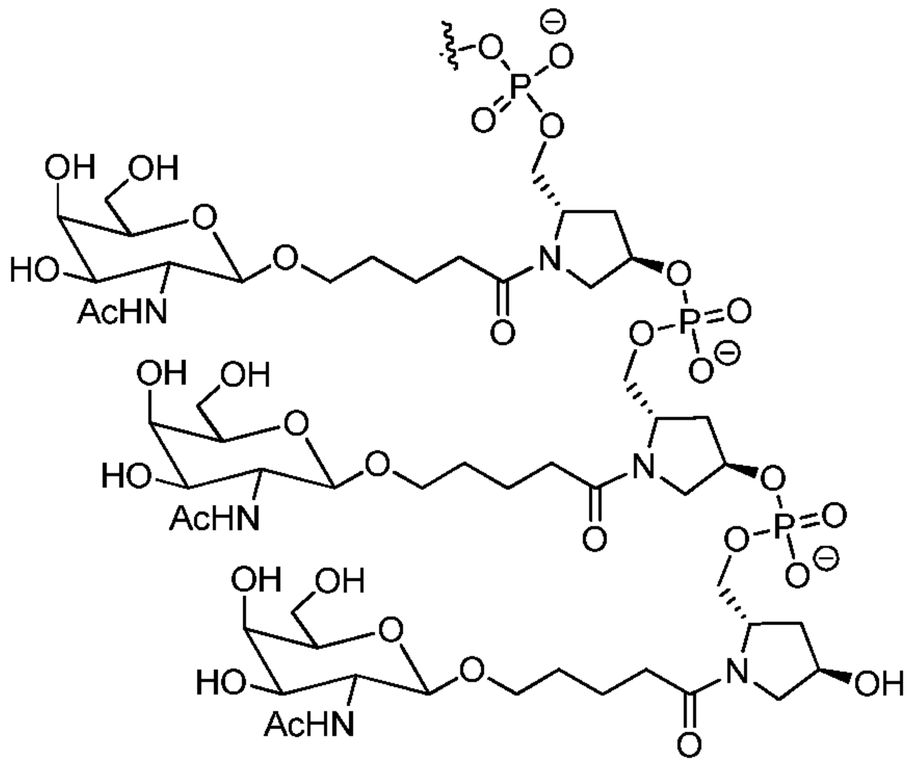


, wherein Y is O or S and n is 3-6 (Formula XXV);

Formula XXVI;

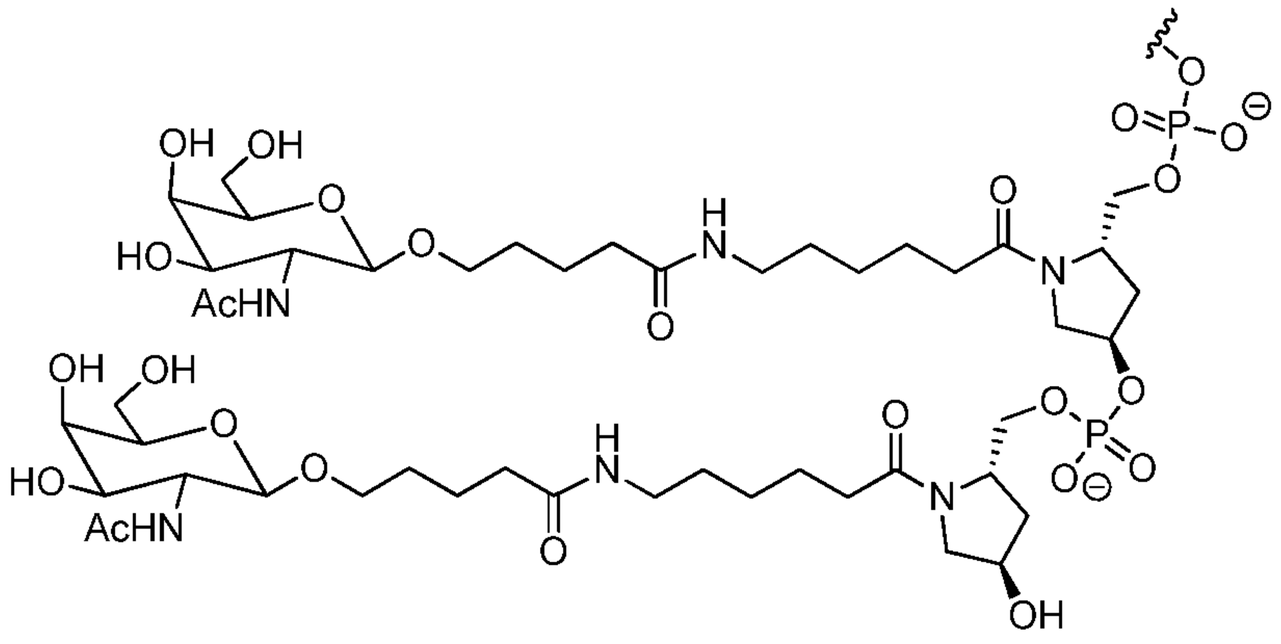
, wherein X is O or S (Formula XXVII);

,

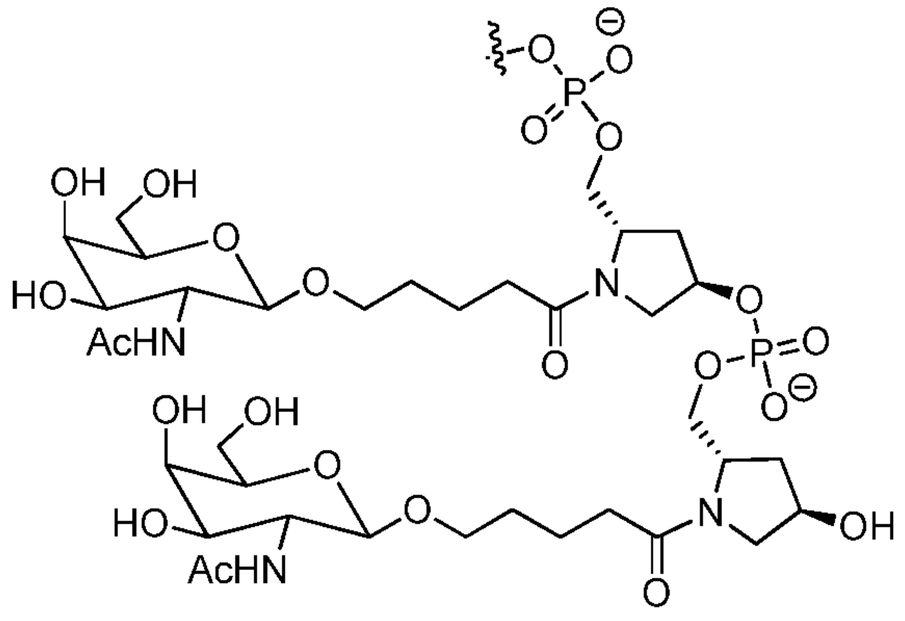


,

Formula XXVII; Formula XXIX;



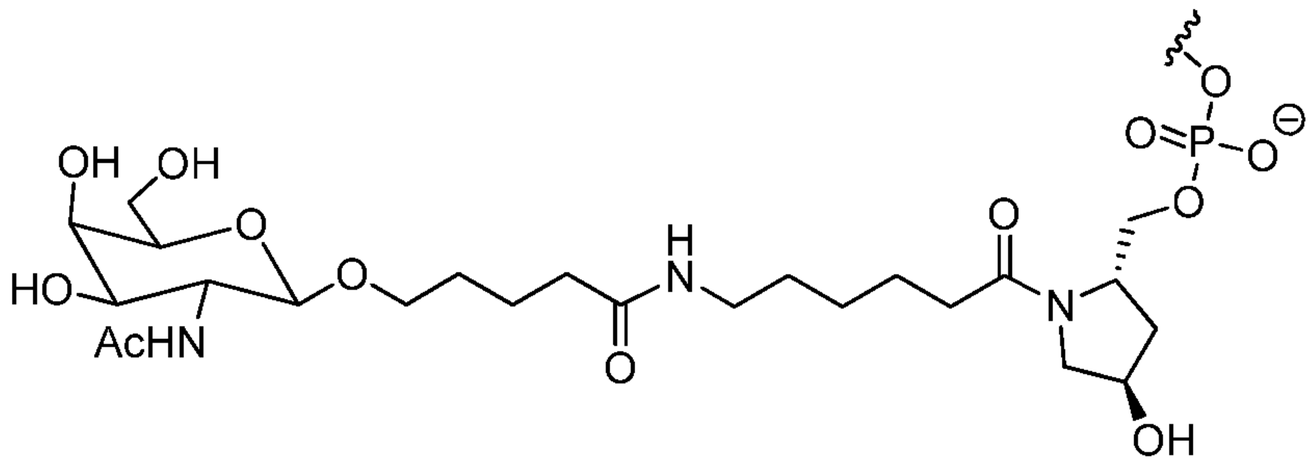
,



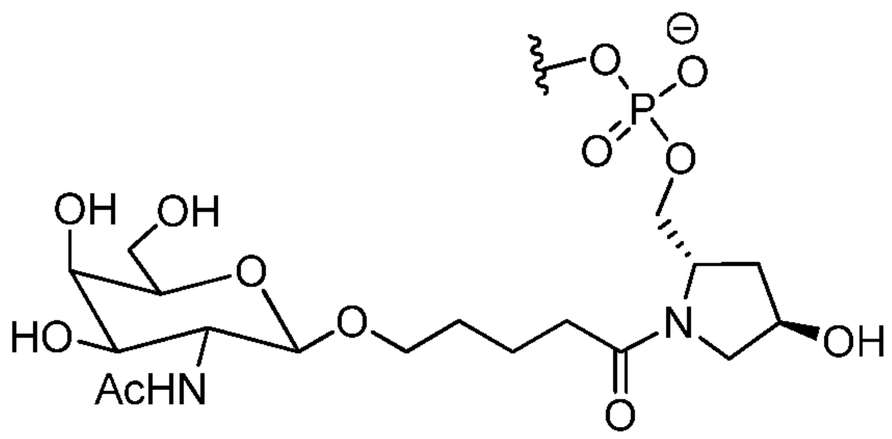
,

Formula XXX;

Formula XXXI;

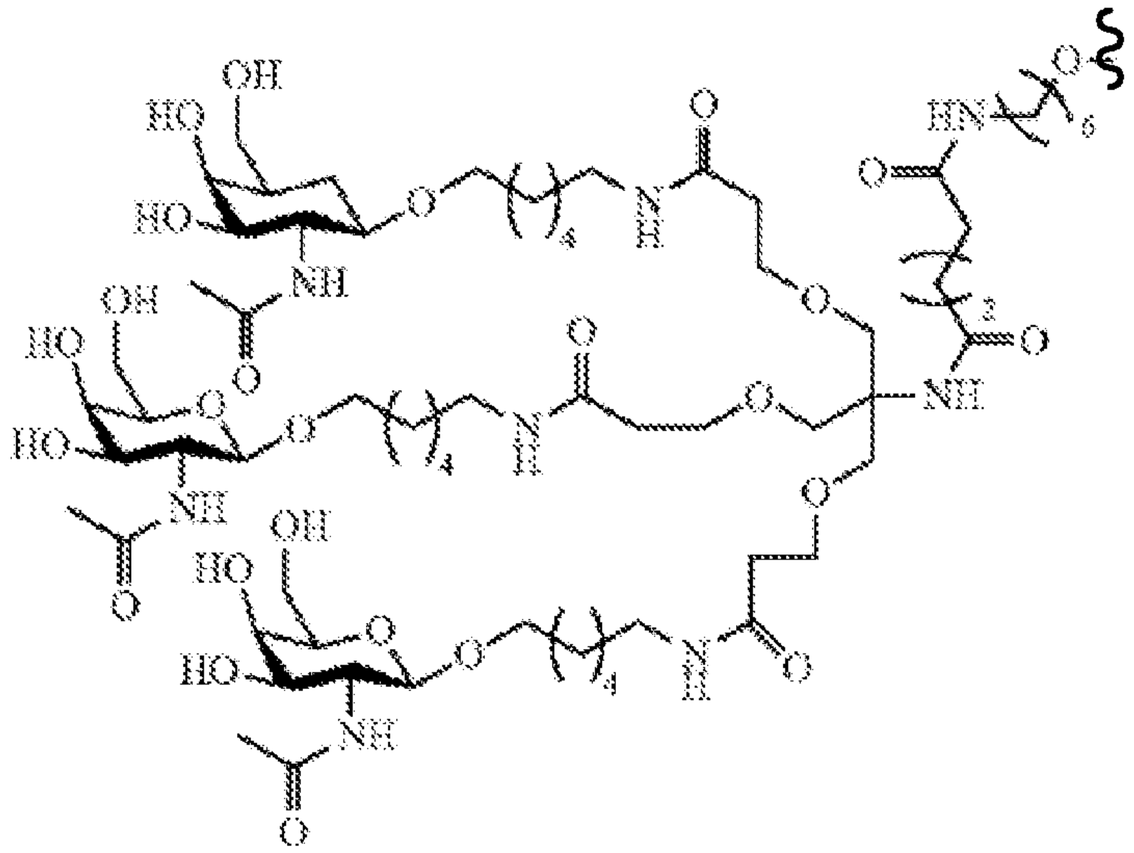


, and



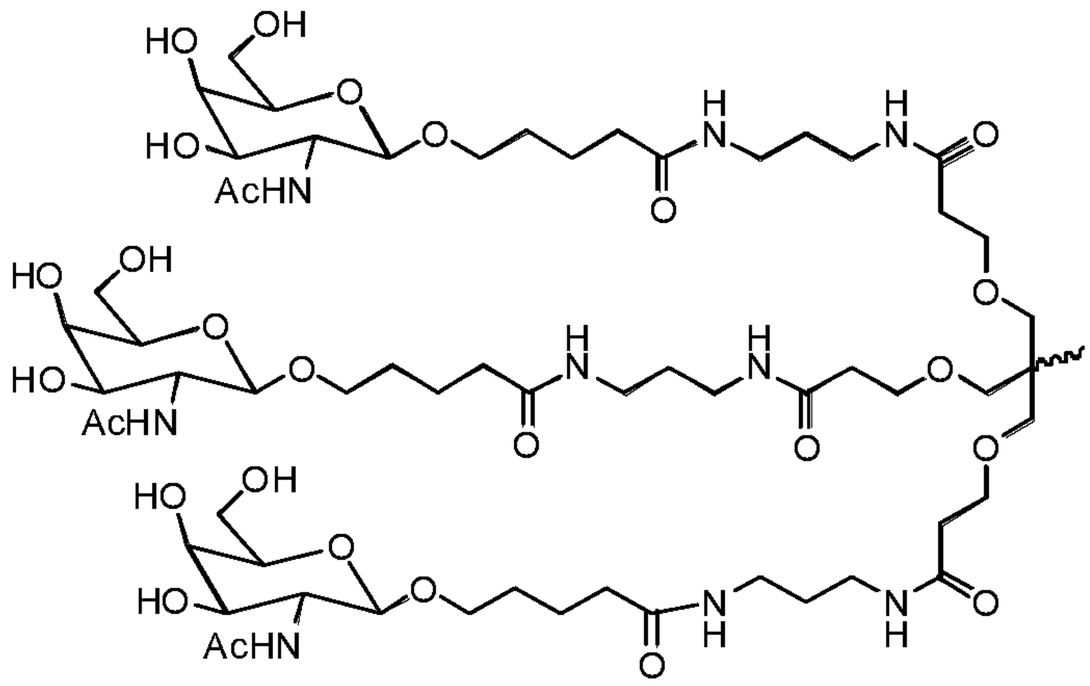
Formula XXXII;

Formula XXXIII.



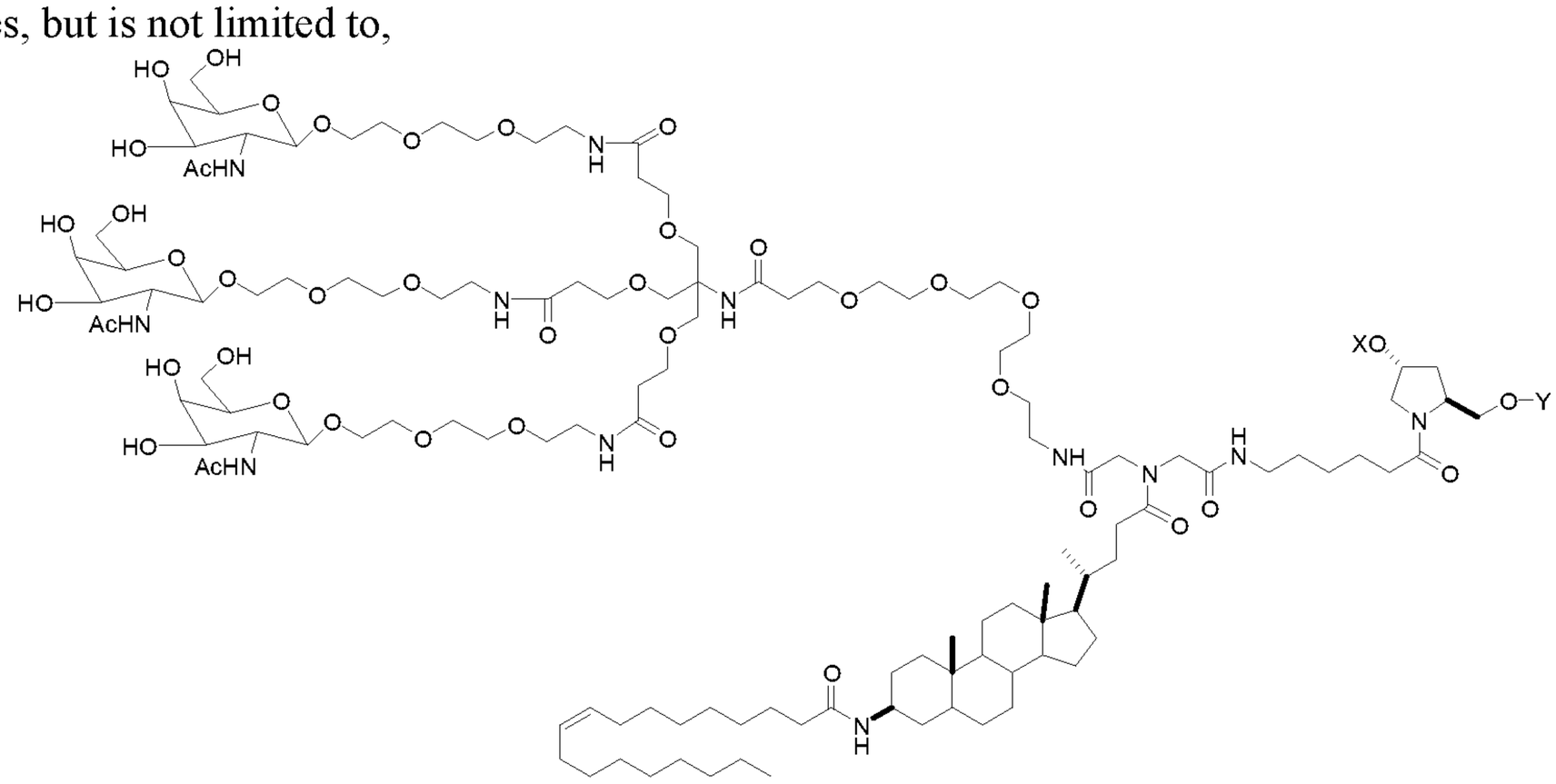
Formula XXXIV.

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.

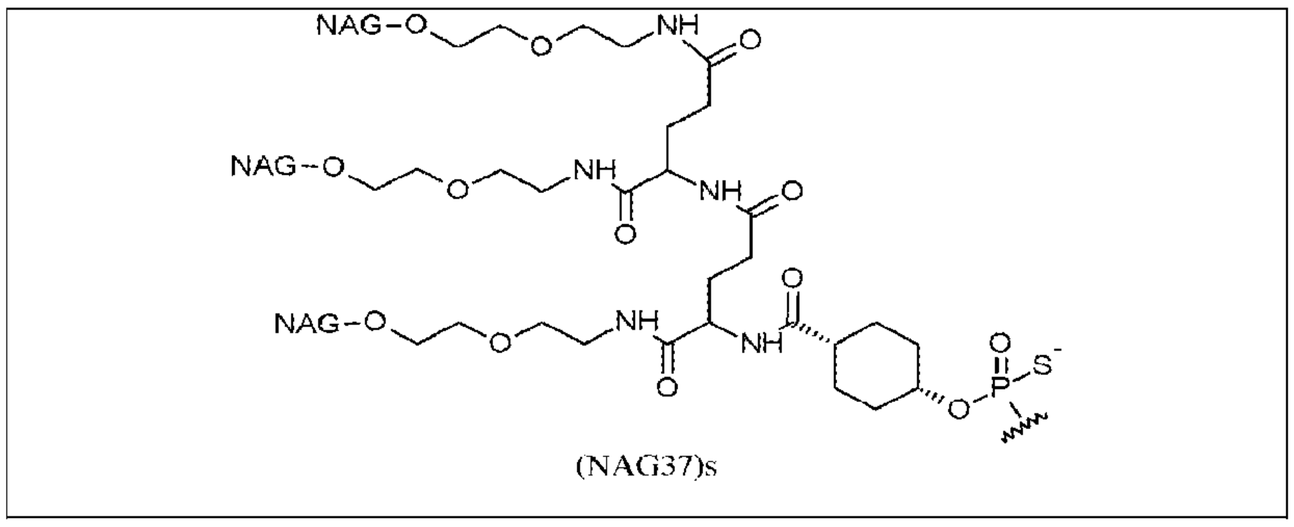
Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



(Formula XXXVI),

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

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:



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.

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 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.

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.

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.

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.

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

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.

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.

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).

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.

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.

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.

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

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

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

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

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.

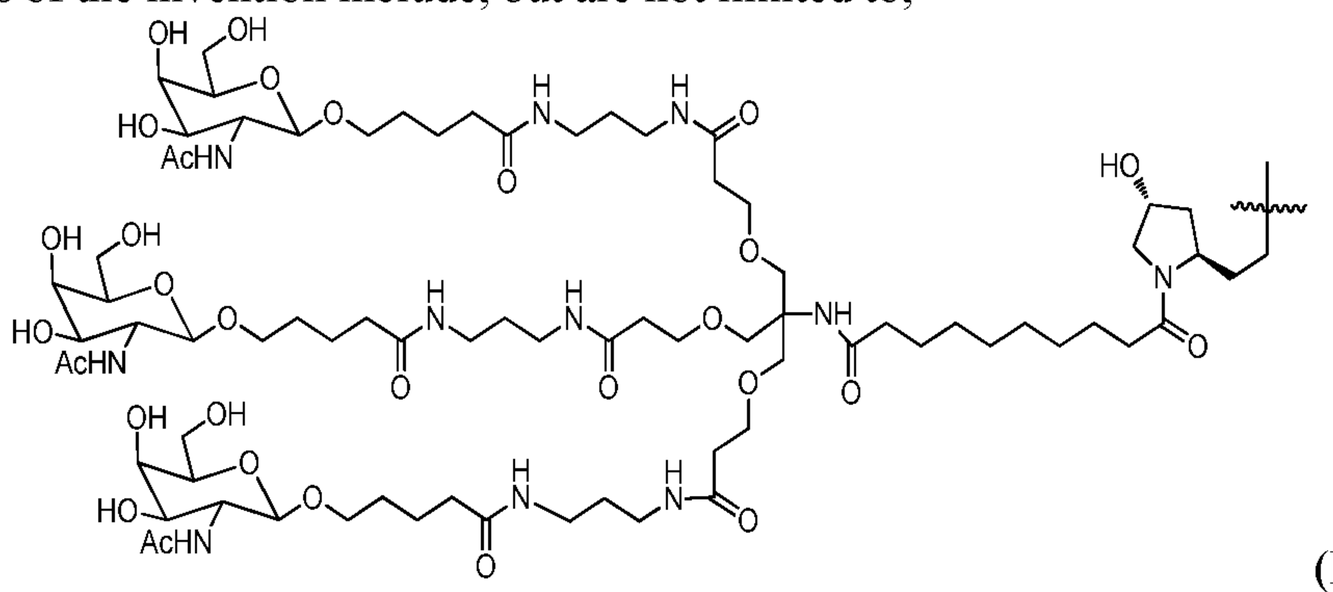
iv. Ester-based cleavable linking groups

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.

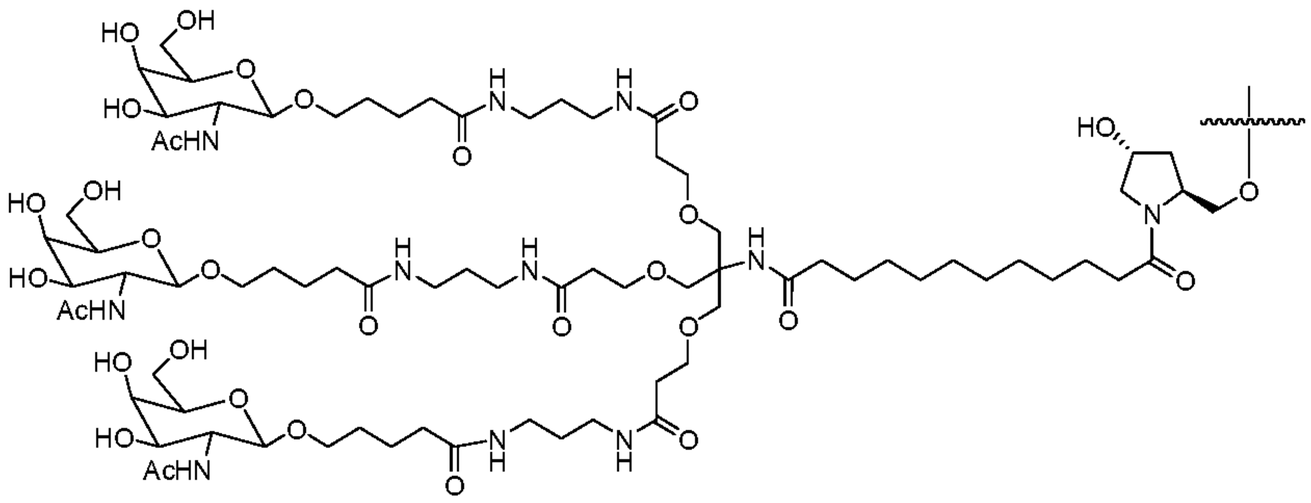
v. Peptide-based cleavable linking groups

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.

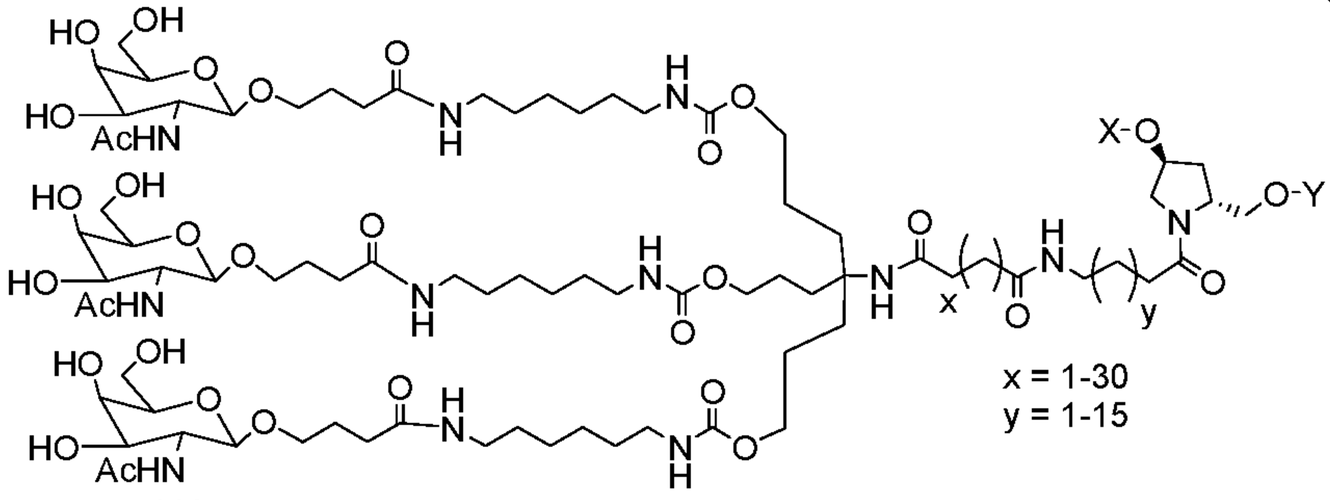
In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



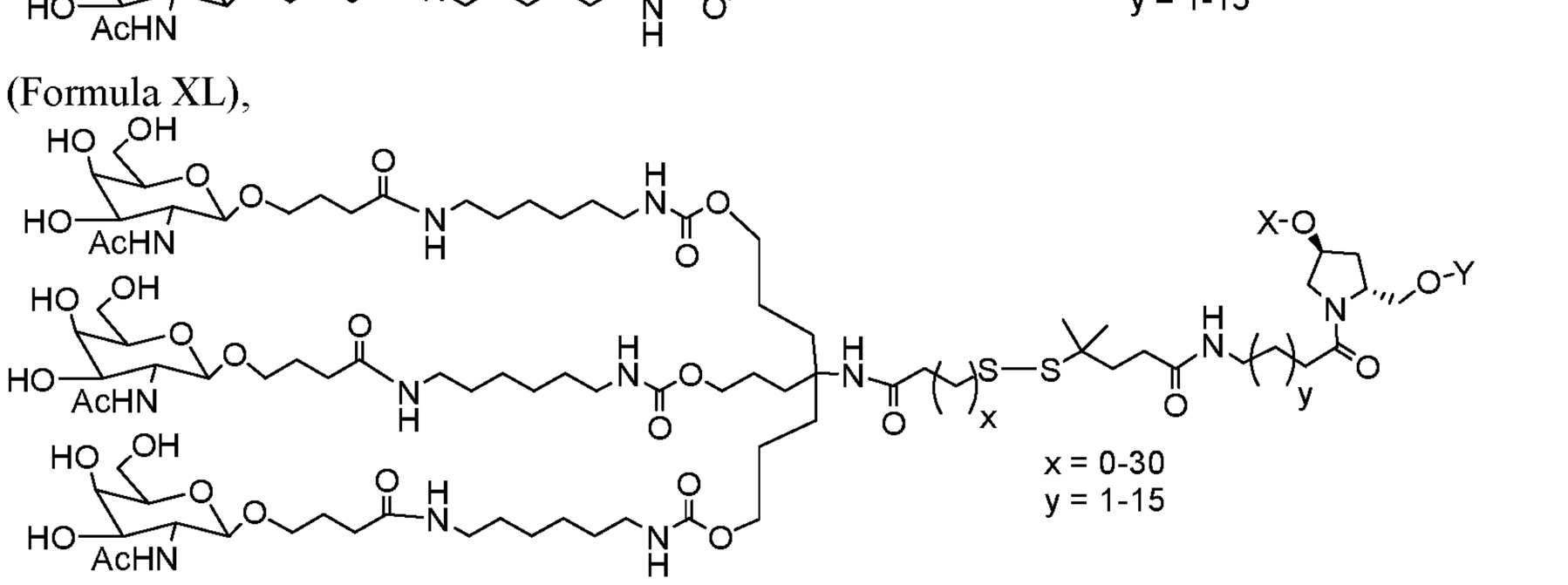
(Formula XXXVII),



(Formula XXXVIII),

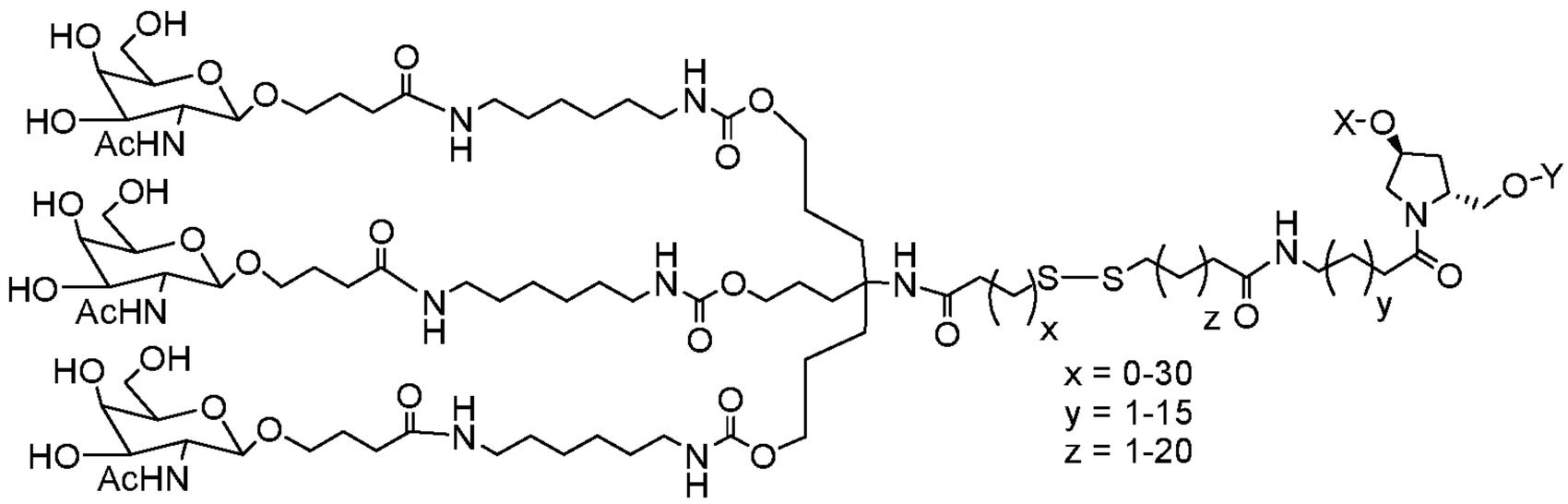


(Formula XXXIX),

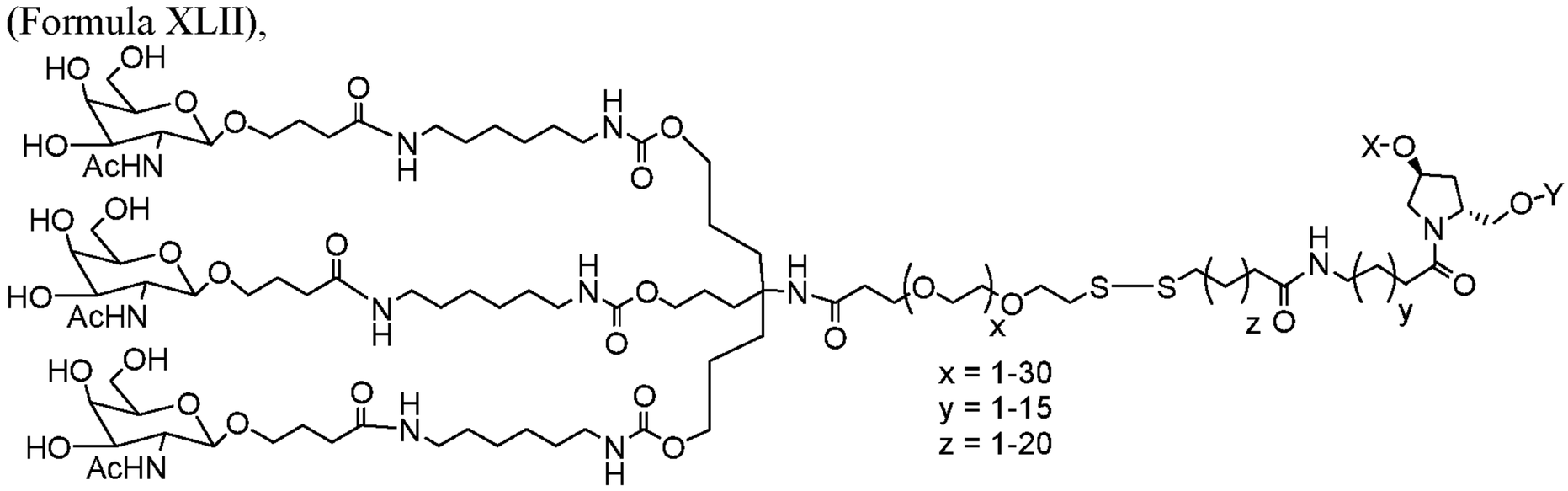


(Formula XL),

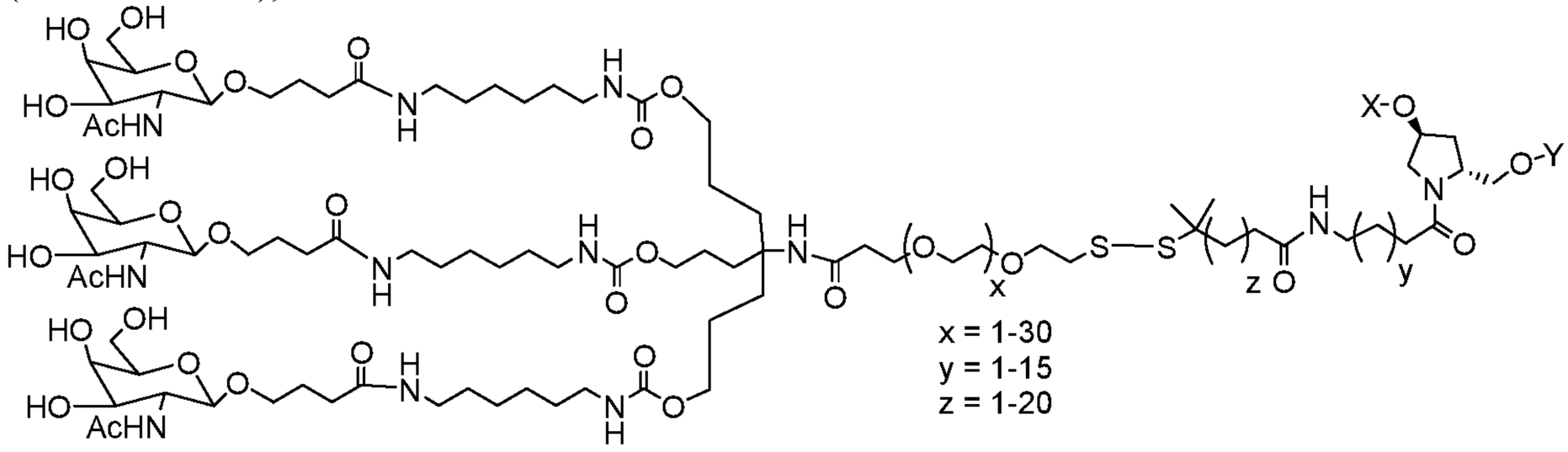
(Formula XLI),



(Formula XLII),



(Formula XLIII), and

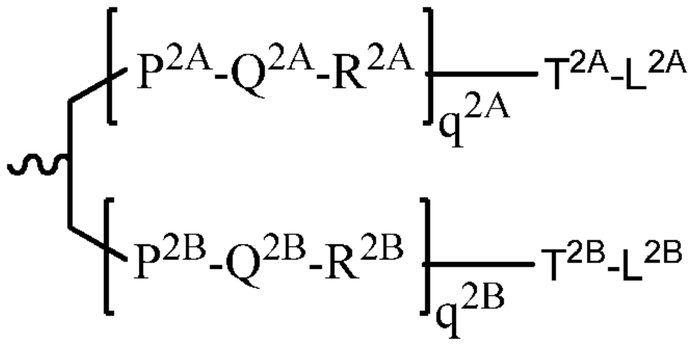


(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

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.

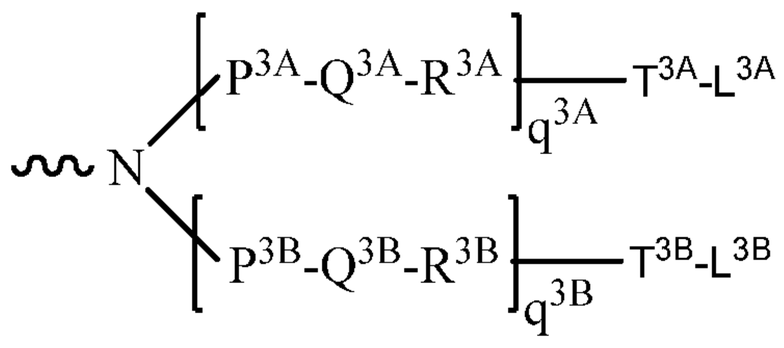
In certain embodiments, a dsRNA of the invention is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XLV) – (XLVI):

Formula XXXXV

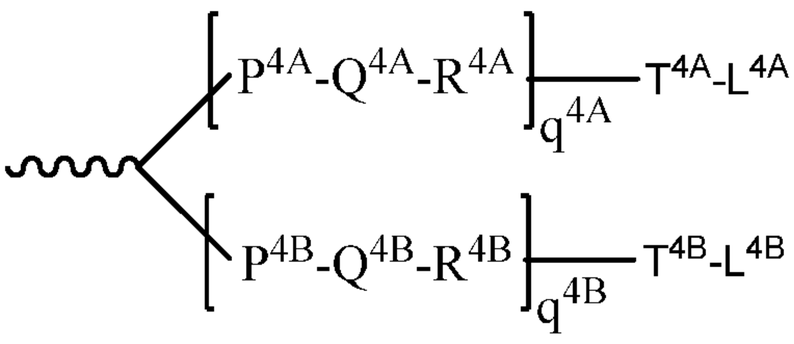


(IV)

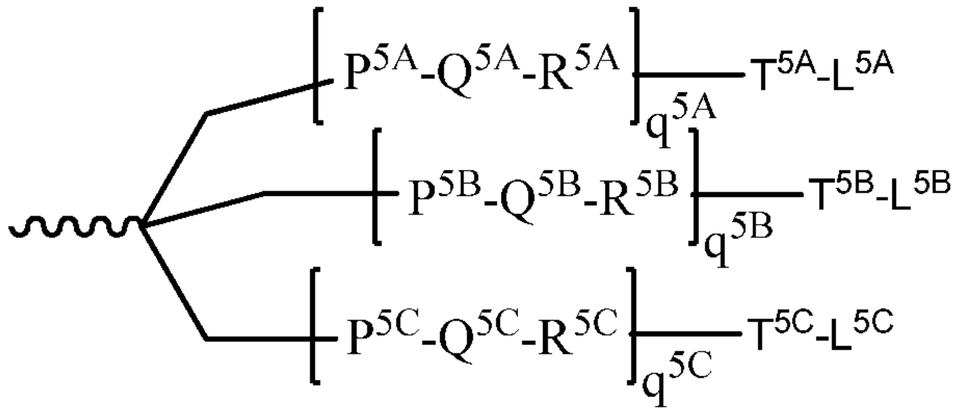
Formula XLVI



V)



Formula XLVII



;

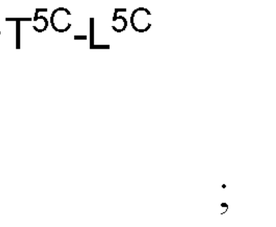
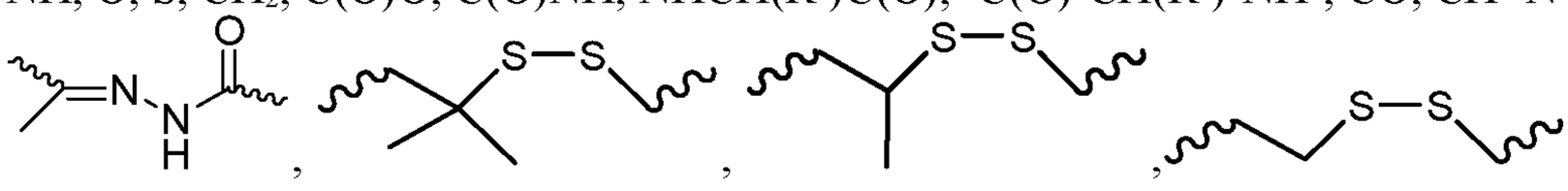
Formula XLVIII

wherein:

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;

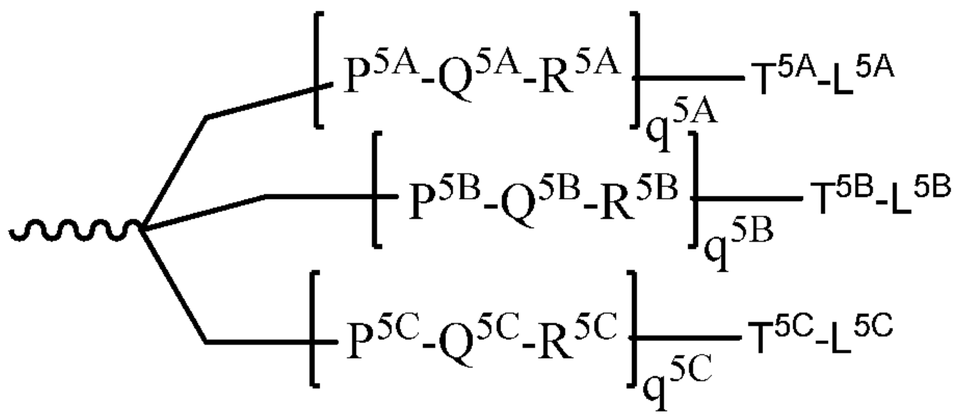
P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

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);

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, , , or heterocyclyl;

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

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

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.

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.

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.

"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.

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

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

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).

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.

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.

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. Pharmaceutical Compositions of the Invention

The present disclosure also includes pharmaceutical compositions and formulations which include the RNAi agents of the disclosure. In one embodiment, provided herein are pharmaceutical compositions containing an RNAi agent, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the RNAi agent are useful for treating a disease or disorder associated with the expression or activity of HTT, *e.g.*, Huntington's disease.

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.

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.

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.

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.

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

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.

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.

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).

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.

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).

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

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.

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.

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.

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.

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).

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).

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.

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.

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).

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).

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*).

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.

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.

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).

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.

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).

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.

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).

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.

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.

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.

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.

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).

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.

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.

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.

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.

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).

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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)

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

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

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.

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

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

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.

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.

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 APP-associated diseases or disorders.

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.

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

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.

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).

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).

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.

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).

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.

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.

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

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).

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.

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.

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.

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

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

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.

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.

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).

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).

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).

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).

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).

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.

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

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*).

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.

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.

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

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.

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.

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.

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.

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.

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

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).

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.

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

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, 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.

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.

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.

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.

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.

"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.

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 C9orf72 expanded protein.

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).

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.

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:

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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).

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.

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

The present disclosure also provides methods of using an RNAi agent of the disclosure or a composition containing 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 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.

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.

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.

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 %.

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. 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.

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.

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.

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.

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. 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).

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.

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.

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.

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

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.

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.

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).

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.

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.

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%.

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.

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.

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.

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

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%.

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.

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).

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

This Example describes methods for the design, synthesis, selection, and *in vitro* evaluation of HTT_RNAi agents.

Source of reagents

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

siRNAs targeting the human huntingtin transcript (HTT; human NCBI refseqID NM_002111.8; NCBI GeneID: 3064) or the mouse HTT transcript (HTT; mouse NCBI refseqID NM_010414.3; NCBI GeneID: 15194) were designed using custom R and Python scripts. The human NM_002111 REFSEQ mRNA, version 8, has a length of 13,498 bases. The mouse NM_010414 REFSEQ mRNA, version 3, has a length of 13,237 bases.

In addition, siRNAs targeting exon 1 of the human huntingtin transcript (HTT; human NCBI refseqID NM_002111.8; NCBI GeneID: 3064) were designed using custom R and Python scripts.

Detailed lists of the unmodified HTT sense and antisense strand nucleotide sequences are shown in Tables 2, 5, 8, 11, 14, 18, 21, 25, 28, 30 and 33. Detailed lists of the modified HTT sense and antisense strand nucleotide sequences are shown in Tables 3, 6, 9, 12, 15, 17, 20, 24, 27, 29 and 32.

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

Cells were transfected by adding 4.9 µL of Opti-MEM plus 0.1 µL of RNAiMAX per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5 µL of siRNA duplexes per well, with 4 replicates of each siRNA duplex, into a 384-well plate, and incubated at room temperature for 15 minutes. Forty µL of MEDIA containing ~5 x10^3 cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Experiments were performed at 50 nM, 10nM, 1nM, and 0.1nM. Transfection experiments were performed in human neuroblastoma BE(2)C cells (ATCC CRL-2268) with EMEM:F12 media (Gibco catalog no. 11765054).

Cell culture and 384-well transfections

Primary cynomolgus hepatocytes (PCH) freshly isolated less than 1 hour prior to transfections were grown in primary hepatocyte media. Hep3B cells were grown in appropriate media.

Transfection was carried out by adding 14.8 µl of Opti-MEM plus 0.2 µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5 µl of each siRNA duplex to an individual well. The mixture was then incubated at room temperature for 15 minutes. Eighty µl of complete growth media without antibiotic containing ~2 x10^4 cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments in Hep3B were performed at 50 nM, 10 nM, 1 nM, and 0.1 nM final duplex concentration. Single dose experiments in PCH were performed at 50 nM, 10 nM, 1 nM, and 0.1 nM final duplex concentration.

Total RNA isolation using DYNABEADS mRNA Isolation Kit

RNA was 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 were added to the plate with cells. Plates were incubated on an electromagnetic shaker for 10 minutes at room temperature and then magnetic beads were captured and the supernatant was removed. Bead-bound RNA was then washed 2 times with 150 µL Wash Buffer A and once with Wash Buffer B. Beads were 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)

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 was added to RNA isolated above. Plates were 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

Two µL of cDNA were 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 was done in a LightCycler480 Real Time PCR system (Roche). Each duplex was tested with N=4 and data were normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with a non-targeting control siRNA.

The results of the screening of the dsRNA agents listed in Tables 2 and 3 in BE(2)C cells are provided in Table 4.

The results of the screening of the dsRNA agents listed in Tables 5 and 6 in BE(2)C cells are provided in Table 7.

The results of the screening of the dsRNA agents listed in Tables 8 and 9 in BE(2)C cells are provided in Table 10.

The results of the screening of the dsRNA agents listed in Tables 11 and 12 in BE(2)C cells are provided in Table 13.

The results of the screening of the dsRNA agents listed in Tables 14 and 15 in BE(2)C cells are provided in Table 16.

The results of the screening of the dsRNA agents listed in Tables 17 and 18 in BE(2)C cells are provided in Table 19.

The results of the screening of the dsRNA agents listed in Tables 20 and 21 in Hep3B cells are provided in Table 22.

The results of the screening of the dsRNA agents listed in Tables 20 and 21 in primary cynomolgus hepatocytes (PCH) cells are provided in Table 23.

The results of the screening of the dsRNA agents listed in Tables 24 and 25 in BE(2)C cells are provided in Table 26.

The results of the screening of the dsRNA agents listed in Tables 27 and 28 in BE(2)C cells are provided in Table 34.

The results of the screening of the dsRNA agents listed in Tables 29 and 30 in BE(2)C cells are provided in Table 31.

Table 1. Abbre*via*tions 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.

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

Abbre*via*tion	**Nucleotide(s)**
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
L10	N-(cholesterylcarboxamidocaproyl)-4-hydroxyprolinol (Hyp-C6-Chol)
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol Hyp-(GalNAc-alkyl)3
Y34	2-hydroxymethyl-tetrahydrofurane-4-methoxy-3-phosphate (abasic 2'-OMe furanose)
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofurane-5-phosphate)
(Agn)	Adenosine-glycol nucleic acid (GNA)
	Cytidine-glycol nucleic acid (GNA)
(Ggn)	Guanosine-glycol nucleic acid (GNA)
(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 Huntingtin (HTT) dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range
AD-384118.1	GGACUAAAACUUUUUAUCAAA	15	NM_010414.3_12016-12036_s	12016-12036	UUUGAUAAAAAGUUUUAGUCCCU	216	NM_010414.3_12014-12036_as	12014-12036
AD-380543.1	CUCUGUUACCAGCUACUACAU	16	NM_010414.3_7846-7866_G21U_s	7846-7866	AUGUAGTAGCUGGUAACAGAGAA	217	NM_010414.3_7844-7866_C1A_as	7844-7866
AD-380533.1	CCUGUCCCUUCUCUGUUACCA	17	NM_010414.3_7836-7856_s	7836-7856	UGGUAACAGAGAAGGGACAGGAU	218	NM_010414.3_7834-7856_as	7834-7856
AD-384038.1	UUUGUGAGUCUAGCAUCUGAU	18	NM_010414.3_11916-11936_G21U_s	11916-11936	AUCAGATGCUAGACUCACAAAGC	219	NM_010414.3_11914-11936_C1A_as	11914-11936
AD-380805.1	GAUCAGUGAAGUGGUUCGAUU	19	NM_010414.3_8189-8209_C21U_s	8189-8209	AAUCGAACCACUUCACUGAUCAG	220	NM_010414.3_8187-8209_G1A_as	8187-8209
AD-380117.1	CCUCUGGUAUGGAAACUCGGU	20	NM_010414.3_7338-7358_G21U_s	7338-7358	ACCGAGTUUCCAUACCAGAGGAG	221	NM_010414.3_7336-7358_C1A_as	7336-7358
AD-381341.1	AGAGUCCUUGGUCAAGCUAAU	21	NM_010414.3_8789-8809_G21U_s	8789-8809	AUUAGCTUGACCAAGGACUCUGU	222	NM_010414.3_8787-8809_C1A_as	8787-8809
AD-379426.1	UUCAACCUAAGCCUUUUGGCU	22	NM_010414.3_6525-6545_s	6525-6545	AGCCAAAAGGCUUAGGUUGAACU	223	NM_010414.3_6523-6545_as	6523-6545
AD-380888.1	UGACAGAACUACGGAGAGUGU	23	NM_010414.3_8272-8292_C21U_s	8272-8292	ACACUCTCCGUAGUUCUGUCAGC	224	NM_010414.3_8270-8292_G1A_as	8270-8292
AD-384841.1	CUCCAUGUGUGCUUGUCACAU	24	NM_010414.3_12871-12891_C21U_s	12871-12891	AUGUGACAAGCACACAUGGAGGG	225	NM_010414.3_12869-12891_G1A_as	12869-12891
AD-380853.1	CGAACGUACCCAGUUUGAAAU	25	NM_010414.3_8237-8257_s	8237-8257	AUUUCAAACUGGGUACGUUCGGU	226	NM_010414.3_8235-8257_as	8235-8257
AD-379602.1	AUACCACAUCAUACCAGUCUU	26	NM_010414.3_6739-6759_C21U_s	6739-6759	AAGACUGGUAUGAUGUGGUAUCA	227	NM_010414.3_6737-6759_G1A_as	6737-6759
AD-38248	CUGCAUGUGACAAAGUUUAUU	27	NM_010414.3_10129-10149_G21U_s	10129-10149	AAUAAACUUUGUCACAUGCAGCA	228	NM_010414.3_10127-10149_C1A_as	10127-10149

4.1								
AD-38074 1.1	UUCACUCCUGUUC GCAGUUUC	28	NM_010414.3_810 4-8124_s	8104-8124	GAAACUGCGAACA GGAGUGAAUA	229	NM_010414.3_8102-8124_as	8102-8124
AD-38053 4.1	CUGUCCCUUCUCU GUUACCAU	29	NM_010414.3_783 7-7857_G21U_s	7837-7857	AUGGUAACAGAGA AGGGACAGGA	230	NM_010414.3_7835-7857_C1A_as	7835-7857
AD-38405 3.1	UCUGAGAAUGGGA CUCAAUUU	30	NM_010414.3_119 31-11951_s	11931-11951	AAAUUGAGUCCCA UUCUCAGAUG	231	NM_010414.3_11929-11951_as	11929-11951
AD-38091 6.1	UCAGAAGAUGAGA UCCUCAUU	31	NM_010414.3_829 8-8318_s	8298-8318	AAUGAGGAUCUCA UCUUCUGAAG	232	NM_010414.3_8296-8318_as	8296-8318
AD-38040 2.1	CCACUGAAGGCUC UCGAUACU	32	NM_010414.3_770 4-7724_C21U_s	7704-7724	AGUAUCGAGAGCC UUCAGUGGCU	233	NM_010414.3_7702-7724_G1A_as	7702-7724
AD-38146 4.1	GAGUCUGUGAUUG UAGCUAUU	33	NM_010414.3_894 6-8966_G21U_s	8946-8966	AAUAGCTACAAUCA CAGACUCGC	234	NM_010414.3_8944-8966_C1A_as	8944-8966
AD-37972 9.1	UCAUGGCAUUUGA UCCAUGAU	34	NM_010414.3_688 8-6908_G21U_s	6888-6908	AUCAUGGAUCAAA UGCCAUGACA	235	NM_010414.3_6886-6908_C1A_as	6886-6908
AD-38106 5.1	ACGGCAUCCUCUA UGUGUUGU	35	NM_010414.3_845 2-8472_G21U_s	8452-8472	ACAACACAUAGAG GAUGCCGUGC	236	NM_010414.3_8450-8472_C1A_as	8450-8472
AD-37946 6.1	UGAGCGAGAUUGC UAAUGGCU	36	NM_010414.3_656 5-6585_C21U_s	6565-6585	AGCCAUTAGCAAUC UCGCUCAUG	237	NM_010414.3_6563-6585_G1A_as	6563-6585
AD-38088 5.1	CGCUGACAGAACU ACGGAGAU	37	NM_010414.3_826 9-8289_G21U_s	8269-8289	AUCUCCGUAGUUCU GUCAGCGUC	238	NM_010414.3_8267-8289_C1A_as	8267-8289
AD-37989 7.1	AAGCAGGUCACAU ACUCCAAU	38	NM_010414.3_709 7-7117_G21U_s	7097-7117	AUUGGAGUAUGUG ACCUGCUUUC	239	NM_010414.3_7095-7117_C1A_as	7095-7117
AD-38112 4.1	CCAGUUGUUAGUG ACUAUCUU	39	NM_010414.3_851 1-8531_G21U_s	8511-8531	AAGAUAGUCACUA ACAACUGGAA	240	NM_010414.3_8509-8531_C1A_as	8509-8531
AD-38080 7.1	UCAGUGAAGUGGU UCGAUCUU	40	NM_010414.3_819 1-8211_C21U_s	8191-8211	AAGAUCGAACCACU UCACUGAUC	241	NM_010414.3_8189-8211_G1A_as	8189-8211
AD-38080 6.1	AUCAGUGAAGUGG UUCGAUCU	41	NM_010414.3_819 0-8210_s	8190-8210	AGAUCGAACCACUU CACUGAUCA	242	NM_010414.3_8188-8210_as	8188-8210

AD-38484 3.1	CCAUGUGUGCUUG UCACACUU	42	NM_010414.3_128 73-12893_C21U_s	12873-12893	AAGUGUGACAAGC ACACAUGGAG	243	NM_010414.3_12871-12893_G1A_as	12871-12893
AD-38125 7.1	UUUCAGCAUCUGU GAUACAGA	43	NM_010414.3_865 3-8673_s	8653-8673	UCUGUATCACAGAU GCUGAAAAU	244	NM_010414.3_8651-8673_as	8651-8673
AD-38040 8.1	AAGGCUCUCGAUA CCAGAUUU	44	NM_010414.3_771 0-7730_s	7710-7730	AAAUCUGGUAUCG AGAGCCUUCA	245	NM_010414.3_7708-7730_as	7708-7730
AD-38157 0.1	UAGAUGACUUCUU UCCACCUU	45	NM_010414.3_905 2-9072_C21U_s	9052-9072	AAGGUGGAAAGAA GUCAUCUAGG	246	NM_010414.3_9050-9072_G1A_as	9050-9072
AD-38009 3.1	GUUAACAGCUAUA CUCGUGUU	46	NM_010414.3_731 4-7334_G21U_s	7314-7334	AACACGAGUAUAG CUGUUAACUA	247	NM_010414.3_7312-7334_C1A_as	7312-7334
AD-38114 8.1	UCCAACCUCAAAG GAAUAGCU	47	NM_010414.3_853 5-8555_C21U_s	8535-8555	AGCUAUTCCUUUGA GGUUGGACA	248	NM_010414.3_8533-8555_G1A_as	8533-8555
AD-37947 5.1	UUGCUAAUGGCCA AAAGAGUU	48	NM_010414.3_657 4-6594_C21U_s	6574-6594	AACUCUTUUGGCCA UUAGCAAUC	249	NM_010414.3_6572-6594_G1A_as	6572-6594
AD-38114 2.1	CUGCUGUCCAACC UCAAAGGA	49	NM_010414.3_852 9-8549_s	8529-8549	UCCUUUGAGGUUG GACAGCAGAU	250	NM_010414.3_8527-8549_as	8527-8549
AD-38085 2.1	CCGAACGUACCCA GUUUGAAA	50	NM_010414.3_823 6-8256_s	8236-8256	UUUCAAACUGGGU ACGUUCGGUG	251	NM_010414.3_8234-8256_as	8234-8256
AD-37993 5.1	AAGUAGACUCAGA UAUACAAA	51	NM_010414.3_713 5-7155_s	7135-7155	UUUGUATAUCUGA GUCUACUUCC	252	NM_010414.3_7133-7155_as	7133-7155
AD-38111 7.1	GCUCAUUCCAGUU GUUAGUGA	52	NM_010414.3_850 4-8524_s	8504-8524	UCACUAACAACUGG AAUGAGCUG	253	NM_010414.3_8502-8524_as	8502-8524
AD-38080 8.1	CAGUGAAGUGGUU CGAUCUCU	53	NM_010414.3_819 2-8212_s	8192-8212	AGAGAUCGAACCAC UUCACUGAU	254	NM_010414.3_8190-8212_as	8190-8212
AD-37947 1.1	GAGAUUGCUAAUG GCCAAAAU	54	NM_010414.3_657 0-6590_G21U_s	6570-6590	AUUUUGGCCAUUA GCAAUCUCGC	255	NM_010414.3_6568-6590_C1A_as	6568-6590
AD-38134 2.1	GAGUCCUUGGUCA AGCUAAGU	55	NM_010414.3_879 0-8810_s	8790-8810	ACUUAGCUUGACCA AGGACUCUG	256	NM_010414.3_8788-8810_as	8788-8810
AD-	GCUCUCGAUACCA	56	NM_010414.3_771	7713-7733	UCCAAATCUGGUAU	257	NM_010414.3_7711-	7711-7733

380411.1	GAUUUGGA		3-7733_s		CGAGAGCCU		7733_as	
AD-382487.1	CAUGUGACAAAGUUUAUGGAA	57	NM_010414.3_10132-10152_s	10132-10152	UUCCAUAAACUUUGUCACAUGCA	258	NM_010414.3_10130-10152_as	10130-10152
AD-380116.1	UCCUCUGGUAUGGAAACUCGU	58	NM_010414.3_7337-7357_G21U_s	7337-7357	ACGAGUTUCCAUACCAGAGGAGG	259	NM_010414.3_7335-7357_C1A_as	7335-7357
AD-381150.1	CAACCUCAAAGGAAUAGCCCA	59	NM_010414.3_8537-8557_s	8537-8557	UGGGCUAUUCCUUUGAGGUUGGA	260	NM_010414.3_8535-8557_as	8535-8557
AD-379476.1	UGCUAAUGGCCAAAAGAGUCU	60	NM_010414.3_6575-6595_C21U_s	6575-6595	AGACUCTUUUGGCCAUUAGCAAU	261	NM_010414.3_6573-6595_G1A_as	6573-6595
AD-382444.1	CCUAUGCCCGUGUAAAGUGUU	61	NM_010414.3_10089-10109_G21U_s	10089-10109	AACACUTUACACGGGCAUAGGAA	262	NM_010414.3_10087-10109_C1A_as	10087-10109
AD-380883.1	GACGCUGACAGAACUACGGAU	62	NM_010414.3_8267-8287_G21U_s	8267-8287	AUCCGUAGUUCUGUCAGCGUCAG	263	NM_010414.3_8265-8287_C1A_as	8265-8287
AD-379941.1	ACUCAGAUAUACAAAACCUCA	63	NM_010414.3_7141-7161_s	7141-7161	UGAGGUTUUGUAUAUCUGAGUCU	264	NM_010414.3_7139-7161_as	7139-7161
AD-381578.1	UUCUUUCCACCUCAAGAUGUU	64	NM_010414.3_9060-9080_C21U_s	9060-9080	AACAUCTUGAGGUGGAAAGAAGU	265	NM_010414.3_9058-9080_G1A_as	9058-9080
AD-381460.1	CAGCGAGUCUGUGAUUGUAGU	65	NM_010414.3_8942-8962_C21U_s	8942-8962	ACUACAAUCACAGACUCGCUGUC	266	NM_010414.3_8940-8962_G1A_as	8940-8962
AD-379939.1	AGACUCAGAUAUACAAAACCU	66	NM_010414.3_7139-7159_s	7139-7159	AGGUUUTGUAUAUCUGAGUCUAC	267	NM_010414.3_7137-7159_as	7137-7159
AD-384039.1	UUGUGAGUCUAGCAUCUGAGA	67	NM_010414.3_11917-11937_s	11917-11937	UCUCAGAUGCUAGACUCACAAAG	268	NM_010414.3_11915-11937_as	11915-11937
AD-380735.1	UUGAUAUUCACUCCUGUUCGU	68	NM_010414.3_8098-8118_C21U_s	8098-8118	ACGAACAGGAGUGAAUAUCAACC	269	NM_010414.3_8096-8118_G1A_as	8096-8118
AD-382525.1	UAGCUACUCAGUCUAGUCGGU	69	NM_010414.3_10188-10208_G21U_s	10188-10208	ACCGACTAGACUGAGUAGCUACA	270	NM_010414.3_10186-10208_C1A_as	10186-10208
AD-38071	CCUGUGUCUCCAGUCAAUUCU	70	NM_010414.3_8058-8078_C21U_s	8058-8078	AGAAUUGACUGGAGACACAGGUG	271	NM_010414.3_8056-8078_G1A_as	8056-8078

3.1								
AD-38214 9.1	AGGGAACAUGCAC UAUGUUGU	71	NM_010414.3_969 6-9716_G21U_s	9696-9716	ACAACATAGUGCAU GUUCCCUGC	272	NM_010414.3_9694-9716_C1A_as	9694-9716
AD-37985 5.1	AGCCAUUGCAGUA CAACCUGU	72	NM_010414.3_705 5-7075_G21U_s	7055-7075	ACAGGUTGUACUGC AAUGGCUUC	273	NM_010414.3_7053-7075_C1A_as	7053-7075
AD-38350 8.1	UGCAAGGUUCCCU ACCAAACA	73	NM_010414.3_112 51-11271_s	11251-11271	UGUUUGGUAGGGA ACCUUGCAUC	274	NM_010414.3_11249-11271_as	11249-11271
AD-38127 3.1	ACAGAUGUGUGGA GUAAUGCU	74	NM_010414.3_866 9-8689_s	8669-8689	AGCAUUACUCCACA CAUCUGUAU	275	NM_010414.3_8667-8689_as	8667-8689
AD-38248 3.1	GCUGCAUGUGACA AAGUUUAU	75	NM_010414.3_101 28-10148_s	10128-10148	AUAAACTUUGUCAC AUGCAGCAC	276	NM_010414.3_10126-10148_as	10126-10148
AD-38248 1.1	GUGCUGCAUGUGA CAAAGUUU	76	NM_010414.3_101 26-10146_s	10126-10146	AAACUUTGUCACAU GCAGCACAG	277	NM_010414.3_10124-10146_as	10124-10146
AD-38248 5.1	UGCAUGUGACAAA GUUUAUGU	77	NM_010414.3_101 30-10150_G21U_s	10130-10150	ACAUAAACUUUGU CACAUGCAGC	278	NM_010414.3_10128-10150_C1A_as	10128-10150
AD-38009 2.1	AGUUAACAGCUAU ACUCGUGU	78	NM_010414.3_731 3-7333_s	7313-7333	ACACGAGUAUAGC UGUUAACUAG	279	NM_010414.3_7311-7333_as	7311-7333
AD-37942 0.1	GCUCGGAGUUCAA CCUAAGCU	79	NM_010414.3_651 7-6537_C21U_s	6517-6537	AGCUUAGGUUGAA CUCCGAGCUC	280	NM_010414.3_6515-6537_G1A_as	6515-6537
AD-38080 0.1	AUCCUGAUCAGUG AAGUGGUU	80	NM_010414.3_818 4-8204_s	8184-8204	AACCACTUCACUGA UCAGGAUGA	281	NM_010414.3_8182-8204_as	8182-8204
AD-38403 0.1	CAGUCAGCUUUGU GAGUCUAU	81	NM_010414.3_119 08-11928_G21U_s	11908-11928	AUAGACTCACAAAG CUGACUGUA	282	NM_010414.3_11906-11928_C1A_as	11906-11928
AD-38073 7.1	GAUAUUCACUCCU GUUCGCAU	82	NM_010414.3_810 0-8120_G21U_s	8100-8120	AUGCGAACAGGAG UGAAUAUCAA	283	NM_010414.3_8098-8120_C1A_as	8098-8120
AD-38278 0.1	UUGAUGCACUCUC CUAGUCUU	83	NM_010414.3_104 63-10483_C21U_s	10463-10483	AAGACUAGGAGAG UGCAUCAACA	284	NM_010414.3_10461-10483_G1A_as	10461-10483
AD-37994 4.1	CAGAUAUACAAAA CCUCAGUU	84	NM_010414.3_714 4-7164_C21U_s	7144-7164	AACUGAGGUUUUG UAUAUCUGAG	285	NM_010414.3_7142-7164_G1A_as	7142-7164

AD-37946 1.1	UGGCAUGAGCGAG AUUGCUAA	85	NM_010414.3_656 0-6580_s	6560-6580	UUAGCAAUCUCGCU CAUGCCAAG	286	NM_010414.3_6558-6580_as	6558-6580
AD-38185 6.1	ACAGGUGGAUGUG AACCUUUU	86	NM_010414.3_935 3-9373_s	9353-9373	AAAAGGTUCACAUC CACCUGUUC	287	NM_010414.3_9351-9373_as	9351-9373
AD-37941 8.1	GAGCUCGGAGUUC AACCUAAU	87	NM_010414.3_651 5-6535_G21U_s	6515-6535	AUUAGGTUGAACUC CGAGCUCAU	288	NM_010414.3_6513-6535_C1A_as	6513-6535
AD-38292 4.1	UGUCCCUUUGUAU CUUCUGCA	88	NM_010414.3_106 07-10627_s	10607-10627	UGCAGAAGAUACA AAGGGACAGA	289	NM_010414.3_10605-10627_as	10605-10627
AD-38375 9.1	ACUCCUCAUGGUA GAUGUUCA	89	NM_010414.3_115 78-11598_s	11578-11598	UGAACATCUACCAU GAGGAGUAA	290	NM_010414.3_11576-11598_as	11576-11598
AD-38040 9.1	AGGCUCUCGAUAC CAGAUUUG	90	NM_010414.3_771 1-7731_s	7711-7731	CAAAUCTGGUAUCG AGAGCCUUC	291	NM_010414.3_7709-7731_as	7709-7731
AD-37938 0.1	CUCGGAGUUCAAC CUAAGCCU	91	NM_002111.8_656 2-6582_s	6562-6582	AGGCUUAGGUUGA ACUCCGAGCU	292	NM_010414.3_6516-6538_as	6562-6582
AD-38114 5.1	CUGUCCAACCUCA AAGGAAUA	92	NM_010414.3_853 2-8552_s	8532-8552	UAUUCCTUUGAGGU UGGACAGCA	293	NM_010414.3_8530-8552_as	8530-8552
AD-38405 4.1	CUGAGAAUGGGAC UCAAUUUU	93	NM_010414.3_119 32-11952_s	11932-11952	AAAAUUGAGUCCC AUUCUCAGAU	294	NM_010414.3_11930-11952_as	11930-11952
AD-38079 6.1	CGUCAUCCUGAUC AGUGAAGU	94	NM_010414.3_818 0-8200_s	8180-8200	ACUUCACUGAUCAG GAUGACGGG	295	NM_010414.3_8178-8200_as	8178-8200
AD-38296 0.1	CAAAGGUGUCUCU GAGCUAUU	95	NM_010414.3_106 63-10683_G21U_s	10663-10683	AAUAGCTCAGAGAC ACCUUUGGG	296	NM_010414.3_10661-10683_C1A_as	10661-10683
AD-38055 5.1	CUACUACAGGUGC UCUUAUCA	96	NM_010414.3_785 8-7878_s	7858-7878	UGAUAAGAGCACC UGUAGUAGCU	297	NM_010414.3_7856-7878_as	7856-7878
AD-37946 2.1	GGCAUGAGCGAGA UUGCUAAU	97	NM_010414.3_656 1-6581_s	6561-6581	AUUAGCAAUCUCGC UCAUGCCAA	298	NM_010414.3_6559-6581_as	6559-6581
AD-38211 8.1	UGGCAGGAGUGCU UUGCAAUU	98	NM_010414.3_966 5-9685_G21U_s	9665-9685	AAUUGCAAAGCAC UCCUGCCAUU	299	NM_010414.3_9663-9685_C1A_as	9663-9685
AD-	CUCGAUACCAGAU	99	NM_010414.3_771	7716-7736	UCUUCCAAAUCUGG	300	NM_010414.3_7714-	7714-7736

380414.1	UUGGAAGA		6-7736_s		UAUCGAGAG		7736_as	
AD-380091.1	UAGUUAACAGCUAUACUCGUU	100	NM_010414.3_7312-7332_G21U_s	7312-7332	AACGAGTAUAGCUGUUAACUAGG	301	NM_010414.3_7310-7332_C1A_as	7310-7332
AD-383761.1	UCCUCAUGGUAGAUGUUCAUA	101	NM_010414.3_11580-11600_s	11580-11600	UAUGAACAUCUACCAUGAGGAGU	302	NM_010414.3_11578-11600_as	11578-11600
AD-380740.1	AUUCACUCCUGUUCGCAGUUU	102	NM_010414.3_8103-8123_s	8103-8123	AAACUGCGAACAGGAGUGAAUAU	303	NM_010414.3_8101-8123_as	8101-8123
AD-379945.1	AGAUAUACAAAACCUCAGUCA	103	NM_010414.3_7145-7165_s	7145-7165	UGACUGAGGUUUUGUAUAUCUGA	304	NM_010414.3_7143-7165_as	7143-7165
AD-379425.1	GUUCAACCUAAGCCUUUUGGU	104	NM_010414.3_6524-6544_C21U_s	6524-6544	ACCAAAAGGCUUAGGUUGAACUC	305	NM_010414.3_6522-6544_G1A_as	6522-6544
AD-380886.1	GCUGACAGAACUACGGAGAGU	105	NM_010414.3_8270-8290_s	8270-8290	ACUCUCCGUAGUUCUGUCAGCGU	306	NM_010414.3_8268-8290_as	8268-8290
AD-384366.1	CUGCACAUGUACCCUUCAGGA	106	NM_010414.3_12307-12327_s	12307-12327	UCCUGAAGGGUACAUGUGCAGAC	307	NM_010414.3_12305-12327_as	12305-12327
AD-380798.1	UCAUCCUGAUCAGUGAAGUGU	107	NM_010414.3_8182-8202_G21U_s	8182-8202	ACACUUCACUGAUCAGGAUGACG	308	NM_010414.3_8180-8202_C1A_as	8180-8202
AD-379463.1	GCAUGAGCGAGAUUGCUAAUU	108	NM_010414.3_6562-6582_G21U_s	6562-6582	AAUUAGCAAUCUCGCUCAUGCCA	309	NM_010414.3_6560-6582_C1A_as	6560-6582
AD-382148.1	CAGGGAACAUGCACUAUGUUU	109	NM_010414.3_9695-9715_G21U_s	9695-9715	AAACAUAGUGCAUGUUCCCUGCA	310	NM_010414.3_9693-9715_C1A_as	9693-9715
AD-357754.1	UUGUUCUUUCUCGUAUUCAGU	110	NM_002111.8_5223-5243_G21U_s	5223-5243	ACUGAATACGAGAAAGAACAAUA	311	NM_002111.8_5221-5243_C1A_as	5221-5243
AD-356938.1	UGCAGAUAAGAAUGCUAUUCA	111	NM_002111.8_4387-4407_s	4387-4407	UGAAUAGCAUUCUUAUCUGCACG	312	NM_002111.8_4385-4407_as	4385-4407
AD-355054.1	CAAACUCUAUAAAGUUCCUCU	112	NM_002111.8_2347-2367_s	2347-2367	AGAGGAACUUUAUAGAGUUUGCU	313	NM_002111.8_2345-2367_as	2345-2367
AD-35774	AAGAUAUUGUUCUUUCUCGUA	113	NM_002111.8_5217-5237_s	5217-5237	UACGAGAAAGAACAAUAUCUUCA	314	NM_002111.8_5215-5237_as	5215-5237

8.1								
AD-35570 4.1	CUGAAACUUCUCA UGCAUGAU	114	NM_002111.8_303 5-3055_G21U_s	3035-3055	AUCAUGCAUGAGA AGUUUCAGGU	315	NM_002111.8_3033-3055_C1A_as	3033-3055
AD-35694 6.1	AGAAUGCUAUUCA UAAUCACA	115	NM_002111.8_439 5-4415_s	4395-4415	UGUGAUTAUGAAU AGCAUUCUUA	316	NM_002111.8_4393-4415_as	4393-4415
AD-35349 9.1	UCAACAAAGUUAU CAAAGCUU	116	NM_002111.8_603 -623_s	603-623	AAGCUUTGAUAACU UUGUUGAGG	317	NM_002111.8_601-623_as	601-623
AD-35407 6.1	GAACUGACGUUAC AUCAUACA	117	NM_002111.8_122 6-1246_s	1226-1246	UGUAUGAUGUAAC GUCAGUUCAU	318	NM_002111.8_1224-1246_as	1224-1246
AD-35663 0.1	CCUGAAAUCCUGC UUUAGUCU	118	NM_002111.8_403 9-4059_G21U_s	4039-4059	AGACUAAAGCAGG AUUUCAGGUA	319	NM_002111.8_4037-4059_C1A_as	4037-4059
AD-35335 1.1	CAUUGUCUGACAA UAUGUGAA	119	NM_002111.8_455 -475_s	455-475	UUCACATAUUGUCA GACAAUGAU	320	NM_002111.8_453-475_as	453-475
AD-35980 3.1	CAGUCGUACUCAG UUUGAAGA	120	NM_002111.8_752 8-7548_s	7528-7548	UCUUCAAACUGAG UACGACUGGU	321	NM_002111.8_7526-7548_as	7526-7548
AD-38252 6.1	AGCUACUCAGUCU AGUCGGGU	121	NM_010414.3_101 89-10209_C21U_s	10189-10209	ACCCGACUAGACUG AGUAGCUAC	322	NM_010414.3_10187-10209_G1A_as	10187-10209
AD-35697 5.1	UUUGAACCUCUUG UUAUAAAA	122	NM_002111.8_442 4-4444_s	4424-4444	UUUUAUAACAAGA GGUUCAAACA	323	NM_002111.8_4422-4444_as	4422-4444
AD-35697 4.1	GUUUGAACCUCUU GUUAUAAA	123	NM_002111.8_442 3-4443_s	4423-4443	UUUAUAACAAGAG GUUCAAACAA	324	NM_002111.8_4421-4443_as	4421-4443
AD-35511 7.1	CUUGAACUACAUC GAUCAUGU	124	NM_002111.8_241 0-2430_G21U_s	2410-2430	ACAUGATCGAUGUA GUUCAAGAU	325	NM_002111.8_2408-2430_C1A_as	2408-2430
AD-35775 5.1	UGUUCUUUCUCGU AUUCAGGA	125	NM_002111.8_522 4-5244_s	5224-5244	UCCUGAAUACGAG AAAGAACAAU	326	NM_002111.8_5222-5244_as	5222-5244
AD-35638 2.1	GCAGCUUCUAGAC AAUCUGAU	126	NM_002111.8_377 3-3793_s	3773-3793	AUCAGATUGUCUAG AAGCUGCAC	327	NM_002111.8_3771-3793_as	3771-3793
AD-35697 3.1	UGUUUGAACCUCU UGUUAUAA	127	NM_002111.8_442 2-4442_s	4422-4442	UUAUAACAAGAGG UUCAAACAAA	328	NM_002111.8_4420-4442_as	4420-4442

AD-35848 8.1	GAAAACCUUUCAA CUCCAACU	128	NM_002111.8_6035-6055_C21U_s	6035-6055	AGUUGGAGUUGAA AGGUUUUCAC	329	NM_002111.8_6033-6055_G1A_as	6033-6055
AD-35407 8.1	ACUGACGUUACAU CAUACACA	129	NM_002111.8_1228-1248_s	1228-1248	UGUGUATGAUGUA ACGUCAGUUC	330	NM_002111.8_1226-1248_as	1226-1248
AD-35663 8.1	CCUGCUUUAGUCG AGAACCAA	130	NM_002111.8_4047-4067_s	4047-4067	UUGGUUCUCGACU AAAGCAGGAU	331	NM_002111.8_4045-4067_as	4045-4067
AD-35709 6.1	UGGAUUCAGAUCA GGUGUUUA	131	NM_002111.8_4545-4565_s	4545-4565	UAAACACCUGAUCU GAAUCCAGA	332	NM_002111.8_4543-4565_as	4543-4565
AD-36149 2.1	CUGCUGACUUGUU UACGAAAU	132	NM_002111.8_9536-9556_s	9536-9556	AUUUCGTAAACAAG UCAGCAGCC	333	NM_002111.8_9534-9556_as	9534-9556
AD-38277 5.1	UGGUGUUGAUGCA CUCUCCUA	133	NM_010414.3_10458-10478_s	10458-10478	UAGGAGAGUGCAU CAACACCAGG	334	NM_010414.3_10456-10478_as	10456-10478
AD-35723 9.1	CAGAUCAUUGGAA UUCCUAAA	134	NM_002111.8_4688-4708_s	4688-4708	UUUAGGAAUUCCA AUGAUCUGUU	335	NM_002111.8_4686-4708_as	4686-4708
AD-35775 6.1	GUUCUUUCUCGUA UUCAGGAU	135	NM_002111.8_5225-5245_G21U_s	5225-5245	AUCCUGAAUACGA GAAAGAACAA	336	NM_002111.8_5223-5245_C1A_as	5223-5245
AD-35638 4.1	AGCUUCUAGACAA UCUGAUAU	136	NM_002111.8_3775-3795_C21U_s	3775-3795	AUAUCAGAUUGUC UAGAAGCUGC	337	NM_002111.8_3773-3795_G1A_as	3773-3795
AD-35787 9.1	AUUUUCAAGGUUU CUAUUACA	137	NM_002111.8_5368-5388_s	5368-5388	UGUAAUAGAAACC UUGAAAAUGU	338	NM_002111.8_5366-5388_as	5366-5388
AD-35638 6.1	CUUCUAGACAAUC UGAUACCU	138	NM_002111.8_3777-3797_s	3777-3797	AGGUAUCAGAUUG UCUAGAAGCU	339	NM_002111.8_3775-3797_as	3775-3797
AD-35699 5.1	AGCUUUAAAACAG UACACGAU	139	NM_002111.8_4444-4464_C21U_s	4444-4464	AUCGUGTACUGUUU UAAAGCUUU	340	NM_002111.8_4442-4464_G1A_as	4442-4464
AD-35351 6.1	GCUUUGAUGGAUU CUAAUCUU	140	NM_002111.8_620-640_s	620-640	AAGAUUAGAAUCC AUCAAAGCUU	341	NM_002111.8_618-640_as	618-640
AD-35407 9.1	CUGACGUUACAUC AUACACAU	141	NM_002111.8_1229-1249_G21U_s	1229-1249	AUGUGUAUGAUGU AACGUCAGUU	342	NM_002111.8_1227-1249_C1A_as	1227-1249
AD-	CUGCUUUAGUCGA	142	NM_002111.8_404	4048-4068	AUUGGUTCUCGACU	343	NM_002111.8_4046-	4046-4068

356639.1	GAACCAAU		8-4068_s		AAAGCAGGA		4068_as	
AD-357649.1	UGUUCGUCACUCCAAACACAA	143	NM_002111.8_5118-5138_s	5118-5138	UUGUGUTUGGAGUGACGAACAUA	344	NM_002111.8_5116-5138_as	5116-5138
AD-361496.1	UGACUUGUUUACGAAAUGUCU	144	NM_002111.8_9540-9560_C21U_s	9540-9560	AGACAUTUCGUAAACAAGUCAGC	345	NM_002111.8_9538-9560_G1A_as	9538-9560
AD-382777.1	GUGUUGAUGCACUCUCCUAGU	145	NM_010414.3_10460-10480_s	10460-10480	ACUAGGAGAGUGCAUCAACACCA	346	NM_010414.3_10458-10480_as	10458-10480
AD-353525.1	GAUUCUAAUCUUCCAAGGUUA	146	NM_002111.8_629-649_s	629-649	UAACCUTGGAAGAUUAGAAUCCA	347	NM_002111.8_627-649_as	627-649
AD-358480.1	CUCGUUGUGAAAACCUUUCAA	147	NM_002111.8_6027-6047_s	6027-6047	UUGAAAGGUUUUCACAACGAGAC	348	NM_002111.8_6025-6047_as	6025-6047
AD-356388.1	UCUAGACAAUCUGAUACCUCA	148	NM_002111.8_3779-3799_s	3779-3799	UGAGGUAUCAGAUUGUCUAGAAG	349	NM_002111.8_3777-3799_as	3777-3799
AD-353500.1	CAACAAAGUUAUCAAAGCUUU	149	NM_002111.8_604-624_s	604-624	AAAGCUTUGAUAACUUUGUUGAG	350	NM_002111.8_602-624_as	602-624
AD-356407.1	CAGGUCCUGUUACAACAAGUA	150	NM_002111.8_3798-3818_s	3798-3818	UACUUGTUGUAACAGGACCUGAG	351	NM_002111.8_3796-3818_as	3796-3818
AD-357068.1	GUUCAGUUACGGGUUAAUUAU	151	NM_002111.8_4517-4537_C21U_s	4517-4537	AUAAUUAACCCGUAACUGAACCA	352	NM_002111.8_4515-4537_G1A_as	4515-4537
AD-359802.1	CCAGUCGUACUCAGUUUGAAU	152	NM_002111.8_7527-7547_G21U_s	7527-7547	AUUCAAACUGAGUACGACUGGUC	353	NM_002111.8_7525-7547_C1A_as	7525-7547
AD-354638.1	UCUGAAAUUGUGUUAGACGGU	153	NM_002111.8_1886-1906_s	1886-1906	ACCGUCTAACACAAUUUCAGAAC	354	NM_002111.8_1884-1906_as	1884-1906
AD-356663.1	GGCAACUGUUUGUGUUCAACA	154	NM_002111.8_4072-4092_s	4072-4092	UGUUGAACACAAACAGUUGCCAU	355	NM_002111.8_4070-4092_as	4070-4092
AD-357651.1	UUCGUCACUCCAAACACAAUU	155	NM_002111.8_5120-5140_G21U_s	5120-5140	AAUUGUGUUUGGAGUGACGAACA	356	NM_002111.8_5118-5140_C1A_as	5118-5140
AD-36208	CUGACAUUUCCGUUGUACAUU	156	NM_002111.8_10314-10334_G21U_s	10314-10334	AAUGUACAACGGAAAUGUCAGCG	357	NM_002111.8_10312-10334_C1A_as	10312-10334

5.1								
AD-38432 9.1	CCACUGCCAAGUG CCCUUUAU	157	NM_010414.3_122 70-12290_s	12270-12290	AUAAAGGGCACUU GGCAGUGGCU	358	NM_010414.3_12268-12290_as	12268-12290
AD-35406 7.1	CAGGUUUAUGAAC UGACGUUA	158	NM_002111.8_121 7-1237_s	1217-1237	UAACGUCAGUUCA UAAACCUGGA	359	NM_002111.8_1215-1237_as	1215-1237
AD-35352 6.1	AUUCUAAUCUUCC AAGGUUAU	159	NM_002111.8_630 -650_C21U_s	630-650	AUAACCTUGGAAGA UUAGAAUCC	360	NM_002111.8_628-650_G1A_as	628-650
AD-35642 2.1	CAAGUAAAUCCUC AUCACUGU	160	NM_002111.8_381 3-3833_G21U_s	3813-3833	ACAGUGAUGAGGA UUUACUUGUU	361	NM_002111.8_3811-3833_C1A_as	3811-3833
AD-35351 9.1	UUGAUGGAUUCUA AUCUUCCA	161	NM_002111.8_623 -643_s	623-643	UGGAAGAUUAGAA UCCAUCAAAG	362	NM_002111.8_621-643_as	621-643
AD-35644 3.1	CUUCAUACCUCAA ACUGCAUU	162	NM_002111.8_385 2-3872_G21U_s	3852-3872	AAUGCAGUUUGAG GUAUGAAGGA	363	NM_002111.8_3850-3872_C1A_as	3850-3872
AD-35711 5.1	UAUUGGCUUUGUA UUGAAACA	163	NM_002111.8_456 4-4584_s	4564-4584	UGUUUCAAUACAA AGCCAAUAAA	364	NM_002111.8_4562-4584_as	4562-4584
AD-36149 3.1	UGCUGACUUGUUU ACGAAAUU	164	NM_002111.8_953 7-9557_G21U_s	9537-9557	AAUUUCGUAAACA AGUCAGCAGC	365	NM_002111.8_9535-9557_C1A_as	9535-9557
AD-35463 9.1	CUGAAAUUGUGUU AGACGGUA	165	NM_002111.8_188 7-1907_s	1887-1907	UACCGUCUAACACA AUUUCAGAA	366	NM_002111.8_1885-1907_as	1885-1907
AD-35695 5.1	UUCAUAAUCACAU UCGUUUGU	166	NM_002111.8_440 4-4424_s	4404-4424	ACAAACGAAUGUG AUUAUGAAUA	367	NM_002111.8_4402-4424_as	4402-4424
AD-35847 1.1	CAAUUCAGUCUCG UUGUGAAA	167	NM_002111.8_601 8-6038_s	6018-6038	UUUCACAACGAGAC UGAAUUGCC	368	NM_002111.8_6016-6038_as	6016-6038
AD-35406 6.1	CCAGGUUUAUGAA CUGACGUU	168	NM_002111.8_121 6-1236_s	1216-1236	AACGUCAGUUCAU AAACCUGGAC	369	NM_002111.8_1214-1236_as	1214-1236
AD-38466 5.1	CCUCCAGGGAUUG GUAUGUGU	169	NM_010414.3_126 95-12715_G21U_s	12695-12715	ACACAUACCAAUCC CUGGAGGAC	370	NM_010414.3_12693-12715_C1A_as	12693-12715
AD-35504 5.1	UUUCUUCAGCAAA CUCUAUAA	170	NM_002111.8_233 8-2358_s	2338-2358	UUAUAGAGUUUGC UGAAGAAAGA	371	NM_002111.8_2336-2358_as	2336-2358

AD-35371 5.1	UGUUCCCAAAAUU AUGGCUUU	171	NM_002111.8_844 -864_C21U_s	844-864	AAAGCCAUAAUUU UGGGAACAGC	372	NM_002111.8_842- 864_G1A_as	842-864
AD-35642 9.1	UUUCUAUCAUCUU CCUUCAUA	172	NM_002111.8_383 8-3858_s	3838-3858	UAUGAAGGAAGAU GAUAGAAACU	373	NM_002111.8_3836- 3858_as	3836-3858
AD-35976 1.1	CUUUAAGGAGUUC AUCUACCU	173	NM_002111.8_748 6-7506_G21U_s	7486-7506	AGGUAGAUGAACU CCUUAAAGAC	374	NM_002111.8_7484- 7506_C1A_as	7484-7506
AD-35666 9.1	UGUUUGUGUUCAA CAAUUGUU	174	NM_002111.8_407 8-4098_s	4078-4098	AACAAUTGUUGAAC ACAAACAGU	375	NM_002111.8_4076- 4098_as	4076-4098
AD-35768 4.1	ACUGUUCAACUGU GGAUAUCU	175	NM_002111.8_515 3-5173_G21U_s	5153-5173	AGAUAUCCACAGU UGAACAGUGC	376	NM_002111.8_5151- 5173_C1A_as	5151-5173
AD-36198 1.1	UAACGUAACUCUU UCUAUGCU	176	NM_002111.8_101 73-10193_C21U_s	10173-10193	AGCAUAGAAAGAG UUACGUUAAA	377	NM_002111.8_10171- 10193_G1A_as	10171-10193
AD-35542 3.1	UCUGAGGAACAGU UCCUAUUU	177	NM_002111.8_271 6-2736_G21U_s	2716-2736	AAAUAGGAACUGU UCCUCAGAGU	378	NM_002111.8_2714- 2736_C1A_as	2714-2736
AD-35695 6.1	UCAUAAUCACAUU CGUUUGUU	178	NM_002111.8_440 5-4425_s	4405-4425	AACAAACGAAUGU GAUUAUGAAU	379	NM_002111.8_4403- 4425_as	4403-4425
AD-35352 2.1	AUGGAUUCUAAUC UUCCAAGU	179	NM_002111.8_626 -646_G21U_s	626-646	ACUUGGAAGAUUA GAAUCCAUCA	380	NM_002111.8_624- 646_C1A_as	624-646
AD-35407 5.1	UGAACUGACGUUA CAUCAUAU	180	NM_002111.8_122 5-1245_C21U_s	1225-1245	AUAUGATGUAACG UCAGUUCAUA	381	NM_002111.8_1223- 1245_G1A_as	1223-1245
AD-35505 9.1	UCUAUAAAGUUCC UCUUGACA	181	NM_002111.8_235 2-2372_s	2352-2372	UGUCAAGAGGAAC UUUAUAGAGU	382	NM_002111.8_2350- 2372_as	2350-2372
AD-35695 1.1	GCUAUUCAUAAUC ACAUUCGU	182	NM_002111.8_440 0-4420_s	4400-4420	ACGAAUGUGAUUA UGAAUAGCAU	383	NM_002111.8_4398- 4420_as	4398-4420
AD-35387 1.1	GCUACUAAAUGUG CUCUUAGU	183	NM_002111.8_102 1-1041_G21U_s	1021-1041	ACUAAGAGCACAU UUAGUAGCCA	384	NM_002111.8_1019- 1041_C1A_as	1019-1041
AD-35699 6.1	GCUUUAAAACAGU ACACGACU	184	NM_002111.8_444 5-4465_s	4445-4465	AGUCGUGUACUGU UUUAAAGCUU	385	NM_002111.8_4443- 4465_as	4443-4465
AD-	AGGUUUAUGAACU	185	NM_002111.8_121	1218-1238	AUAACGTCAGUUCA	386	NM_002111.8_1216-	1216-1238

354068.1	GACGUUAU		8-1238_C21U_s		UAAACCUGG		1238_G1A_as	
AD-356678.1	UCAACAAUUGUUGAAGACUCU	186	NM_002111.8_4087-4107_s	4087-4107	AGAGUCTUCAACAAUUGUUGAAC	387	NM_002111.8_4085-4107_as	4085-4107
AD-357963.1	GCAACAUACUUUCUAUUGCCA	187	NM_002111.8_5452-5472_s	5452-5472	UGGCAATAGAAAGUAUGUUGCUG	388	NM_002111.8_5450-5472_as	5450-5472
AD-362090.1	AUUUCCGUUGUACAUGUUCCU	188	NM_002111.8_10319-10339_s	10319-10339	AGGAACAUGUACAACGGAAAUGU	389	NM_002111.8_10317-10339_as	10317-10339
AD-355745.1	CUCCGUCAGCACAAUAACCAU	189	NM_002111.8_3076-3096_G21U_s	3076-3096	AUGGUUAUUGUGCUGACGGAGAA	390	NM_002111.8_3074-3096_C1A_as	3074-3096
AD-357066.1	UGGUUCAGUUACGGGUUAAUU	190	NM_002111.8_4515-4535_s	4515-4535	AAUUAACCCGUAACUGAACCAGC	391	NM_002111.8_4513-4535_as	4513-4535
AD-353527.1	UUCUAAUCUUCCAAGGUUACA	191	NM_002111.8_631-651_s	631-651	UGUAACCUUGGAAGAUUAGAAUC	392	NM_002111.8_629-651_as	629-651
AD-354236.1	GAGUAUUGUGGAACUUAUAGU	192	NM_002111.8_1405-1425_C21U_s	1405-1425	ACUAUAAGUUCCACAAUACUCCC	393	NM_002111.8_1403-1425_G1A_as	1403-1425
AD-357750.1	GAUAUUGUUCUUUCUCGUAUU	193	NM_002111.8_5219-5239_s	5219-5239	AAUACGAGAAAGAACAAUAUCUU	394	NM_002111.8_5217-5239_as	5217-5239
AD-356389.1	CUAGACAAUCUGAUACCUCAU	194	NM_002111.8_3780-3800_G21U_s	3780-3800	AUGAGGTAUCAGAUUGUCUAGAA	395	NM_002111.8_3778-3800_C1A_as	3778-3800
AD-354939.1	CGCCUUUUAUCUGCUUCGUUU	195	NM_002111.8_2207-2227_s	2207-2227	AAACGAAGCAGAUAAAAGGCGGA	396	NM_002111.8_2205-2227_as	2205-2227
AD-357218.1	UAUGAACGCUAUCAUUCAAAA	196	NM_002111.8_4667-4687_s	4667-4687	UUUUGAAUGAUAGCGUUCAUAAG	397	NM_002111.8_4665-4687_as	4665-4687
AD-354640.1	UGAAAUUGUGUUAGACGGUAU	197	NM_002111.8_1888-1908_C21U_s	1888-1908	AUACCGTCUAACACAAUUUCAGA	398	NM_002111.8_1886-1908_G1A_as	1886-1908
AD-358018.1	AUCUUCAAGUCUGGAAUGUUU	198	NM_002111.8_5507-5527_C21U_s	5507-5527	AAACAUTCCAGACUUGAAGAUGU	399	NM_002111.8_5505-5527_G1A_as	5505-5527
AD-36209	UCCGUUGUACAUGUUCCUGUU	199	NM_002111.8_10322-10342_s	10322-10342	AACAGGAACAUGUACAACGGAAA	400	NM_002111.8_10320-10342_as	10320-10342

3.1								
AD-35638 5.1	GCUUCUAGACAAU CUGAUACU	200	NM_002111.8_3776-3796_C21U_s	3776-3796	AGUAUCAGAUUGU CUAGAAGCUG	401	NM_002111.8_3774-3796_G1A_as	3774-3796
AD-35706 9.1	UUCAGUUACGGGU UAAUUACU	201	NM_002111.8_4518-4538_s	4518-4538	AGUAAUTAACCCGU AACUGAACC	402	NM_002111.8_4516-4538_as	4516-4538
AD-35876 4.1	CAUGCAAGACUCA CUUAGUCU	202	NM_002111.8_6349-6369_C21U_s	6349-6369	AGACUAAGUGAGU CUUGCAUGGU	403	NM_002111.8_6347-6369_G1A_as	6347-6369
AD-35431 6.1	GAUGACUCUGAAU CGAGAUCU	203	NM_002111.8_1508-1528_G21U_s	1508-1528	AGAUCUCGAUUCA GAGUCAUCCU	404	NM_002111.8_1506-1528_C1A_as	1506-1528
AD-35577 5.1	AGGCUAUAACCUA CUACCAAU	204	NM_002111.8_3106-3126_G21U_s	3106-3126	AUUGGUAGUAGGU UAUAGCCUCU	405	NM_002111.8_3104-3126_C1A_as	3104-3126
AD-35432 0.1	ACUCUGAAUCGAG AUCGGAUU	205	NM_002111.8_1512-1532_G21U_s	1512-1532	AAUCCGAUCUCGAU UCAGAGUCA	406	NM_002111.8_1510-1532_C1A_as	1510-1532
AD-35578 3.1	ACCUACUACCAAG CAUAACAU	206	NM_002111.8_3114-3134_G21U_s	3114-3134	AUGUUATGCUUGG UAGUAGGUUA	407	NM_002111.8_3112-3134_C1A_as	3112-3134
AD-35432 2.1	UCUGAAUCGAGAU CGGAUGUU	207	NM_002111.8_1514-1534_C21U_s	1514-1534	AACAUCCGAUCUCG AUUCAGAGU	408	NM_002111.8_1512-1534_G1A_as	1512-1534
AD-35640 8.1	AGGUCCUGUUACA ACAAGUAA	208	NM_002111.8_3799-3819_s	3799-3819	UUACUUGUUGUAA CAGGACCUGA	409	NM_002111.8_3797-3819_as	3797-3819
AD-35480 5.1	ACAGCAGUGUUGA UAAAUUUG	209	NM_002111.8_2073-2093_s	2073-2093	CAAAUUTAUCAACA CUGCUGUCA	410	NM_002111.8_2071-2093_as	2071-2093
AD-35640 9.1	GGUCCUGUUACAA CAAGUAAA	210	NM_002111.8_3800-3820_s	3800-3820	UUUACUTGUUGUA ACAGGACCUG	411	NM_002111.8_3798-3820_as	3798-3820
AD-35511 8.1	UUGAACUACAUCG AUCAUGGA	211	NM_002111.8_2411-2431_s	2411-2431	UCCAUGAUCGAUG UAGUUCAAGA	412	NM_002111.8_2409-2431_as	2409-2431
AD-35895 8.1	ACUCGGAGUUCAA CCUAAGCU	212	NM_002111.8_6561-6581_C21U_s	6561-6581	AGCUUAGGUUGAA CUCCGAGUUC	413	NM_002111.8_6559-6581_G1A_as	6559-6581
AD-35542 2.1	CUCUGAGGAACAG UUCCUAUU	213	NM_002111.8_2715-2735_s	2715-2735	AAUAGGAACUGUU CCUCAGAGUC	414	NM_002111.8_2713-2735_as	2713-2735

AD-358959.1	CUCGGAGUUCAACCUAAGCCU	91	NM_002111.8_6562-6582_s	6562-6582	AGGCUUAGGUUGAACUCCGAGUU	415	NM_002111.8_6560-6582_as	6560-6582
AD-355424.1	CUGAGGAACAGUUCCUAUUGU	214	NM_002111.8_2717-2737_G21U_s	2717-2737	ACAAUAGGAACUGUUCCUCAGAG	416	NM_002111.8_2715-2737_C1A_as	2715-2737
AD-379420.2	GCUCGGAGUUCAACCUAAGCU	79	NM_010414.3_6517-6537_C21U_s	6517-6537	AGCUUAGGUUGAACUCCGAGCUC	280	NM_010414.3_6515-6537_G1A_as	6515-6537
AD-355524.1	AUCAUUAUACAGGGCUUUUAA	215	NM_002111.8_2835-2855_s	2835-2855	UUAAAAGCCCUGUAUAAUGAUGA	417	NM_002111.8_2833-2855_as	2833-2855
AD-379380.2	CUCGGAGUUCAACCUAAGCCU	91	NM_002111.8_6562-6582_s	6562-6582	AGGCUUAGGUUGAACUCCGAGCU	292	NM_010414.3_6516-6538_as	6562-6582

Table 3. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-384118.1	gsgsacuaAfaAfCfUfuuuuaucaaaL96	418	usUfsugau(Agn)aaaaguUfuUfaguccscsu	619	AGGGACUAAAACUUUUUAUCAAA	821
AD-380543.1	csuscuguUfaCfCfAfgcuacuacauL96	419	asUfsguag(Tgn)agcuggUfaAfcagagsasa	620	UUCUCUGUUACCAGCUACUACAG	822
AD-380533.1	cscsugucCfcUfUfCfucuguuaccaL96	420	usGfsguaa(Cgn)agagaaGfgGfacaggsasu	621	AUCCUGUCCCUUCUCUGUUACCA	823
AD-384038.1	ususugugAfgUfCfUfagcaucugauL96	421	asUfscaga(Tgn)gcuagaCfuCfacaaasgsc	622	GCUUUGUGAGUCUAGCAUCUGAG	824
AD-380805.1	gsasucagUfgAfAfGfugguucgauuL96	422	asAfsucga(Agn)ccacuuCfaCfugaucsasg	623	CUGAUCAGUGAAGUGGUUCGAUC	825
AD-380117.1	cscsucugGfuAfUfGfgaaacucgguL96	423	asCfscgag(Tgn)uuccauAfcCfagaggsasg	624	CUCCUCUGGUAUGGAAACUCGGG	826
AD-381341.1	asgsagucCfuUfGfGfucaagcuaauL96	424	asUfsuagc(Tgn)ugaccaAfgGfacucusgsu	625	ACAGAGUCCUUGGUCAAGCUAAG	827
AD-379426.1	ususcaacCfuAfAfGfccuuuuggcuL96	425	asGfsccaa(Agn)aggcuuAfgGfuugaascsu	626	AGUUCAACCUAAGCCUUUUGGCU	828
AD-380888.1	usgsacagAfaCfUfAfcggagaguguL96	426	asCfsacuc(Tgn)ccguagUfuCfugucasgsc	627	GCUGACAGAACUACGGAGAGUGC	829
AD-384841.1	csusccauGfuGfUfGfcuugucacauL96	427	asUfsguga(Cgn)aagcacAfcAfuggagsgsg	628	CCCUCCAUGUGUGCUUGUCACAC	830
AD-380853.1	csgsaacgUfaCfCfCfaguuugaaauL96	428	asUfsuuca(Agn)acugggUfaCfguucgsgsu	629	ACCGAACGUACCCAGUUUGAAAU	831
AD-379602.1	asusaccaCfaUfCfAfuaccagucuuL96	429	asAfsgacu(Ggn)guaugaUfgUfgguauscsa	630	UGAUACCACAUCAUACCAGUCUC	832
AD-382484.1	csusgcauGfuGfAfCfaaaguuuauuL96	430	asAfsuaaa(Cgn)uuugucAfcAfugcagscsa	631	UGCUGCAUGUGACAAAGUUUAUG	833
AD-380741.1	ususcacuCfcUfGfUfucgcaguuucL96	431	gsAfsaacu(Ggn)cgaacaGfgAfgugaasusa	632	UAUUCACUCCUGUUCGCAGUUUC	834

Duplex ID	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-380534.1	csusguccCfuUfCfUfcuguuaccauL96	432	asUfsggua(Agn)cagagaAfgGfgacagsgsa	633	UCCUGUCCCUUCUCUGUUACCAG	835
AD-384053.1	uscsugagAfaUfGfGfgacucaauuuL96	433	asAfsauug(Agn)gucccaUfuCfucagasusg	634	CAUCUGAGAAUGGGACUCAAUUU	836
AD-380916.1	uscsagaaGfaUfGfAfgauccucauuL96	434	asAfsugag(Ggn)aucucaUfcUfucugasasg	635	CUUCAGAAGAUGAGAUCCUCAUU	837
AD-380402.1	cscsacugAfaGfGfCfucucgauacuL96	435	asGfsuauc(Ggn)agagccUfuCfaguggscsu	636	AGCCACUGAAGGCUCUCGAUACC	838
AD-381464.1	gsasgucuGfuGfAfUfuguagcuauuL96	436	asAfsuagc(Tgn)acaaucAfcAfgacucsgsc	637	GCGAGUCUGUGAUUGUAGCUAUG	839
AD-379729.1	uscsauggCfaUfUfUfgauccaugauL96	437	asUfscaug(Ggn)aucaaaUfgCfcaugascsa	638	UGUCAUGGCAUUUGAUCCAUGAG	840
AD-381065.1	ascsggcaUfcCfUfCfuauguguuguL96	438	asCfsaaca(Cgn)auagagGfaUfgccgusgsc	639	GCACGGCAUCCUCUAUGUGUUGG	841
AD-379466.1	usgsagcgAfgAfUfUfgcuaauggcuL96	439	asGfsccau(Tgn)agcaauCfuCfgcucasusg	640	CAUGAGCGAGAUUGCUAAUGGCC	842
AD-380885.1	csgscugaCfaGfAfAfcuacggagauL96	440	asUfscucc(Ggn)uaguucUfgUfcagcgsusc	641	GACGCUGACAGAACUACGGAGAG	843
AD-379897.1	asasgcagGfuCfAfCfauacuccaauL96	441	asUfsugga(Ggn)uaugugAfcCfugcuususc	642	GAAAGCAGGUCACAUACUCCAAG	844
AD-381124.1	cscsaguuGfuUfAfGfugacuaucuuL96	442	asAfsgaua(Ggn)ucacuaAfcAfacuggsasa	643	UUCCAGUUGUUAGUGACUAUCUG	845
AD-380807.1	uscsagugAfaGfUfGfguucgaucuuL96	443	asAfsgauc(Ggn)aaccacUfuCfacugasusc	644	GAUCAGUGAAGUGGUUCGAUCUC	846
AD-380806.1	asuscaguGfaAfGfUfgguucgaucuL96	444	asGfsaucg(Agn)accacuUfcAfcugauscsa	645	UGAUCAGUGAAGUGGUUCGAUCU	847
AD-384843.1	cscsauguGfuGfCfUfugucacacuuL96	445	asAfsgugu(Ggn)acaagcAfcAfcauggsasg	646	CUCCAUGUGUGCUUGUCACACUC	848
AD-381257.1	ususucagCfaUfCfUfgugauacagaL96	446	usCfsugua(Tgn)cacagaUfgCfugaaasasu	647	AUUUUCAGCAUCUGUGAUACAGA	849
AD-380408.1	asasggcuCfuCfGfAfuaccagauuuL96	447	asAfsaucu(Ggn)guaucgAfgAfgccuuscsa	648	UGAAGGCUCUCGAUACCAGAUUU	850
AD-381570.1	usasgaugAfcUfUfCfuuuccaccuuL96	448	asAfsggug(Ggn)aaagaaGfuCfaucuasgsg	649	CCUAGAUGACUUCUUUCCACCUC	851
AD-380093.1	gsusuaacAfgCfUfAfuacucguguuL96	449	asAfscacg(Agn)guauagCfuGfuuaacsusa	650	UAGUUAACAGCUAUACUCGUGUG	852
AD-381148.1	uscscaacCfuCfAfAfaggaauagcuL96	450	asGfscuau(Tgn)ccuuugAfgGfuuggascsa	651	UGUCCAACCUCAAAGGAAUAGCC	853
AD-379475.1	ususgcuaAfuGfGfCfcaaaagaguuL96	451	asAfscucu(Tgn)uuggccAfuUfagcaasusc	652	GAUUGCUAAUGGCCAAAAGAGUC	854
AD-381142.1	csusgcugUfcCfAfAfccucaaaggaL96	452	usCfscuuu(Ggn)agguugGfaCfagcagsasu	653	AUCUGCUGUCCAACCUCAAAGGA	855
AD-380852.1	cscsgaacGfuAfCfCfcaguuugaaaL96	453	usUfsucaa(Agn)cuggguAfcGfuucggsusg	654	CACCGAACGUACCCAGUUUGAAA	856
AD-379935.1	asasguagAfcUfCfAfgauauacaaaL96	454	usUfsugua(Tgn)aucugaGfuCfuacuuscsc	655	GGAAGUAGACUCAGAUAUACAAA	857
AD-381117.1	gscsucauUfcCfAfGfuuguuagugaL96	455	usCfsacua(Agn)caacugGfaAfugagcsusg	656	CAGCUCAUUCCAGUUGUUAGUGA	858
AD-380808.1	csasgugaAfgUfGfGfuucgaucucuL96	456	asGfsagau(Cgn)gaaccaCfuUfcacugsasu	657	AUCAGUGAAGUGGUUCGAUCUCU	859
AD-379471.1	gsasgauuGfcUfAfAfuggccaaaauL96	457	asUfsuuug(Ggn)ccauuaGfcAfaucucsgsc	658	GCGAGAUUGCUAAUGGCCAAAAG	860
AD-381342.1	gsasguccUfuGfGfUfcaagcuaaguL96	458	asCfsuuag(Cgn)uugaccAfaGfgacucsusg	659	CAGAGUCCUUGGUCAAGCUAAGU	861

Duplex ID	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-380411.1	gscsucucGfaUfAfCfcagauuuggaL96	459	usCfscaaa(Tgn)cugguaUfcGfagagcscsu	660	AGGCUCUCGAUACCAGAUUUGGA	862
AD-382487.1	csasugugAfcAfAfAfguuuauggaaL96	460	usUfsccau(Agn)aacuuuGfuCfacaugscsa	661	UGCAUGUGACAAAGUUUAUGGAA	863
AD-380116.1	uscscucuGfgUfAfUfggaaacucguL96	461	asCfsgagu(Tgn)uccauaCfcAfgaggasgsg	662	CCUCCUCUGGUAUGGAAACUCGG	864
AD-381150.1	csasaccuCfaAfAfGfgaauagcccaL96	462	usGfsggcu(Agn)uuccuuUfgAfgguugsgsa	663	UCCAACCUCAAAGGAAUAGCCCA	865
AD-379476.1	usgscuaaUfgGfCfCfaaaagagucuL96	463	asGfsacuc(Tgn)uuuggcCfaUfuagcasasu	664	AUUGCUAAUGGCCAAAAGAGUCC	866
AD-382444.1	cscsuaugCfcCfGfUfguaaaguguuL96	464	asAfscacu(Tgn)uacacgGfgCfauaggsasa	665	UUCCUAUGCCCGUGUAAAGUGUG	867
AD-380883.1	gsascgcuGfaCfAfGfaacuacggauL96	465	asUfsccgu(Agn)guucugUfcAfgcgucsasg	666	CUGACGCUGACAGAACUACGGAG	868
AD-379941.1	ascsucagAfuAfUfAfcaaaaccucaL96	466	usGfsaggu(Tgn)uuguauAfuCfugaguscsu	667	AGACUCAGAUAUACAAAACCUCA	869
AD-381578.1	ususcuuuCfcAfCfCfcucaagauguuL96	467	asAfscauc(Tgn)ugagguGfgAfaagaasgsu	668	ACUUCUUUCCACCUCAAGAUGUC	870
AD-381460.1	csasgcgaGfuCfUfGfugauuguaguL96	468	asCfsuaca(Agn)ucacagAfcUfcgcugsusc	669	GACAGCGAGUCUGUGAUUGUAGC	871
AD-379939.1	asgsacucAfgAfUfAfuacaaaaccuL96	469	asGfsguuu(Tgn)guauauCfuGfagucusasc	670	GUAGACUCAGAUAUACAAAACCU	872
AD-384039.1	ususgugaGfuCfUfAfgcaucugagaL96	470	usCfsucag(Agn)ugcuagAfcUfcacaasasg	671	CUUUGUGAGUCUAGCAUCUGAGA	873
AD-380735.1	ususgauaUfuCfAfCfuccuguucguL96	471	asCfsgaac(Agn)ggagugAfaUfaucaascsc	672	GGUUGAUAUUCACUCCUGUUCGC	874
AD-382525.1	usasgcuaCfuCfAfGfucuagucgguL96	472	asCfscgac(Tgn)agacugAfgUfagcuascsa	673	UGUAGCUACUCAGUCUAGUCGGG	875
AD-380713.1	cscsugugUfcUfCfCfagucaauucuL96	473	asGfsaauu(Ggn)acuggaGfaCfacaggsusg	674	CACCUGUGUCUCCAGUCAAUUCC	876
AD-382149.1	asgsggaaCfaUfGfCfacuauguuguL96	474	asCfsaaca(Tgn)agugcaUfgUfucccusgsc	675	GCAGGGAACAUGCACUAUGUUGG	877
AD-379855.1	asgsccauUfgCfAfGfuacaaccuguL96	475	asCfsaggu(Tgn)guacugCfaAfuggcususc	676	GAAGCCAUUGCAGUACAACCUGG	878
AD-383508.1	usgscaagGfuUfCfCfcuaccaaacaL96	476	usGfsuuug(Ggn)uagggaAfcCfuugcasusc	677	GAUGCAAGGUUCCCUACCAAACA	879
AD-381273.1	ascsagauGfuGfUfGfgaguaaugcuL96	477	asGfscauu(Agn)cuccacAfcAfucugusasu	678	AUACAGAUGUGUGGAGUAAUGCU	880
AD-382483.1	gscsugcaUfgUfGfAfcaaaguuuauL96	478	asUfsaaac(Tgn)uugucaCfaUfgcagcsasc	679	GUGCUGCAUGUGACAAAGUUUAU	881
AD-382481.1	gsusgcugCfaUfGfUfgacaaaguuuL96	479	asAfsacuu(Tgn)gucacaUfgCfagcacsasg	680	CUGUGCUGCAUGUGACAAAGUUU	882
AD-382485.1	usgscaugUfgAfCfAfaaguuuauguL96	480	asCfsauaa(Agn)cuuuguCfaCfaugcasgsc	681	GCUGCAUGUGACAAAGUUUAUGG	883
AD-380092.1	asgsuuaaCfaGfCfUfauacucguguL96	481	asCfsacga(Ggn)uauagcUfgUfuaacusasg	682	CUAGUUAACAGCUAUACUCGUGU	884
AD-379420.1	gscsucggAfgUfUfCfaaccuaagcuL96	482	asGfscuua(Ggn)guugaaCfuCfcgagcsusc	683	GAGCUCGGAGUUCAACCUAAGCC	885
AD-380800.1	asusccugAfuCfAfGfugaaggugguuL96	483	asAfsccac(Tgn)ucacugAfuCfaggausgsa	684	UCAUCCUGAUCAGUGAAGUGGUU	886
AD-384030.1	csasgucaGfcUfUfUfgugagucuauL96	484	asUfsagac(Tgn)cacaaaGfcUfgacugsusa	685	UACAGUCAGCUUUGUGAGUCUAG	887
AD-380737.1	gsasuauuCfaCfUfCfcuguucgcauL96	485	asUfsgcga(Agn)caggagUfgAfauaucsasa	686	UUGAUAUUCACUCCUGUUCGCAG	888

Duplex ID	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-382780.1	ususgaugCfaCfUfCfuccuagucuuL96	486	asAfsgacu(Agn)ggagagUfgCfaucaascsa	687	UGUUGAUGCACUCUCCUAGUCUC	889
AD-379944.1	csasgauaUfaCfAfAfaaccucaguuL96	487	asAfscuga(Ggn)guuuugUfaUfaucugsasg	688	CUCAGAUAUACAAAACCUCAGUC	890
AD-379461.1	usgsgcauGfaGfCfGfagauugcuaaL96	488	usUfsagca(Agn)ucucgcUfcAfugccasasg	689	CUUGGCAUGAGCGAGAUUGCUAA	891
AD-381856.1	ascsagguGfgAfUfGfugaaccuuuuL96	489	asAfsaagg(Tgn)ucacauCfcAfccugususc	690	GAACAGGUGGAUGUGAACCUUUU	892
AD-379418.1	gsasgcucGfgAfGfUfucaaccuaauL96	490	asUfsuagg(Tgn)ugaacuCfcGfagcucsasu	691	AUGAGCUCGGAGUUCAACCUAAG	893
AD-382924.1	usgsucccUfuUfGfUfaucuucugcaL96	491	usGfscaga(Agn)gauacaAfaGfggacasgsa	692	UCUGUCCCUUUGUAUCUUCUGCA	894
AD-383759.1	ascsuccuCfaUfGfGfuagauguucaL96	492	usGfsaaca(Tgn)cuaccaUfgAfggagusasa	693	UUACUCCUCAUGGUAGAUGUUCA	895
AD-380409.1	asgsgcucUfcGfAfUfaccagauuugL96	493	csAfsaauc(Tgn)gguaucGfaGfagccususc	694	GAAGGCUCUCGAUACCAGAUUUG	896
AD-379380.1	csuscggaGfuUfCfAfaccuaagccuL96	494	asGfsgcuu(Agn)gguugaAfcUfccgagscsu	695	CAAAUCUGGUAUCGAGAGCCUUC	897
AD-381145.1	csusguccAfaCfCfUfcaaaggaauaL96	495	usAfsuucc(Tgn)uugaggUfuGfgacagscsa	696	UGCUGUCCAACCUCAAAGGAAUA	898
AD-384054.1	csusgagaAfuGfGfGfacucaauuuuL96	496	asAfsaauu(Ggn)agucccAfuUfcucagsasu	697	AUCUGAGAAUGGGACUCAAUUUU	899
AD-380796.1	csgsucauCfcUfGfAfucagugaaguL96	497	asCfsuuca(Cgn)ugaucaGfgAfugacgsgsg	698	CCCGUCAUCCUGAUCAGUGAAGU	900
AD-382960.1	csasaaggUfgUfCfUfcugagcuauuL96	498	asAfsuagc(Tgn)cagagaCfaCfcuuugsgsg	699	CCCAAAGGUGUCUCUGAGCUAUG	901
AD-380555.1	csusacuaCfaGfGfUfgcucuuaucaL96	499	usGfsauaa(Ggn)agcaccUfgUfaguagscsu	700	AGCUACUACAGGUGCUCUUAUCA	902
AD-379462.1	gsgscaugAfgCfGfAfgauugcuaauL96	500	asUfsuagc(Agn)aucucgCfuCfaugccsasa	701	UUGGCAUGAGCGAGAUUGCUAAU	903
AD-382118.1	usgsgcagGfaGfUfGfcuuugcaauuL96	501	asAfsuugc(Agn)aagcacUfcCfugccasusu	702	AAUGGCAGGAGUGCUUUGCAAUG	904
AD-380414.1	csuscgauAfcCfAfGfauuuggaagaL96	502	usCfsuucc(Agn)aaucugGfuAfucgagsasg	703	CUCUCGAUACCAGAUUUGGAAGA	905
AD-380091.1	usasguuaAfcAfGfCfuauacucguuL96	503	asAfscgag(Tgn)auagcuGfuUfaacuasgsg	704	CCUAGUUAACAGCUAUACUCGUG	906
AD-383761.1	uscscucaUfgGfUfAfgauguucauaL96	504	usAfsugaa(Cgn)aucuacCfaUfgaggasgsu	705	ACUCCUCAUGGUAGAUGUUCAUA	907
AD-380740.1	asusucacUfcCfUfGfuucgcaguuuL96	505	asAfsacug(Cgn)gaacagGfaGfugaausasu	706	AUAUUCACUCCUGUUCGCAGUUU	908
AD-379945.1	asgsauauAfcAfAfAfaccucagucaL96	506	usGfsacug(Agn)gguuuuGfuAfuaucusgsa	707	UCAGAUAUACAAAACCUCAGUCA	909
AD-379425.1	gsusucaaCfcUfAfAfgccuuuugguL96	507	asCfscaaa(Agn)ggcuuaGfgUfugaacsusc	708	GAGUUCAACCUAAGCCUUUUGGC	910
AD-380886.1	gscsugacAfgAfAfCfuacggagaguL96	508	asCfsucuc(Cgn)guaguuCfuGfucagcsgsu	709	ACGCUGACAGAACUACGGAGAGU	911
AD-384366.1	csusgcacAfuGfUfAfcccuucaggaL96	509	usCfscuga(Agn)ggguacAfuGfugcagsasc	710	GUCUGCACAUGUACCCUUCAGGA	912
AD-380798.1	uscsauccUfgAfUfCfagugaaguguL96	510	asCfsacuu(Cgn)acugauCfaGfgaugascsg	711	CGUCAUCCUGAUCAGUGAAGUGG	913
AD-379463.1	gscsaugaGfcGfAfGfauugcuaauuL96	511	asAfsuuag(Cgn)aaucucGfcUfcaugcscsa	712	UGGCAUGAGCGAGAUUGCUAAUG	914
AD-382148.1	csasgggaAfcAfUfGfcacuauguuuL96	512	asAfsacau(Agn)gugcauGfuUfcccugscsa	713	UGCAGGGAACAUGCACUAUGUUG	915

Duplex ID	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-357754.1	ususguucUfuUfCfUfcguauucaguL96	513	asCfsugaa(Tgn)acgagaAfaGfaacaasusa	714	UAUUGUUCUUUCUCGUAUUCAGG	916
AD-356938.1	usgscagaUfaAfGfAfaugcuauucaL96	514	usGfsaaua(Ggn)cauucuUfaUfcugcascsg	715	CGUGCAGAUAAGAAUGCUAUUCA	917
AD-355054.1	csasaacuCfuAfUfAfaaguuccucuL96	515	asGfsagga(Agn)cuuuauAfgAfguuugscsu	716	AGCAAACUCUAUAAAGUUCCUCU	918
AD-357748.1	asasgauaUfuGfUfUfcuuucucguaL96	516	usAfscgag(Agn)aagaacAfaUfaucuuscsa	717	UGAAGAUAUUGUUCUUUCUCGUA	919
AD-355704.1	csusgaaaCfuUfCfUfcaugcaugauL96	517	asUfscaug(Cgn)augagaAfgUfuucagsgsu	718	ACCUGAAACUUCUCAUGCAUGAG	920
AD-356946.1	asgsaaugCfuAfUfUfcauaaucacaL96	518	usGfsugau(Tgn)augaauAfgCfauucususa	719	UAAGAAUGCUAUUCAUAAUCACA	921
AD-353499.1	uscsaacaAfaGfUfUfaucaaagcuuL96	519	asAfsgcuu(Tgn)gauaacUfuUfguugasgsg	720	CCUCAACAAAGUUAUCAAAGCUU	922
AD-354076.1	gsasacugAfcGfUfUfacaucauacaL96	520	usGfsuaug(Agn)uguaacGfuCfaguucsasu	721	AUGAACUGACGUUACAUCAUACA	923
AD-356630.1	cscsugaaAfuCfCfUfgcuuuagucuL96	521	asGfsacua(Agn)agcaggAfuUfucaggsusa	722	UACCUGAAAUCCUGCUUUAGUCG	924
AD-353351.1	csasuuguCfuGfAfCfaauaugugaaL96	522	usUfscaca(Tgn)auugucAfgAfcaaugsasu	723	AUCAUUGUCUGACAAUAUGUGAA	925
AD-359803.1	csasgucgUfaCfUfCfaguuugaagaL96	523	usCfsuuca(Agn)acugagUfaCfgacugsgsu	724	ACCAGUCGUACUCAGUUUGAAGA	926
AD-382526.1	asgscuacUfcAfGfUfcuagucgggguL96	524	asCfsccga(Cgn)uagacuGfaGfuagcusasc	725	GUAGCUACUCAGUCUAGUCGGGC	927
AD-356975.1	ususugaaCfcUfCfUfuguuauaaaaL96	525	usUfsuuau(Agn)acaagaGfgUfucaaascsa	726	UGUUUGAACCUCUUGUUAUAAAA	928
AD-356974.1	gsusuugaAfcCfUfCfuuguuauaaaL96	526	usUfsuaua(Agn)caagagGfuUfcaaacsasa	727	UUGUUUGAACCUCUUGUUAUAAA	929
AD-355117.1	csusugaaCfuAfCfAfucgaucauguL96	527	asCfsauga(Tgn)cgauguAfgUfucaagsasu	728	AUCUUGAACUACAUCGAUCAUGG	930
AD-357755.1	usgsuucuUfuCfUfCfguauucaggaL96	528	usCfscuga(Agn)uacgagAfaAfgaacasasu	729	AUUGUUCUUUCUCGUAUUCAGGA	931
AD-356382.1	gscsagcuUfcUfAfGfacaaucugauL96	529	asUfscaga(Tgn)ugucuaGfaAfgcugcsasc	730	GUGCAGCUUCUAGACAAUCUGAU	932
AD-356973.1	usgsuuugAfaCfCfUfcuuguuauaaL96	530	usUfsauaa(Cgn)aagaggUfuCfaaacasasa	731	UUUGUUUGAACCUCUUGUUAUAA	933
AD-358488.1	gsasaaacCfuUfUfCfaacuccaacuL96	531	asGfsuugg(Agn)guugaaAfgGfuuuucsasc	732	GUGAAAACCUUUCAACUCCAACC	934
AD-354078.1	ascsugacGfuUfAfCfaucauacacaL96	532	usGfsugua(Tgn)gauguaAfcGfucagususc	733	GAACUGACGUUACAUCAUACACA	935
AD-356638.1	cscsugcuUfuAfGfUfcgagaaccaaL96	533	usUfsgguu(Cgn)ucgacuAfaAfgcaggsasu	734	AUCCUGCUUUAGUCGAGAACCAA	936
AD-357096.1	usgsgauuCfaGfAfUfcagguguuuaL96	534	usAfsaaca(Cgn)cugaucUfgAfauccasgsa	735	UCUGGAUUCAGAUCAGGUGUUUA	937
AD-361492.1	csusgcugAfcUfUfGfuuuacgaaauL96	535	asUfsuucg(Tgn)aaacaaGfuCfagcagscsc	736	GGCUGCUGACUUGUUUACGAAAU	938
AD-382775.1	usgsguguUfgAfUfGfcacucuccuaL96	536	usAfsggag(Agn)gugcauCfaAfcaccasgsg	737	CCUGGUGUUGAUGCACUCUCCUA	939
AD-357239.1	csasgaucAfuUfGfGfaauuccuaaaL96	537	usUfsuagg(Agn)auuccaAfuGfaucugsusu	738	AACAGAUCAUUGGAAUUCCUAAA	940
AD-357756.1	gsusucuuUfcUfCfGfuauucaggauL96	538	asUfsccug(Agn)auacgaGfaAfagaacsasa	739	UUGUUCUUUCUCGUAUUCAGGAG	941
AD-356384.1	asgscuucUfaGfAfCfaaucugauauL96	539	asUfsauca(Ggn)auugucUfaGfaagcusgsc	740	GCAGCUUCUAGACAAUCUGAUAC	942

Duplex ID	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-357879.1	asusuuucAfaGfGfUfuucuauuacaL96	540	usGfsuaau(Agn)gaaaccUfuGfaaaausgsu	741	ACAUUUUCAAGGUUUCUAUUACA	943
AD-356386.1	csusucuaGfaCfAfAfucugauaccuL96	541	asGfsguau(Cgn)agauugUfcUfagaagscsu	742	AGCUUCUAGACAAUCUGAUACCU	944
AD-356995.1	asgscuuuAfaAfAfCfaguacacgauL96	542	asUfscgug(Tgn)acuguuUfuAfaagcususu	743	AAAGCUUUAAAACAGUACACGAC	945
AD-353516.1	gscsuuugAfuGfGfAfuucuaaucuuL96	543	asAfsgauu(Agn)gaauccAfuCfaaagcsusu	744	AAGCUUUGAUGGAUUCUAAUCUU	946
AD-354079.1	csusgacgUfuAfCfAfucauacacauL96	544	asUfsgugu(Agn)ugauguAfaCfgucagsusu	745	AACUGACGUUACAUCAUACACAG	947
AD-356639.1	csusgcuuUfaGfUfCfgagaaccaauL96	545	asUfsuggu(Tgn)cucgacUfaAfagcagsgsa	746	UCCUGCUUUAGUCGAGAACCAAU	948
AD-357649.1	usgsuucgUfcAfCfUfccaaacacaaL96	546	usUfsgugu(Tgn)uggaguGfaCfgaacasusa	747	UAUGUUCGUCACUCCAAACACAA	949
AD-361496.1	usgsacuuGfuUfUfAfcgaaaugucuL96	547	asGfsacau(Tgn)ucguaaAfcAfagucasgsc	748	GCUGACUUGUUUACGAAAUGUCC	950
AD-382777.1	gsusguugAfuGfCfAfcucuccuaguL96	548	asCfsuagg(Agn)gagugcAfuCfaacacscsa	749	UGGUGUUGAUGCACUCUCCUAGU	951
AD-353525.1	gsasuucuAfaUfCfUfuccaagguuaL96	549	usAfsaccu(Tgn)ggaagaUfuAfgaaucscsa	750	UGGAUUCUAAUCUUCCAAGGUUA	952
AD-358480.1	csuscguuGfuGfAfAfaaccuuucaaL96	550	usUfsgaaa(Ggn)guuuucAfcAfacgagsasc	751	GUCUCGUUGUGAAAACCUUUCAA	953
AD-356388.1	uscsuagaCfaAfUfCfugauaccucaL96	551	usGfsaggu(Agn)ucagauUfgUfcuagasasg	752	CUUCUAGACAAUCUGAUACCUCA	954
AD-353500.1	csasacaaAfgUfUfAfucaaagcuuuL96	552	asAfsagcu(Tgn)ugauaaCfuUfuguugsasg	753	CUCAACAAAGUUAUCAAAGCUUU	955
AD-356407.1	csasggucCfuGfUfUfacaacaaguaL96	553	usAfscuug(Tgn)uguaacAfgGfaccugsasg	754	CUCAGGUCCUGUUACAACAAGUA	956
AD-357068.1	gsusucagUfuAfCfGfgguuaauuauL96	554	asUfsaauu(Agn)acccguAfaCfugaacscsa	755	UGGUUCAGUUACGGGUUAAUUAC	957
AD-359802.1	cscsagucGfuAfCfUfcaguuugaauL96	555	asUfsucaa(Agn)cugaguAfcGfacuggsusc	756	GACCAGUCGUACUCAGUUUGAAG	958
AD-354638.1	uscsugaaAfuUfGfUfguuagacgguL96	556	asCfscguc(Tgn)aacacaAfuUfucagasasc	757	GUUCUGAAAUUGUGUUAGACGGU	959
AD-356663.1	gsgscaacUfgUfUfUfguguucaacaL96	557	usGfsuuga(Agn)cacaaaCfaGfuugccsasu	758	AUGGCAACUGUUUGUGUUCAACA	960
AD-357651.1	ususcgucAfcUfCfCfaaacacaauuL96	558	asAfsuugu(Ggn)uuuggaGfuGfacgaascsa	759	UGUUCGUCACUCCAAACACAAUG	961
AD-362085.1	csusgacaUfuUfCfCfguuguacauuL96	559	asAfsugua(Cgn)aacggaAfaUfgucagscsg	760	CGCUGACAUUUCCGUUGUACAUG	962
AD-384329.1	cscsacugCfcAfAfGfugcccuuuauL96	560	asUfsaaag(Ggn)gcacuuGfgCfaguggscsu	761	AGCCACUGCCAAGUGCCCUUUAU	963
AD-354067.1	csasgguuUfaUfGfAfacugacguuaL96	561	usAfsacgu(Cgn)aguucaUfaAfaccugsgsa	762	UCCAGGUUUAUGAACUGACGUUA	964
AD-353526.1	asusucuaAfuCfUfUfccaagguuauL96	562	asUfsaacc(Tgn)uggaagAfuUfagaauscsc	763	GGAUUCUAAUCUUCCAAGGUUAC	965
AD-356422.1	csasaguaAfaUfCfCfucaucacuguL96	563	asCfsagug(Agn)ugaggaUfuUfacuugsusu	764	AACAAGUAAAUCCUCAUCACUGG	966
AD-353519.1	ususgaugGfaUfUfCfuaaucuuccaL96	564	usGfsgaag(Agn)uuagaaUfcCfaucaasasg	765	CUUUGAUGGAUUCUAAUCUUCCA	967
AD-356443.1	csusucauAfcCfUfCfaaacugcauuL96	565	asAfsugca(Ggn)uuugagGfuAfugaagsgsa	766	UCCUUCAUACCUCAAACUGCAUG	968
AD-357115.1	usasuuggCfuUfUfGfuauugaaacaL96	566	usGfsuuuc(Agn)auacaaAfgCfcaauasasa	767	UUUAUUGGCUUUGUAUUGAAACA	969

Duplex ID	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-361493.1	usgscugaCfuUfGfUfuuacgaaauuL96	567	asAfsuuuc(Ggn)uaaacaAfgUfcagcasgsc	768	GCUGCUGACUUGUUUACGAAAUG	970
AD-354639.1	csusgaaaUfuGfUfGfuuagacgguaL96	568	usAfsccgu(Cgn)uaacacAfaUfuucagsasa	769	UUCUGAAAUUGUGUUAGACGGUA	971
AD-356955.1	ususcauaAfuCfAfCfauucguuuguL96	569	asCfsaaac(Ggn)aaugugAfuUfaugaasusa	770	UAUUCAUAAUCACAUUCGUUUGU	972
AD-358471.1	csasauucAfgUfCfUfcguugugaaaL96	570	usUfsucac(Agn)acgagaCfuGfaauugscsc	771	GGCAAUUCAGUCUCGUUGUGAAA	973
AD-354066.1	cscsagguUfuAfUfGfaacugacguuL96	571	asAfscguc(Agn)guucauAfaAfccuggsasc	772	GUCCAGGUUUAUGAACUGACGUU	974
AD-384665.1	cscsuccaGfgGfAfUfugguauguguL96	572	asCfsacau(Agn)ccaaucCfcUfggaggsasc	773	GUCCUCCAGGGAUUGGUAUGUGG	975
AD-355045.1	ususucuuCfaGfCfAfaacucuauaaL96	573	usUfsauag(Agn)guuugcUfgAfagaaasgsa	774	UCUUUCUUCAGCAAACUCUAUAA	976
AD-353715.1	usgsuuccCfaAfAfAfuuauggcuuuL96	574	asAfsagcc(Agn)uaauuuUfgGfgaacasgsc	775	GCUGUUCCCAAAAUUAUGGCUUC	977
AD-356429.1	ususucuaUfcAfUfCfuuccuucauaL96	575	usAfsugaa(Ggn)gaagauGfaUfagaaascsu	776	AGUUUCUAUCAUCUUCCUUCAUA	978
AD-359761.1	csusuuaaGfgAfGfUfucaucuaccuL96	576	asGfsguag(Agn)ugaacuCfcUfuaaagsasc	777	GUCUUUAAGGAGUUCAUCUACCG	979
AD-356669.1	usgsuuugUfgUfUfCfaacaauuguuL96	577	asAfscaau(Tgn)guugaaCfaCfaaacasgsu	778	ACUGUUUGUGUUCAACAAUUGUU	980
AD-357684.1	ascsuguuCfaAfCfUfguggauaucuL96	578	asGfsauau(Cgn)cacaguUfgAfacagusgsc	779	GCACUGUUCAACUGUGGAUAUCG	981
AD-361981.1	usasacguAfaCfUfCfuuucuaugcuL96	579	asGfscaua(Ggn)aaagagUfuAfcguuasasa	780	UUUAACGUAACUCUUUCUAUGCC	982
AD-355423.1	uscsugagGfaAfCfAfguuccuauuuL96	580	asAfsauag(Ggn)aacuguUfcCfucagasgsu	781	ACUCUGAGGAACAGUUCCUAUUG	983
AD-356956.1	uscsauaaUfcAfCfAfuucguuuguuL96	581	asAfscaaa(Cgn)gaauguGfaUfuaugasasu	782	AUUCAUAAUCACAUUCGUUUGUU	984
AD-353522.1	asusggauUfcUfAfAfucuuccaaguL96	582	asCfsuugg(Agn)agauuaGfaAfuccauscsa	783	UGAUGGAUUCUAAUCUUCCAAGG	985
AD-354075.1	usgsaacuGfaCfGfUfuacaucauauL96	583	asUfsauga(Tgn)guaacgUfcAfguucasusa	784	UAUGAACUGACGUUACAUCAUAC	986
AD-355059.1	uscsuauaAfaGfUfUfccucuugacaL96	584	usGfsucaa(Ggn)aggaacUfuUfauagasgsu	785	ACUCUAUAAAGUUCCUCUUGACA	987
AD-356951.1	gscsuauuCfaUfAfAfucacauucguL96	585	asCfsgaau(Ggn)ugauuaUfgAfauagcsasu	786	AUGCUAUUCAUAAUCACAUUCGU	988
AD-353871.1	gscsuacuAfaAfUfGfugcucuuaguL96	586	asCfsuaag(Agn)gcacauUfuAfguagcscsa	787	UGGCUACUAAAUGUGCUCUUAGG	989
AD-356996.1	gscsuuuaAfaAfCfCfAfguacacgacuL96	587	asGfsucgu(Ggn)uacuguUfuUfaaagcsusu	788	AAGCUUUAAAACAGUACACGACU	990
AD-354068.1	asgsguuuAfuGfAfAfcugacguuauL96	588	asUfsaacg(Tgn)caguucAfuAfaaccusgsg	789	CCAGGUUUAUGAACUGACGUUAC	991
AD-356678.1	uscsaacaAfuUfGfUfugaagacucuL96	589	asGfsaguc(Tgn)ucaacaAfuUfguugasasc	790	GUUCAACAAUUGUUGAAGACUCU	992
AD-357963.1	gscsaacaUfaCfUfUfucuauugccaL96	590	usGfsgcaa(Tgn)agaaagUfaUfguugcsusg	791	CAGCAACAUACUUUCUAUUGCCA	993
AD-362090.1	asusuuccGfuUfGfUfacauguuccuL96	591	asGfsgaac(Agn)uguacaAfcGfgaaausgsu	792	ACAUUUCCGUUGUACAUGUUCCU	994
AD-355745.1	csusccguCfaGfCfAfcaauaaccauL96	592	asUfsgguu(Agn)uugugcUfgAfcggagsasa	793	UUCUCCGUCAGCACAAUAACCAG	995
AD-357066.1	usgsguucAfgUfUfAfcggguuaauuL96	593	asAfsuuaa(Cgn)ccguaaCfuGfaaccasgsc	794	GCUGGUUCAGUUACGGGUUAAUU	996

Duplex ID	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-353527.1	ususcuaaUfcUfUfCfcaagguuacaL96	594	usGfsuaac(Cgn)uuggaaGfaUfuagaasusc	795	GAUUCUAAUCUUCCAAGGUUACA	997
AD-354236.1	gsasguauUfgUfGfGfaacuuauaguL96	595	asCfsuaua(Agn)guuccaCfaAfuacucscsc	796	GGGAGUAUUGUGGAACUUAUAGC	998
AD-357750.1	gsasuauuGfuUfCfUfuucucguauuL96	596	asAfsuacg(Agn)gaaagaAfcAfauaucsusu	797	AAGAUAUUGUUCUUUCUCGUAUU	999
AD-356389.1	csusagacAfaUfCfUfgauaccucauL96	597	asUfsgagg(Tgn)aucagaUfuGfucuagsasa	798	UUCUAGACAAUCUGAUACCUCAG	1000
AD-354939.1	csgsccuuUfuAfUfCfugcuucguuuL96	598	asAfsacga(Agn)gcagauAfaAfaggcgsgsa	799	UCCGCCUUUUAUCUGCUUCGUUU	1001
AD-357218.1	usasugaaCfgCfUfAfucauucaaaaL96	599	usUfsuuga(Agn)ugauagCfgUfucauasasg	800	CUUAUGAACGCUAUCAUUCAAAA	1002
AD-354640.1	usgsaaauUfgUfGfUfuagacgguauL96	600	asUfsaccg(Tgn)cuaacaCfaAfuuucasgsa	801	UCUGAAAUUGUGUUAGACGGUAC	1003
AD-358018.1	asuscuucAfaGfUfCfuggaauguuuL96	601	asAfsacau(Tgn)ccagacUfuGfaagausgsu	802	ACAUCUUCAAGUCUGGAAUGUUC	1004
AD-362093.1	uscscguuGfuAfCfAfuguuccuguuL96	602	asAfscagg(Agn)acauguAfcAfacggasasa	803	UUUCCGUUGUACAUGUUCCUGUU	1005
AD-356385.1	gscsuucuAfgAfCfAfaucugauacuL96	603	asGfsuauc(Agn)gauuguCfuAfgaagcsusg	804	CAGCUUCUAGACAAUCUGAUACC	1006
AD-357069.1	ususcaguUfaCfGfGfguuaauuacuL96	604	asGfsuaau(Tgn)aacccgUfaAfcugaascsc	805	GGUUCAGUUACGGGUUAAUUACU	1007
AD-358764.1	csasugcaAfgAfCfUfcacuuagucuL96	605	asGfsacua(Agn)gugaguCfuUfgcaugsgsu	806	ACCAUGCAAGACUCACUUAGUCC	1008
AD-354316.1	gsasugacUfcUfGfAfaucgagaucuL96	606	asGfsaucu(Cgn)gauucaGfaGfucaucscsu	807	AGGAUGACUCUGAAUCGAGAUCG	1009
AD-355775.1	asgsgcuaUfaAfCfCfcuacuaccaauL96	607	asUfsuggu(Agn)guagguUfaUfagccuscsu	808	AGAGGCUAUAACCUACUACCAAG	1010
AD-354320.1	ascsucugAfaUfCfGfagaucggauuL96	608	asAfsuccg(Agn)ucucgaUfuCfagaguscsa	809	UGACUCUGAAUCGAGAUCGGAUG	1011
AD-355783.1	ascscuacUfaCfCfAfagcauaacauL96	609	asUfsguua(Tgn)gcuuggUfaGfuaggususa	810	UAACCUACUACCAAGCAUAACAG	1012
AD-354322.1	uscsugaaUfcGfAfGfaucggauguuL96	610	asAfscauc(Cgn)gaucucGfaUfucagasgsu	811	ACUCUGAAUCGAGAUCGGAUGUC	1013
AD-356408.1	asgsguccUfgUfUfAfcaacaaguaaL96	611	usUfsacuu(Ggn)uuguaaCfaGfgaccusgsa	812	UCAGGUCCUGUUACAACAAGUAA	1014
AD-354805.1	ascsagcaGfuGfUfUfgauaaauuugL96	612	csAfsaauu(Tgn)aucaacAfcUfgcuguscsa	813	UGACAGCAGUGUUGAUAAAUUUG	1015
AD-356409.1	gsgsuccuGfuUfAfCfaacaaguaaaL96	613	usUfsuacu(Tgn)guuguaAfcAfggaccsusg	814	CAGGUCCUGUUACAACAAGUAAA	1016
AD-355118.1	ususgaacUfaCfAfUfcgaucauggaL96	614	usCfscaug(Agn)ucgaugUfaGfuucaasgsa	815	UCUUGAACUACAUCGAUCAUGGA	1017
AD-358958.1	ascsucggAfgUfUfCfaaccuaagcuL96	615	asGfscuua(Ggn)guugaaCfuCfcgagususc	816	GAACUCGGAGUUCAACCUAAGCC	1018
AD-355422.1	csuscugaGfgAfAfCfaguuccuauuL96	616	asAfsuagg(Agn)acuguuCfcUfcagagsusc	817	GACUCUGAGGAACAGUUCCUAUU	1019
AD-358959.1	csuscggaGfuUfCfAfaccuaagccuL96	494	asGfsgcuu(Agn)gguugaAfcUfccgagsusu	818	AACUCGGAGUUCAACCUAAGCCU	1020
AD-355424.1	csusgaggAfaCfAfGfuuccuauuguL96	617	asCfsaaua(Ggn)gaacugUfuCfcucagsasg	819	CUCUGAGGAACAGUUCCUAUUGG	1021
AD-379420.2	gscsucggAfgUfUfCfaaccuaagcuL96	482	asGfscuua(Ggn)guugaaCfuCfcgagcsusc	683	GAGCUCGGAGUUCAACCUAAGCC	885
AD-355524.1	asuscauuAfuAfCfAfgggcuuuuaaL96	618	usUfsaaaa(Ggn)cccuguAfuAfaugausgsa	820	UCAUCAUUAUACAGGGCUUUUAA	1022

Duplex ID	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-379380.2	csuscggaGfuUfCfAfaccuaagccuL96	494	asGfsgcuu(Agn)gguugaAfcUfccgagscsu	695	AGGCUUAGGUUGAACUCCGAGCU	292

Table 5. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953583.1	GCUGCCGGGACGGGUCCAA	1023	1-19	UUGGACCCGUCCCGGCAGC	1194	1-19
AD-953591.1	GACGGGUCCAAGAUGGACG	1024	9-27	CGUCCAUCUUGGACCCGUC	1195	9-27
AD-953599.1	CAAGAUGGACGGCCGCUCA	1025	17-35	UGAGCGGCCGUCCAUCUUG	1196	17-35
AD-953607.1	ACGGCCGCUCAGGUUCUGC	1026	25-43	GCAGAACCUGAGCGGCCGU	1197	25-43
AD-953615.1	UCAGGUUCUGCUUUUACCU	1027	33-51	AGGUAAAAGCAGAACCUGA	1198	33-51
AD-953623.1	UGCUUUUACCUGCGGCCCA	1028	41-59	UGGGCCGCAGGUAAAAGCA	1199	41-59
AD-953630.1	ACCUGCGGCCCAGAGCCCC	1029	48-66	GGGGCUCUGGGCCGCAGGU	1200	48-66
AD-953638.1	CCCAGAGCCCCAUUCAUUG	1030	56-74	CAAUGAAUGGGGCUCUGGG	1201	56-74
AD-953646.1	CCCAUUCAUUGCCCCGGUG	1031	64-82	CACCGGGGCAAUGAAUGGG	1202	64-82
AD-953654.1	UUGCCCCGGUGCUGAGCGG	1032	72-90	CCGCUCAGCACCGGGGCAA	1203	72-90
AD-953662.1	GUGCUGAGCGGCGCCGCGA	1033	80-98	UCGCGGCGCCGCUCAGCAC	1204	80-98
AD-953670.1	CGGCGCCGCGAGUCGGCCC	1034	88-106	GGGCCGACUCGCGGCGCCG	1205	88-106
AD-953584.1	CUGCCGGGACGGGUCCAAG	1035	2-20	CUUGGACCCGUCCCGGCAG	1206	2-20
AD-953592.1	ACGGGUCCAAGAUGGACGG	1036	10-28	CCGUCCAUCUUGGACCCGU	1207	10-28
AD-953600.1	AAGAUGGACGGCCGCUCAG	1037	18-36	CUGAGCGGCCGUCCAUCUU	1208	18-36
AD-953608.1	CGGCCGCUCAGGUUCUGCU	1038	26-44	AGCAGAACCUGAGCGGCCG	1209	26-44
AD-953616.1	CAGGUUCUGCUUUUACCUG	1039	34-52	CAGGUAAAAGCAGAACCUG	1210	34-52
AD-953624.1	GCUUUUACCUGCGGCCCAG	1040	42-60	CUGGGCCGCAGGUAAAAGC	1211	42-60
AD-953631.1	CCUGCGGCCCAGAGCCCCA	1041	49-67	UGGGGCUCUGGGCCGCAGG	1212	49-67
AD-953639.1	CCAGAGCCCCAUUCAUUGC	1042	57-75	GCAAUGAAUGGGGCUCUGG	1213	57-75
AD-953647.1	CCAUUCAUUGCCCCGGUGC	1043	65-83	GCACCGGGGCAAUGAAUGG	1214	65-83
AD-953655.1	UGCCCCGGUGCUGAGCGGC	1044	73-91	GCCGCUCAGCACCGGGGCA	1215	73-91

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953663.1	UGCUGAGCGGCGCCGCGAG	1045	81-99	CUCGCGGCGCCGCUCAGCA	1216	81-99
AD-953671.1	GGCGCCGCGAGUCGGCCCG	1046	89-107	CGGGCCGACUCGCGGCGCC	1217	89-107
AD-953585.1	UGCCGGGACGGGUCCAAGA	1047	3-21	UCUUGGACCCGUCCCGGCA	1218	3-21
AD-953593.1	CGGGUCCAAGAUGGACGGC	1048	11-29	GCCGUCCAUCUUGGACCCG	1219	11-29
AD-953601.1	AGAUGGACGGCCGCUCAGG	1049	19-37	CCUGAGCGGCCGUCCAUCU	1220	19-37
AD-953609.1	GGCCGCUCAGGUUCUGCUU	1050	27-45	AAGCAGAACCUGAGCGGCC	1221	27-45
AD-953617.1	AGGUUCUGCUUUUACCUGC	1051	35-53	GCAGGUAAAAGCAGAACCU	1222	35-53
AD-953625.1	CUUUUACCUGCGGCCCAGA	1052	43-61	UCUGGGCCGCAGGUAAAAG	1223	43-61
AD-953632.1	CUGCGGCCCAGAGCCCCAU	1053	50-68	AUGGGGCUCUGGGCCGCAG	1224	50-68
AD-953640.1	CAGAGCCCCAUUCAUUGCC	1054	58-76	GGCAAUGAAUGGGGCUCUG	1225	58-76
AD-953648.1	CAUUCAUUGCCCCGGUGCU	1055	66-84	AGCACCGGGGCAAUGAAUG	1226	66-84
AD-953656.1	GCCCCGGUGCUGAGCGGCG	1056	74-92	CGCCGCUCAGCACCGGGGC	1227	74-92
AD-953664.1	GCUGAGCGGCGCCGCGAGU	1057	82-100	ACUCGCGGCGCCGCUCAGC	1228	82-100
AD-953672.1	GCGCCGCGAGUCGGCCCGA	1058	90-108	UCGGGCCGACUCGCGGCGC	1229	90-108
AD-953586.1	GCCGGGACGGGUCCAAGAU	1059	4-22	AUCUUGGACCCGUCCCGGC	1230	4-22
AD-953594.1	GGGUCCAAGAUGGACGGCC	1060	12-30	GGCCGUCCAUCUUGGACCC	1231	12-30
AD-953602.1	GAUGGACGGCCGCUCAGGU	1061	20-38	ACCUGAGCGGCCGUCCAUC	1232	20-38
AD-953610.1	GCCGCUCAGGUUCUGCUUU	1062	28-46	AAAGCAGAACCUGAGCGGC	1233	28-46
AD-953618.1	GGUUCUGCUUUUACCUGCG	1063	36-54	CGCAGGUAAAAGCAGAACC	1234	36-54
AD-953626.1	UUUUACCUGCGGCCCAGAG	1064	44-62	CUCUGGGCCGCAGGUAAAA	1235	44-62
AD-953633.1	UGCGGCCCAGAGCCCCAUU	1065	51-69	AAUGGGGCUCUGGGCCGCA	1236	51-69
AD-953641.1	AGAGCCCCAUUCAUUGCCC	1066	59-77	GGGCAAUGAAUGGGGCUCU	1237	59-77
AD-953649.1	AUUCAUUGCCCCGGUGCUG	1067	67-85	CAGCACCGGGGCAAUGAAU	1238	67-85
AD-953657.1	CCCCGGUGCUGAGCGGCGC	1068	75-93	GCGCCGCUCAGCACCGGGG	1239	75-93
AD-953665.1	CUGAGCGGCGCCGCGAGUC	1069	83-101	GACUCGCGGCGCCGCUCAG	1240	83-101
AD-953673.1	CGCCGCGAGUCGGCCCGAG	1070	91-109	CUCGGGCCGACUCGCGGCG	1241	91-109
AD-953587.1	CCGGGACGGGUCCAAGAUG	1071	5-23	CAUCUUGGACCCGUCCCGG	1242	5-23
AD-953595.1	GGUCCAAGAUGGACGGCCG	1072	13-31	CGGCCGUCCAUCUUGGACC	1243	13-31

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953603.1	AUGGACGGCCGCUCAGGUU	1073	21-39	AACCUGAGCGGCCGUCCAU	1244	21-39
AD-953611.1	CCGCUCAGGUUCUGCUUUU	1074	29-47	AAAAGCAGAACCUGAGCGG	1245	29-47
AD-953619.1	GUUCUGCUUUUACCUGCGG	1075	37-55	CCGCAGGUAAAAGCAGAAC	1246	37-55
AD-953627.1	UUUACCUGCGGCCCAGAGC	1076	45-63	GCUCUGGGCCGCAGGUAAA	1247	45-63
AD-953634.1	GCGGCCCAGAGCCCCAUUC	1077	52-70	GAAUGGGGCUCUGGGCCGC	1248	52-70
AD-953642.1	GAGCCCCAUUCAUUGCCCC	1078	60-78	GGGGCAAUGAAUGGGGCUC	1249	60-78
AD-953650.1	UUCAUUGCCCCGGUGCUGA	1079	68-86	UCAGCACCGGGGCAAUGAA	1250	68-86
AD-953658.1	CCCGGUGCUGAGCGGCGCC	1080	76-94	GGCGCCGCUCAGCACCGGG	1251	76-94
AD-953666.1	UGAGCGGCGCCGCGAGUCG	1081	84-102	CGACUCGCGGCGCCGCUCA	1252	84-102
AD-953674.1	GCCGCGAGUCGGCCCGAGG	1082	92-110	CCUCGGGCCGACUCGCGGC	1253	92-110
AD-953588.1	CGGGACGGGUCCAAGAUGG	1083	6-24	CCAUCUUGGACCCGUCCCG	1254	6-24
AD-953596.1	GUCCAAGAUGGACGGCCGC	1084	14-32	GCGGCCGUCCAUCUUGGAC	1255	14-32
AD-953604.1	UGGACGGCCGCUCAGGUUC	1085	22-40	GAACCUGAGCGGCCGUCCA	1256	22-40
AD-953612.1	CGCUCAGGUUCUGCUUUUA	1086	30-48	UAAAAGCAGAACCUGAGCG	1257	30-48
AD-953620.1	UUCUGCUUUUACCUGCGGC	1087	38-56	GCCGCAGGUAAAAGCAGAA	1258	38-56
AD-953628.1	UUACCUGCGGCCCAGAGCC	1088	46-64	GGCUCUGGGCCGCAGGUAA	1259	46-64
AD-953635.1	CGGCCCAGAGCCCCAUUCA	1089	53-71	UGAAUGGGGCUCUGGGCCG	1260	53-71
AD-953643.1	AGCCCCAUUCAUUGCCCCG	1090	61-79	CGGGGCAAUGAAUGGGGCU	1261	61-79
AD-953651.1	UCAUUGCCCCGGUGCUGAG	1091	69-87	CUCAGCACCGGGGCAAUGA	1262	69-87
AD-953659.1	CCGGUGCUGAGCGGCGCCG	1092	77-95	CGGCGCCGCUCAGCACCGG	1263	77-95
AD-953667.1	GAGCGGCGCCGCGAGUCGG	1093	85-103	CCGACUCGCGGCGCCGCUC	1264	85-103
AD-953675.1	CCGCGAGUCGGCCCGAGGC	1094	93-111	GCCUCGGGCCGACUCGCGG	1265	93-111
AD-953589.1	GGGACGGGUCCAAGAUGGA	1095	7-25	UCCAUCUUGGACCCGUCCC	1266	7-25
AD-953597.1	UCCAAGAUGGACGGCCGCU	1096	15-33	AGCGGCCGUCCAUCUUGGA	1267	15-33
AD-953605.1	GGACGGCCGCUCAGGUUCU	1097	23-41	AGAACCUGAGCGGCCGUCC	1268	23-41
AD-953613.1	GCUCAGGUUCUGCUUUUAC	1098	31-49	GUAAAAGCAGAACCUGAGC	1269	31-49
AD-953621.1	UCUGCUUUUACCUGCGGCC	1099	39-57	GGCCGCAGGUAAAAGCAGA	1270	39-57
AD-953629.1	UACCUGCGGCCCAGAGCCC	1100	47-65	GGGCUCUGGGCCGCAGGUA	1271	47-65

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953636.1	GGCCCAGAGCCCCAUUCAU	1101	54-72	AUGAAUGGGGCUCUGGGCC	1272	54-72
AD-953644.1	GCCCCAUUCAUUGCCCCGG	1102	62-80	CCGGGGCAAUGAAUGGGGC	1273	62-80
AD-953652.1	CAUUGCCCCGGUGCUGAGC	1103	70-88	GCUCAGCACCGGGGCAAUG	1274	70-88
AD-953660.1	CGGUGCUGAGCGGCGCCGC	1104	78-96	GCGGCGCCGCUCAGCACCG	1275	78-96
AD-953676.1	CGCGAGUCGGCCCGAGGCC	1105	94-112	GGCCUCGGGCCGACUCGCG	1276	94-112
AD-953590.1	GGACGGGUCCAAGAUGGAC	1106	8-26	GUCCAUCUUGGACCCGUCC	1277	8-26
AD-953598.1	CCAAGAUGGACGGCCGCUC	1107	16-34	GAGCGGCCGUCCAUCUUGG	1278	16-34
AD-953606.1	GACGGCCGCUCAGGUUCUG	1108	24-42	CAGAACCUGAGCGGCCGUC	1279	24-42
AD-953614.1	CUCAGGUUCUGCUUUUACC	1109	32-50	GGUAAAAGCAGAACCUGAG	1280	32-50
AD-953622.1	CUGCUUUUACCUGCGGCCC	1110	40-58	GGGCCGCAGGUAAAAGCAG	1281	40-58
AD-953637.1	GCCCAGAGCCCCAUUCAUU	1111	55-73	AAUGAAUGGGGCUCUGGGC	1282	55-73
AD-953645.1	CCCCAUUCAUUGCCCCGGU	1112	63-81	ACCGGGGCAAUGAAUGGGG	1283	63-81
AD-953653.1	AUUGCCCCGGUGCUGAGCG	1113	71-89	CGCUCAGCACCGGGGCAAU	1284	71-89
AD-953661.1	GGUGCUGAGCGGCGCCGCG	1114	79-97	CGCGGCGCCGCUCAGCACC	1285	79-97
AD-953677.1	GCGAGUCGGCCCGAGGCCU	1115	95-113	AGGCCUCGGGCCGACUCGC	1286	95-113
AD-953685.1	GCCCGAGGCCUCCGGGGAC	1116	103-121	GUCCCCGGAGGCCUCGGGC	1287	103-121
AD-953693.1	CCUCCGGGGACUGCCGUGC	1117	111-129	GCACGGCAGUCCCCGGAGG	1288	111-129
AD-953701.1	GACUGCCGUGCCGGGCGGG	1118	119-137	CCCGCCCGGCACGGCAGUC	1289	119-137
AD-953709.1	UGCCGGGCGGGAGACCGCC	1119	127-145	GGCGGUCUCCCGCCCGGCA	1290	127-145
AD-953717.1	GGGAGACCGCCAUGGCGAC	1120	135-153	GUCGCCAUGGCGGUCUCCC	1291	135-153
AD-953724.1	CGCCAUGGCGACCCUGGAA	1121	142-160	UUCCAGGGUCGCCAUGGCG	1292	142-160
AD-953732.1	CGACCCUGGAAAAGCUGAU	1122	150-168	AUCAGCUUUUCCAGGGUCG	1293	150-168
AD-953702.1	ACUGCCGUGCCGGGCGGGA	1123	120-138	UCCCGCCCGGCACGGCAGU	1294	120-138
AD-953710.1	GCCGGGCGGGAGACCGCCA	1124	128-146	UGGCGGUCUCCCGCCCGGC	1295	128-146
AD-953718.1	GGAGACCGCCAUGGCGACC	1125	136-154	GGUCGCCAUGGCGGUCUCC	1296	136-154
AD-953733.1	GACCCUGGAAAAGCUGAUG	1126	151-169	CAUCAGCUUUUCCAGGGUC	1297	151-169
AD-953741.1	AAAAGCUGAUGAAGGCCUU	1127	159-177	AAGGCCUUCAUCAGCUUUU	1298	159-177
AD-953749.1	AUGAAGGCCUUCGAGUCCC	1128	167-185	GGGACUCGAAGGCCUUCAU	1299	167-185

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953757.1	CUUCGAGUCCCUCAAGUCC	1129	175-193	GGACUUGAGGGACUCGAAG	1300	175-193
AD-953679.1	GAGUCGGCCCGAGGCCUCC	1130	97-115	GGAGGCCUCGGGCCGACUC	1301	97-115
AD-953687.1	CCGAGGCCUCCGGGGACUG	1131	105-123	CAGUCCCCGGAGGCCUCGG	1302	105-123
AD-953695.1	UCCGGGGACUGCCGUGCCG	1132	113-131	CGGCACGGCAGUCCCCGGA	1303	113-131
AD-953703.1	CUGCCGUGCCGGGCGGGAG	1133	121-139	CUCCCGCCCGGCACGGCAG	1304	121-139
AD-953711.1	CCGGGCGGGAGACCGCCAU	1134	129-147	AUGGCGGUCUCCCGCCCGG	1305	129-147
AD-953719.1	GAGACCGCCAUGGCGACCC	1135	137-155	GGGUCGCCAUGGCGGUCUC	1306	137-155
AD-953726.1	CCAUGGCGACCCUGGAAAA	1136	144-162	UUUUCCAGGGUCGCCAUGG	1307	144-162
AD-953734.1	ACCCUGGAAAAGCUGAUGA	1137	152-170	UCAUCAGCUUUUCCAGGGU	1308	152-170
AD-953742.1	AAAGCUGAUGAAGGCCUUC	1138	160-178	GAAGGCCUUCAUCAGCUUU	1309	160-178
AD-953750.1	UGAAGGCCUUCGAGUCCCU	1139	168-186	AGGGACUCGAAGGCCUUCA	1310	168-186
AD-953758.1	UUCGAGUCCCUCAAGUCCU	1140	176-194	AGGACUUGAGGGACUCGAA	1311	176-194
AD-953680.1	AGUCGGCCCGAGGCCUCCG	1141	98-116	CGGAGGCCUCGGGCCGACU	1312	98-116
AD-953688.1	CGAGGCCUCCGGGGACUGC	1142	106-124	GCAGUCCCCGGAGGCCUCG	1313	106-124
AD-953696.1	CCGGGGACUGCCGUGCCGG	1143	114-132	CCGGCACGGCAGUCCCCGG	1314	114-132
AD-953704.1	UGCCGUGCCGGGCGGGAGA	1144	122-140	UCUCCCGCCCGGCACGGCA	1315	122-140
AD-953712.1	CGGGCGGGAGACCGCCAUG	1145	130-148	CAUGGCGGUCUCCCGCCCG	1316	130-148
AD-953720.1	AGACCGCCAUGGCGACCCU	1146	138-156	AGGGUCGCCAUGGCGGUCU	1317	138-156
AD-953727.1	CAUGGCGACCCUGGAAAAG	1147	145-163	CUUUUCCAGGGUCGCCAUG	1318	145-163
AD-953735.1	CCCUGGAAAAGCUGAUGAA	1148	153-171	UUCAUCAGCUUUUCCAGGG	1319	153-171
AD-953743.1	AAGCUGAUGAAGGCCUUCG	1149	161-179	CGAAGGCCUUCAUCAGCUU	1320	161-179
AD-953751.1	GAAGGCCUUCGAGUCCCUC	1150	169-187	GAGGGACUCGAAGGCCUUC	1321	169-187
AD-953759.1	UCGAGUCCCUCAAGUCCUU	1151	177-195	AAGGACUUGAGGGACUCGA	1322	177-195
AD-953681.1	GUCGGCCCGAGGCCUCCGG	1152	99-117	CCGGAGGCCUCGGGCCGAC	1323	99-117
AD-953689.1	GAGGCCUCCGGGGACUGCC	1153	107-125	GGCAGUCCCCGGAGGCCUC	1324	107-125
AD-953697.1	CGGGGACUGCCGUGCCGGG	1154	115-133	CCCGGCACGGCAGUCCCCG	1325	115-133
AD-953705.1	GCCGUGCCGGGCGGGAGAC	1155	123-141	GUCUCCCGCCCGGCACGGC	1326	123-141
AD-953713.1	GGGCGGGAGACCGCCAUGG	1156	131-149	CCAUGGCGGUCUCCCGCCC	1327	131-149

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953721.1	GACCGCCAUGGCGACCCUG	1157	139-157	CAGGGUCGCCAUGGCGGUC	1328	139-157
AD-953728.1	AUGGCGACCCUGGAAAAGC	1158	146-164	GCUUUUCCAGGGUCGCCAU	1329	146-164
AD-953736.1	CCUGGAAAAGCUGAUGAAG	1159	154-172	CUUCAUCAGCUUUUCCAGG	1330	154-172
AD-953744.1	AGCUGAUGAAGGCCUUCGA	1160	162-180	UCGAAGGCCUUCAUCAGCU	1331	162-180
AD-953752.1	AAGGCCUUCGAGUCCCUCA	1161	170-188	UGAGGGACUCGAAGGCCUU	1332	170-188
AD-953760.1	CGAGUCCCUCAAGUCCUUC	1162	178-196	GAAGGACUUGAGGGACUCG	1333	178-196
AD-953682.1	UCGGCCCGAGGCCUCCGGG	1163	100-118	CCCGGAGGCCUCGGGCCGA	1334	100-118
AD-953690.1	AGGCCUCCGGGGACUGCCG	1164	108-126	CGGCAGUCCCCGGAGGCCU	1335	108-126
AD-953698.1	GGGGACUGCCGUGCCGGGC	1165	116-134	GCCCGGCACGGCAGUCCCC	1336	116-134
AD-953706.1	CCGUGCCGGGCGGGAGACC	1166	124-142	GGUCUCCCGCCCGGCACGG	1337	124-142
AD-953714.1	GGCGGGAGACCGCCAUGGC	1167	132-150	GCCAUGGCGGUCUCCCGCC	1338	132-150
AD-953722.1	ACCGCCAUGGCGACCCUGG	1168	140-158	CCAGGGUCGCCAUGGCGGU	1339	140-158
AD-953729.1	UGGCGACCCUGGAAAAGCU	1169	147-165	AGCUUUUCCAGGGUCGCCA	1340	147-165
AD-953737.1	CUGGAAAAGCUGAUGAAGG	1170	155-173	CCUUCAUCAGCUUUUCCAG	1341	155-173
AD-953745.1	GCUGAUGAAGGCCUUCGAG	1171	163-181	CUCGAAGGCCUUCAUCAGC	1342	163-181
AD-953753.1	AGGCCUUCGAGUCCCUCAA	1172	171-189	UUGAGGGACUCGAAGGCCU	1343	171-189
AD-953761.1	GAGUCCCUCAAGUCCUUCC	1173	179-197	GGAAGGACUUGAGGGACUC	1344	179-197
AD-953683.1	CGGCCCGAGGCCUCCGGGG	1174	101-119	CCCCGGAGGCCUCGGGCCG	1345	101-119
AD-953691.1	GGCCUCCGGGGACUGCCGU	1175	109-127	ACGGCAGUCCCCGGAGGCC	1346	109-127
AD-953699.1	GGGACUGCCGUGCCGGGCG	1176	117-135	CGCCCGGCACGGCAGUCCC	1347	117-135
AD-953707.1	CGUGCCGGGCGGGAGACCG	1177	125-143	CGGUCUCCCGCCCGGCACG	1348	125-143
AD-953715.1	GCGGGAGACCGCCAUGGCG	1178	133-151	CGCCAUGGCGGUCUCCCGC	1349	133-151
AD-953723.1	CCGCCAUGGCGACCCUGGA	1179	141-159	UCCAGGGUCGCCAUGGCGG	1350	141-159
AD-953730.1	GGCGACCCUGGAAAAGCUG	1180	148-166	CAGCUUUUCCAGGGUCGCC	1351	148-166
AD-953738.1	UGGAAAAGCUGAUGAAGGC	1181	156-174	GCCUUCAUCAGCUUUUCCA	1352	156-174
AD-953746.1	CUGAUGAAGGCCUUCGAGU	1182	164-182	ACUCGAAGGCCUUCAUCAG	1353	164-182
AD-953754.1	GGCCUUCGAGUCCCUCAAG	1183	172-190	CUUGAGGGACUCGAAGGCC	1354	172-190
AD-953762.1	AGUCCCUCAAGUCCUUCCA	1184	180-198	UGGAAGGACUUGAGGGACU	1355	180-198

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953684.1	GGCCCGAGGCCUCCGGGGA	1185	102-120	UCCCCGGAGGCCUCGGGCC	1356	102-120
AD-953692.1	GCCUCCGGGGACUGCCGUG	1186	110-128	CACGGCAGUCCCCGGAGGC	1357	110-128
AD-953700.1	GGACUGCCGUGCCGGGCGG	1187	118-136	CCGCCCGGCACGGCAGUCC	1358	118-136
AD-953708.1	GUGCCGGGCGGGAGACCGC	1188	126-144	GCGGUCUCCCGCCCGGCAC	1359	126-144
AD-953716.1	CGGGAGACCGCCAUGGCGA	1189	134-152	UCGCCAUGGCGGUCUCCCG	1360	134-152
AD-953731.1	GCGACCCUGGAAAAGCUGA	1190	149-167	UCAGCUUUUCCAGGGUCGC	1361	149-167
AD-953739.1	GGAAAAGCUGAUGAAGGCC	1191	157-175	GGCCUUCAUCAGCUUUUCC	1362	157-175
AD-953747.1	UGAUGAAGGCCUUCGAGUC	1192	165-183	GACUCGAAGGCCUUCAUCA	1363	165-183
AD-953755.1	GCCUUCGAGUCCCUCAAGU	1193	173-191	ACUUGAGGGACUCGAAGGC	1364	173-191

Table 6. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-953583.1	GCUGCCGGGACGGGUCCAAdTdT	1365	UUGGACCCGUCCCGGCAGCdTdT	1536	GCUGCCGGGACGGGUCCAA	1023
AD-953591.1	GACGGGUCCAAGAUGGACGdTdT	1366	CGUCCAUCUUGGACCCGUCdTdT	1537	GACGGGUCCAAGAUGGACG	1024
AD-953599.1	CAAGAUGGACGGCCGCUCAdTdT	1367	UGAGCGGCCGUCCAUCUUGdTdT	1538	CAAGAUGGACGGCCGCUCA	1025
AD-953607.1	ACGGCCGCUCAGGUUCUGCdTdT	1368	GCAGAACCUGAGCGGCCGUdTdT	1539	ACGGCCGCUCAGGUUCUGC	1026
AD-953615.1	UCAGGUUCUGCUUUUACCUdTdT	1369	AGGUAAAAGCAGAACCUGAdTdT	1540	UCAGGUUCUGCUUUUACCU	1027
AD-953623.1	UGCUUUUACCUGCGGCCCAdTdT	1370	UGGGCCGCAGGUAAAAGCAdTdT	1541	UGCUUUUACCUGCGGCCCA	1028
AD-953630.1	ACCUGCGGCCCAGAGCCCCdTdT	1371	GGGGCUCUGGGCCGCAGGUdTdT	1542	ACCUGCGGCCCAGAGCCCC	1029
AD-953638.1	CCCAGAGCCCCAUUCAUUGdTdT	1372	CAAUGAAUGGGGCUCUGGGdTdT	1543	CCCAGAGCCCCAUUCAUUG	1030
AD-953646.1	CCCAUUCAUUGCCCCGGUGdTdT	1373	CACCGGGGCAAUGAAUGGGdTdT	1544	CCCAUUCAUUGCCCCGGUG	1031
AD-953654.1	UUGCCCCGGUGCUGAGCGGdTdT	1374	CCGCUCAGCACCGGGGCAAdTdT	1545	UUGCCCCGGUGCUGAGCGG	1032
AD-953662.1	GUGCUGAGCGGCGCCGCGAdTdT	1375	UCGCGGCGCCGCUCAGCACdTdT	1546	GUGCUGAGCGGCGCCGCGA	1033
AD-953670.1	CGGCGCCGCGAGUCGGCCCdTdT	1376	GGGCCGACUCGCGGCGCCGdTdT	1547	CGGCGCCGCGAGUCGGCCC	1034
AD-953584.1	CUGCCGGGACGGGUCCAAGdTdT	1377	CUUGGACCCGUCCCGGCAGdTdT	1548	CUGCCGGGACGGGUCCAAG	1035
AD-953592.1	ACGGGUCCAAGAUGGACGGdTdT	1378	CCGUCCAUCUUGGACCCGUdTdT	1549	ACGGGUCCAAGAUGGACGG	1036

Duplex ID	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-953600.1	AAGAUGGACGGCCGCUCAGdTdT	1379	CUGAGCGGCCGUCCAUCUUdTdT	1550	AAGAUGGACGGCCGCUCAG	1037
AD-953608.1	CGGCCGCUCAGGUUCUGCUdTdT	1380	AGCAGAACCUGAGCGGCCGdTdT	1551	CGGCCGCUCAGGUUCUGCU	1038
AD-953616.1	CAGGUUCUGCUUUUACCUGdTdT	1381	CAGGUAAAAGCAGAACCUGdTdT	1552	CAGGUUCUGCUUUUACCUG	1039
AD-953624.1	GCUUUUACCUGCGGCCCAGdTdT	1382	CUGGGCCGCAGGUAAAAGCdTdT	1553	GCUUUUACCUGCGGCCCAG	1040
AD-953631.1	CCUGCGGCCCAGAGCCCCAdTdT	1383	UGGGGCUCUGGGCCGCAGGdTdT	1554	CCUGCGGCCCAGAGCCCCA	1041
AD-953639.1	CCAGAGCCCCAUUCAUUGCdTdT	1384	GCAAUGAAUGGGGCUCUGGdTdT	1555	CCAGAGCCCCAUUCAUUGC	1042
AD-953647.1	CCAUUCAUUGCCCCGGUGCdTdT	1385	GCACCGGGGCAAUGAAUGGdTdT	1556	CCAUUCAUUGCCCCGGUGC	1043
AD-953655.1	UGCCCCGGUGCUGAGCGGCdTdT	1386	GCCGCUCAGCACCGGGGCAdTdT	1557	UGCCCCGGUGCUGAGCGGC	1044
AD-953663.1	UGCUGAGCGGCGCCGCGAGdTdT	1387	CUCGCGGCGCCGCUCAGCAdTdT	1558	UGCUGAGCGGCGCCGCGAG	1045
AD-953671.1	GGCGCCGCGAGUCGGCCCGdTdT	1388	CGGGCCGACUCGCGGCGCCdTdT	1559	GGCGCCGCGAGUCGGCCCG	1046
AD-953585.1	UGCCGGGACGGGUCCAAGAdTdT	1389	UCUUGGACCCGUCCCGGCAdTdT	1560	UGCCGGGACGGGUCCAAGA	1047
AD-953593.1	CGGGUCCAAGAUGGACGGCdTdT	1390	GCCGUCCAUCUUGGACCCGdTdT	1561	CGGGUCCAAGAUGGACGGC	1048
AD-953601.1	AGAUGGACGGCCGCUCAGGdTdT	1391	CCUGAGCGGCCGUCCAUCUdTdT	1562	AGAUGGACGGCCGCUCAGG	1049
AD-953609.1	GGCCGCUCAGGUUCUGCUUdTdT	1392	AAGCAGAACCUGAGCGGCCdTdT	1563	GGCCGCUCAGGUUCUGCUU	1050
AD-953617.1	AGGUUCUGCUUUUACCUGCdTdT	1393	GCAGGUAAAAGCAGAACCUdTdT	1564	AGGUUCUGCUUUUACCUGC	1051
AD-953625.1	CUUUUACCUGCGGCCCAGAdTdT	1394	UCUGGGCCGCAGGUAAAAGdTdT	1565	CUUUUACCUGCGGCCCAGA	1052
AD-953632.1	CUGCGGCCCAGAGCCCCAUdTdT	1395	AUGGGGCUCUGGGCCGCAGdTdT	1566	CUGCGGCCCAGAGCCCCAU	1053
AD-953640.1	CAGAGCCCCAUUCAUUGCCdTdT	1396	GGCAAUGAAUGGGGCUCUGdTdT	1567	CAGAGCCCCAUUCAUUGCC	1054
AD-953648.1	CAUUCAUUGCCCCGGUGCUdTdT	1397	AGCACCGGGGCAAUGAAUGdTdT	1568	CAUUCAUUGCCCCGGUGCU	1055
AD-953656.1	GCCCCGGUGCUGAGCGGCGdTdT	1398	CGCCGCUCAGCACCGGGGCdTdT	1569	GCCCCGGUGCUGAGCGGCG	1056
AD-953664.1	GCUGAGCGGCGCCGCGAGUdTdT	1399	ACUCGCGGCGCCGCUCAGCdTdT	1570	GCUGAGCGGCGCCGCGAGU	1057
AD-953672.1	GCGCCGCGAGUCGGCCCGAdTdT	1400	UCGGGCCGACUCGCGGCGCdTdT	1571	GCGCCGCGAGUCGGCCCGA	1058
AD-953586.1	GCCGGGACGGGUCCAAGAUdTdT	1401	AUCUUGGACCCGUCCCGGCdTdT	1572	GCCGGGACGGGUCCAAGAU	1059
AD-953594.1	GGGUCCAAGAUGGACGGCCdTdT	1402	GGCCGUCCAUCUUGGACCCdTdT	1573	GGGUCCAAGAUGGACGGCC	1060
AD-953602.1	GAUGGACGGCCGCUCAGGUdTdT	1403	ACCUGAGCGGCCGUCCAUCdTdT	1574	GAUGGACGGCCGCUCAGGU	1061
AD-953610.1	GCCGCUCAGGUUCUGCUUUdTdT	1404	AAAGCAGAACCUGAGCGGCdTdT	1575	GCCGCUCAGGUUCUGCUUU	1062
AD-953618.1	GGUUCUGCUUUUACCUGCGdTdT	1405	CGCAGGUAAAAGCAGAACCdTdT	1576	GGUUCUGCUUUUACCUGCG	1063

Duplex ID	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-953626.1	UUUUACCUGCGGCCCAGAGdTdT	1406	CUCUGGGCCGCAGGUAAAAdTdT	1577	UUUUACCUGCGGCCCAGAG	1064
AD-953633.1	UGCGGCCCAGAGCCCCAUUdTdT	1407	AAUGGGGCUCUGGGCCGCAdTdT	1578	UGCGGCCCAGAGCCCCAUU	1065
AD-953641.1	AGAGCCCCAUUCAUUGCCCdTdT	1408	GGGCAAUGAAUGGGGCUCUdTdT	1579	AGAGCCCCAUUCAUUGCCC	1066
AD-953649.1	AUUCAUUGCCCCGGUGCUGdTdT	1409	CAGCACCGGGGCAAUGAAUdTdT	1580	AUUCAUUGCCCCGGUGCUG	1067
AD-953657.1	CCCCGGUGCUGAGCGGCGCdTdT	1410	GCGCCGCUCAGCACCGGGGdTdT	1581	CCCCGGUGCUGAGCGGCGC	1068
AD-953665.1	CUGAGCGGCGCCGCGAGUCdTdT	1411	GACUCGCGGCGCCGCUCAGdTdT	1582	CUGAGCGGCGCCGCGAGUC	1069
AD-953673.1	CGCCGCGAGUCGGCCCGAGdTdT	1412	CUCGGGCCGACUCGCGGCGdTdT	1583	CGCCGCGAGUCGGCCCGAG	1070
AD-953587.1	CCGGGACGGGUCCAAGAUGdTdT	1413	CAUCUUGGACCCGUCCCGGdTdT	1584	CCGGGACGGGUCCAAGAUG	1071
AD-953595.1	GGUCCAAGAUGGACGGCCGdTdT	1414	CGGCCGUCCAUCUUGGACCdTdT	1585	GGUCCAAGAUGGACGGCCG	1072
AD-953603.1	AUGGACGGCCGCUCAGGUUdTdT	1415	AACCUGAGCGGCCGUCCAUdTdT	1586	AUGGACGGCCGCUCAGGUU	1073
AD-953611.1	CCGCUCAGGUUCUGCUUUUdTdT	1416	AAAAGCAGAACCUGAGCGGdTdT	1587	CCGCUCAGGUUCUGCUUUU	1074
AD-953619.1	GUUCUGCUUUUACCUGCGGdTdT	1417	CCGCAGGUAAAAGCAGAACdTdT	1588	GUUCUGCUUUUACCUGCGG	1075
AD-953627.1	UUUACCUGCGGCCCAGAGCdTdT	1418	GCUCUGGGCCGCAGGUAAAdTdT	1589	UUUACCUGCGGCCCAGAGC	1076
AD-953634.1	GCGGCCCAGAGCCCCAUUCdTdT	1419	GAAUGGGGCUCUGGGCCGCdTdT	1590	GCGGCCCAGAGCCCCAUUC	1077
AD-953642.1	GAGCCCCAUUCAUUGCCCCdTdT	1420	GGGGCAAUGAAUGGGGCUCdTdT	1591	GAGCCCCAUUCAUUGCCCC	1078
AD-953650.1	UUCAUUGCCCCGGUGCUGAdTdT	1421	UCAGCACCGGGGCAAUGAAdTdT	1592	UUCAUUGCCCCGGUGCUGA	1079
AD-953658.1	CCCGGUGCUGAGCGGCGCCdTdT	1422	GGCGCCGCUCAGCACCGGGdTdT	1593	CCCGGUGCUGAGCGGCGCC	1080
AD-953666.1	UGAGCGGCGCCGCGAGUCGdTdT	1423	CGACUCGCGGCGCCGCUCAdTdT	1594	UGAGCGGCGCCGCGAGUCG	1081
AD-953674.1	GCCGCGAGUCGGCCCGAGGdTdT	1424	CCUCGGGCCGACUCGCGGCdTdT	1595	GCCGCGAGUCGGCCCGAGG	1082
AD-953588.1	CGGGACGGGUCCAAGAUGGdTdT	1425	CCAUCUUGGACCCGUCCCGdTdT	1596	CGGGACGGGUCCAAGAUGG	1083
AD-953596.1	GUCCAAGAUGGACGGCCGCdTdT	1426	GCGGCCGUCCAUCUUGGACdTdT	1597	GUCCAAGAUGGACGGCCGC	1084
AD-953604.1	UGGACGGCCGCUCAGGUUCdTdT	1427	GAACCUGAGCGGCCGUCCAdTdT	1598	UGGACGGCCGCUCAGGUUC	1085
AD-953612.1	CGCUCAGGUUCUGCUUUUAdTdT	1428	UAAAAGCAGAACCUGAGCGdTdT	1599	CGCUCAGGUUCUGCUUUUA	1086
AD-953620.1	UUCUGCUUUUACCUGCGGCdTdT	1429	GCCGCAGGUAAAAGCAGAAdTdT	1600	UUCUGCUUUUACCUGCGGC	1087
AD-953628.1	UUACCUGCGGCCCAGAGCCdTdT	1430	GGCUCUGGGCCGCAGGUAAdTdT	1601	UUACCUGCGGCCCAGAGCC	1088
AD-953635.1	CGGCCCAGAGCCCCAUUCAdTdT	1431	UGAAUGGGGCUCUGGGCCGdTdT	1602	CGGCCCAGAGCCCCAUUCA	1089
AD-953643.1	AGCCCCAUUCAUUGCCCCGdTdT	1432	CGGGGCAAUGAAUGGGGCUdTdT	1603	AGCCCCAUUCAUUGCCCCG	1090

Duplex ID	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-953651.1	UCAUUGCCCCGGUGCUGAGdTdT	1433	CUCAGCACCGGGGCAAUGAdTdT	1604	UCAUUGCCCCGGUGCUGAG	1091
AD-953659.1	CCGGUGCUGAGCGGCGCCGdTdT	1434	CGGCGCCGCUCAGCACCGGdTdT	1605	CCGGUGCUGAGCGGCGCCG	1092
AD-953667.1	GAGCGGCGCCGCGAGUCGGdTdT	1435	CCGACUCGCGGCGCCGCUCdTdT	1606	GAGCGGCGCCGCGAGUCGG	1093
AD-953675.1	CCGCGAGUCGGCCCGAGGCdTdT	1436	GCCUCGGGCCGACUCGCGGdTdT	1607	CCGCGAGUCGGCCCGAGGC	1094
AD-953589.1	GGGACGGGUCCAAGAUGGAdTdT	1437	UCCAUCUUGGACCCGUCCCdTdT	1608	GGGACGGGUCCAAGAUGGA	1095
AD-953597.1	UCCAAGAUGGACGGCCGCUdTdT	1438	AGCGGCCGUCCAUCUUGGAdTdT	1609	UCCAAGAUGGACGGCCGCU	1096
AD-953605.1	GGACGGCCGCUCAGGUUCUdTdT	1439	AGAACCUGAGCGGCCGUCCdTdT	1610	GGACGGCCGCUCAGGUUCU	1097
AD-953613.1	GCUCAGGUUCUGCUUUUACdTdT	1440	GUAAAAGCAGAACCUGAGCdTdT	1611	GCUCAGGUUCUGCUUUUAC	1098
AD-953621.1	UCUGCUUUUACCUGCGGCCdTdT	1441	GGCCGCAGGUAAAAGCAGAdTdT	1612	UCUGCUUUUACCUGCGGCC	1099
AD-953629.1	UACCUGCGGCCCAGAGCCCdTdT	1442	GGGCUCUGGGCCGCAGGUAdTdT	1613	UACCUGCGGCCCAGAGCCC	1100
AD-953636.1	GGCCCAGAGCCCCAUUCAUdTdT	1443	AUGAAUGGGGCUCUGGGCCdTdT	1614	GGCCCAGAGCCCCAUUCAU	1101
AD-953644.1	GCCCCAUUCAUUGCCCCGGdTdT	1444	CCGGGGCAAUGAAUGGGGCdTdT	1615	GCCCCAUUCAUUGCCCCGG	1102
AD-953652.1	CAUUGCCCCGGUGCUGAGCdTdT	1445	GCUCAGCACCGGGGCAAUGdTdT	1616	CAUUGCCCCGGUGCUGAGC	1103
AD-953660.1	CGGUGCUGAGCGGCGCCGCdTdT	1446	GCGGCGCCGCUCAGCACCGdTdT	1617	CGGUGCUGAGCGGCGCCGC	1104
AD-953676.1	CGCGAGUCGGCCCGAGGCCdTdT	1447	GGCCUCGGGCCGACUCGCGdTdT	1618	CGCGAGUCGGCCCGAGGCC	1105
AD-953590.1	GGACGGGUCCAAGAUGGACdTdT	1448	GUCCAUCUUGGACCCGUCCdTdT	1619	GGACGGGUCCAAGAUGGAC	1106
AD-953598.1	CCAAGAUGGACGGCCGCUCdTdT	1449	GAGCGGCCGUCCAUCUUGGdTdT	1620	CCAAGAUGGACGGCCGCUC	1107
AD-953606.1	GACGGCCGCUCAGGUUCUGdTdT	1450	CAGAACCUGAGCGGCCGUCdTdT	1621	GACGGCCGCUCAGGUUCUG	1108
AD-953614.1	CUCAGGUUCUGCUUUUACCdTdT	1451	GGUAAAAGCAGAACCUGAGdTdT	1622	CUCAGGUUCUGCUUUUACC	1109
AD-953622.1	CUGCUUUUACCUGCGGCCCdTdT	1452	GGGCCGCAGGUAAAAGCAGdTdT	1623	CUGCUUUUACCUGCGGCCC	1110
AD-953637.1	GCCCAGAGCCCCAUUCAUUdTdT	1453	AAUGAAUGGGGCUCUGGGCdTdT	1624	GCCCAGAGCCCCAUUCAUU	1111
AD-953645.1	CCCCAUUCAUUGCCCCGGUdTdT	1454	ACCGGGGCAAUGAAUGGGGdTdT	1625	CCCCAUUCAUUGCCCCGGU	1112
AD-953653.1	AUUGCCCCGGUGCUGAGCGdTdT	1455	CGCUCAGCACCGGGGCAAUdTdT	1626	AUUGCCCCGGUGCUGAGCG	1113
AD-953661.1	GGUGCUGAGCGGCGCCGCGdTdT	1456	CGCGGCGCCGCUCAGCACCdTdT	1627	GGUGCUGAGCGGCGCCGCG	1114
AD-953677.1	GCGAGUCGGCCCGAGGCCUdTdT	1457	AGGCCUCGGGCCGACUCGCdTdT	1628	GCGAGUCGGCCCGAGGCCU	1115
AD-953685.1	GCCCGAGGCCUCCGGGGACdTdT	1458	GUCCCCGGAGGCCUCGGGCdTdT	1629	GCCCGAGGCCUCCGGGGAC	1116
AD-953693.1	CCUCCGGGGACUGCCGUGCdTdT	1459	GCACGGCAGUCCCCGGAGGdTdT	1630	CCUCCGGGGACUGCCGUGC	1117

Duplex ID	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-953701.1	GACUGCCGUGCCGGGCGGGdTdT	1460	CCCGCCCGGCACGGCAGUCdTdT	1631	GACUGCCGUGCCGGGCGGG	1118
AD-953709.1	UGCCGGGCGGGAGACCGCCdTdT	1461	GGCGGUCUCCCGCCCGGCAdTdT	1632	UGCCGGGCGGGAGACCGCC	1119
AD-953717.1	GGGAGACCGCCAUGGCGACdTdT	1462	GUCGCCAUGGCGGUCUCCCdTdT	1633	GGGAGACCGCCAUGGCGAC	1120
AD-953724.1	CGCCAUGGCGACCCUGGAAdTdT	1463	UUCCAGGGUCGCCAUGGCGdTdT	1634	CGCCAUGGCGACCCUGGAA	1121
AD-953732.1	CGACCCUGGAAAAGCUGAUdTdT	1464	AUCAGCUUUUCCAGGGUCGdTdT	1635	CGACCCUGGAAAAGCUGAU	1122
AD-953702.1	ACUGCCGUGCCGGGCGGGAdTdT	1465	UCCCGCCCGGCACGGCAGUdTdT	1636	ACUGCCGUGCCGGGCGGGA	1123
AD-953710.1	GCCGGGCGGGAGACCGCCAdTdT	1466	UGGCGGUCUCCCGCCCGGCdTdT	1637	GCCGGGCGGGAGACCGCCA	1124
AD-953718.1	GGAGACCGCCAUGGCGACCdTdT	1467	GGUCGCCAUGGCGGUCUCCdTdT	1638	GGAGACCGCCAUGGCGACC	1125
AD-953733.1	GACCCUGGAAAAGCUGAUGdTdT	1468	CAUCAGCUUUUCCAGGGUCdTdT	1639	GACCCUGGAAAAGCUGAUG	1126
AD-953741.1	AAAAGCUGAUGAAGGCCUUdTdT	1469	AAGGCCUUCAUCAGCUUUUdTdT	1640	AAAAGCUGAUGAAGGCCUU	1127
AD-953749.1	AUGAAGGCCUUCGAGUCCCdTdT	1470	GGGACUCGAAGGCCUUCAUdTdT	1641	AUGAAGGCCUUCGAGUCCC	1128
AD-953757.1	CUUCGAGUCCCUCAAGUCCdTdT	1471	GGACUUGAGGGACUCGAAGdTdT	1642	CUUCGAGUCCCUCAAGUCC	1129
AD-953679.1	GAGUCGGCCCGAGGCCUCCdTdT	1472	GGAGGCCUCGGGCCGACUCdTdT	1643	GAGUCGGCCCGAGGCCUCC	1130
AD-953687.1	CCGAGGCCUCCGGGGACUGdTdT	1473	CAGUCCCCGGAGGCCUCGGdTdT	1644	CCGAGGCCUCCGGGGACUG	1131
AD-953695.1	UCCGGGGACUGCCGUGCCGdTdT	1474	CGGCACGGCAGUCCCCGGAdTdT	1645	UCCGGGGACUGCCGUGCCG	1132
AD-953703.1	CUGCCGUGCCGGGCGGGAGdTdT	1475	CUCCCGCCCGGCACGGCAGdTdT	1646	CUGCCGUGCCGGGCGGGAG	1133
AD-953711.1	CCGGGCGGGAGACCGCCAUdTdT	1476	AUGGCGGUCUCCCGCCCGGdTdT	1647	CCGGGCGGGAGACCGCCAU	1134
AD-953719.1	GAGACCGCCAUGGCGACCCdTdT	1477	GGGUCGCCAUGGCGGUCUCdTdT	1648	GAGACCGCCAUGGCGACCC	1135
AD-953726.1	CCAUGGCGACCCUGGAAAAdTdT	1478	UUUUCCAGGGUCGCCAUGGdTdT	1649	CCAUGGCGACCCUGGAAAA	1136
AD-953734.1	ACCCUGGAAAAGCUGAUGAdTdT	1479	UCAUCAGCUUUUCCAGGGUdTdT	1650	ACCCUGGAAAAGCUGAUGA	1137
AD-953742.1	AAAGCUGAUGAAGGCCUUCdTdT	1480	GAAGGCCUUCAUCAGCUUUdTdT	1651	AAAGCUGAUGAAGGCCUUC	1138
AD-953750.1	UGAAGGCCUUCGAGUCCCUdTdT	1481	AGGGACUCGAAGGCCUUCAdTdT	1652	UGAAGGCCUUCGAGUCCCU	1139
AD-953758.1	UUCGAGUCCCUCAAGUCCUdTdT	1482	AGGACUUGAGGGACUCGAAdTdT	1653	UUCGAGUCCCUCAAGUCCU	1140
AD-953680.1	AGUCGGCCCGAGGCCUCCGdTdT	1483	CGGAGGCCUCGGGCCGACUdTdT	1654	AGUCGGCCCGAGGCCUCCG	1141
AD-953688.1	CGAGGCCUCCGGGGACUGCdTdT	1484	GCAGUCCCCGGAGGCCUCGdTdT	1655	CGAGGCCUCCGGGGACUGC	1142
AD-953696.1	CCGGGGACUGCCGUGCCGGdTdT	1485	CCGGCACGGCAGUCCCCGGdTdT	1656	CCGGGGACUGCCGUGCCGG	1143
AD-953704.1	UGCCGUGCCGGGCGGGAGAdTdT	1486	UCUCCCGCCCGGCACGGCAdTdT	1657	UGCCGUGCCGGGCGGGAGA	1144

Duplex ID	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-953712.1	CGGGCGGGAGACCGCCAUGdTdT	1487	CAUGGCGGUCUCCCGCCCGdTdT	1658	CGGGCGGGAGACCGCCAUG	1145
AD-953720.1	AGACCGCCAUGGCGACCCUdTdT	1488	AGGGUCGCCAUGGCGGUCUdTdT	1659	AGACCGCCAUGGCGACCCU	1146
AD-953727.1	CAUGGCGACCCUGGAAAAGdTdT	1489	CUUUUCCAGGGUCGCCAUGdTdT	1660	CAUGGCGACCCUGGAAAAG	1147
AD-953735.1	CCCUGGAAAAGCUGAUGAAdTdT	1490	UUCAUCAGCUUUUCCAGGGdTdT	1661	CCCUGGAAAAGCUGAUGAA	1148
AD-953743.1	AAGCUGAUGAAGGCCUUCGdTdT	1491	CGAAGGCCUUCAUCAGCUUdTdT	1662	AAGCUGAUGAAGGCCUUCG	1149
AD-953751.1	GAAGGCCUUCGAGUCCCUCdTdT	1492	GAGGGACUCGAAGGCCUUCdTdT	1663	GAAGGCCUUCGAGUCCCUC	1150
AD-953759.1	UCGAGUCCCUCAAGUCCUUdTdT	1493	AAGGACUUGAGGGACUCGAdTdT	1664	UCGAGUCCCUCAAGUCCUU	1151
AD-953681.1	GUCGGCCCGAGGCCUCCGGdTdT	1494	CCGGAGGCCUCGGGCCGACdTdT	1665	GUCGGCCCGAGGCCUCCGG	1152
AD-953689.1	GAGGCCUCCGGGGACUGCCdTdT	1495	GGCAGUCCCCGGAGGCCUCdTdT	1666	GAGGCCUCCGGGGACUGCC	1153
AD-953697.1	CGGGGACUGCCGUGCCGGGdTdT	1496	CCCGGCACGGCAGUCCCCGdTdT	1667	CGGGGACUGCCGUGCCGGG	1154
AD-953705.1	GCCGUGCCGGGCGGGAGACdTdT	1497	GUCUCCCGCCCGGCACGGCdTdT	1668	GCCGUGCCGGGCGGGAGAC	1155
AD-953713.1	GGGCGGGAGACCGCCAUGGdTdT	1498	CCAUGGCGGUCUCCCGCCCdTdT	1669	GGGCGGGAGACCGCCAUGG	1156
AD-953721.1	GACCGCCAUGGCGACCCUGdTdT	1499	CAGGGUCGCCAUGGCGGUCdTdT	1670	GACCGCCAUGGCGACCCUG	1157
AD-953728.1	AUGGCGACCCUGGAAAAGCdTdT	1500	GCUUUUCCAGGGUCGCCAUdTdT	1671	AUGGCGACCCUGGAAAAGC	1158
AD-953736.1	CCUGGAAAAGCUGAUGAAGdTdT	1501	CUUCAUCAGCUUUUCCAGGdTdT	1672	CCUGGAAAAGCUGAUGAAG	1159
AD-953744.1	AGCUGAUGAAGGCCUUCGAdTdT	1502	UCGAAGGCCUUCAUCAGCUdTdT	1673	AGCUGAUGAAGGCCUUCGA	1160
AD-953752.1	AAGGCCUUCGAGUCCCUCAdTdT	1503	UGAGGGACUCGAAGGCCUUdTdT	1674	AAGGCCUUCGAGUCCCUCA	1161
AD-953760.1	CGAGUCCCUCAAGUCCUUCdTdT	1504	GAAGGACUUGAGGGACUCGdTdT	1675	CGAGUCCCUCAAGUCCUUC	1162
AD-953682.1	UCGGCCCGAGGCCUCCGGGdTdT	1505	CCCGGAGGCCUCGGGCCGAdTdT	1676	UCGGCCCGAGGCCUCCGGG	1163
AD-953690.1	AGGCCUCCGGGGACUGCCGdTdT	1506	CGGCAGUCCCCGGAGGCCUdTdT	1677	AGGCCUCCGGGGACUGCCG	1164
AD-953698.1	GGGGACUGCCGUGCCGGGCdTdT	1507	GCCCGGCACGGCAGUCCCCdTdT	1678	GGGGACUGCCGUGCCGGGC	1165
AD-953706.1	CCGUGCCGGGCGGGAGACCdTdT	1508	GGUCUCCCGCCCGGCACGGdTdT	1679	CCGUGCCGGGCGGGAGACC	1166
AD-953714.1	GGCGGGAGACCGCCAUGGCdTdT	1509	GCCAUGGCGGUCUCCCGCCdTdT	1680	GGCGGGAGACCGCCAUGGC	1167
AD-953722.1	ACCGCCAUGGCGACCCUGGdTdT	1510	CCAGGGUCGCCAUGGCGGUdTdT	1681	ACCGCCAUGGCGACCCUGG	1168
AD-953729.1	UGGCGACCCUGGAAAAGCUdTdT	1511	AGCUUUUCCAGGGUCGCCAdTdT	1682	UGGCGACCCUGGAAAAGCU	1169
AD-953737.1	CUGGAAAAGCUGAUGAAGGdTdT	1512	CCUUCAUCAGCUUUUCCAGdTdT	1683	CUGGAAAAGCUGAUGAAGG	1170
AD-953745.1	GCUGAUGAAGGCCUUCGAGdTdT	1513	CUCGAAGGCCUUCAUCAGCdTdT	1684	GCUGAUGAAGGCCUUCGAG	1171

Duplex ID	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-953753.1	AGGCCUUCGAGUCCCUCAAdTdT	1514	UUGAGGGACUCGAAGGCCUdTdT	1685	AGGCCUUCGAGUCCCUCAA	1172
AD-953761.1	GAGUCCCUCAAGUCCUUCCdTdT	1515	GGAAGGACUUGAGGGACUCdTdT	1686	GAGUCCCUCAAGUCCUUCC	1173
AD-953683.1	CGGCCCGAGGCCUCCGGGGdTdT	1516	CCCCGGAGGCCUCGGGCCGdTdT	1687	CGGCCCGAGGCCUCCGGGG	1174
AD-953691.1	GGCCUCCGGGGACUGCCGUdTdT	1517	ACGGCAGUCCCCGGAGGCCdTdT	1688	GGCCUCCGGGGACUGCCGU	1175
AD-953699.1	GGGACUGCCGUGCCGGGCGdTdT	1518	CGCCCGGCACGGCAGUCCCdTdT	1689	GGGACUGCCGUGCCGGGCG	1176
AD-953707.1	CGUGCCGGGCGGGAGACCGdTdT	1519	CGGUCUCCCGCCCGGCACGdTdT	1690	CGUGCCGGGCGGGAGACCG	1177
AD-953715.1	GCGGGAGACCGCCAUGGCGdTdT	1520	CGCCAUGGCGGUCUCCCGCdTdT	1691	GCGGGAGACCGCCAUGGCG	1178
AD-953723.1	CCGCCAUGGCGACCCUGGAdTdT	1521	UCCAGGGUCGCCAUGGCGGdTdT	1692	CCGCCAUGGCGACCCUGGA	1179
AD-953730.1	GGCGACCCUGGAAAAGCUGdTdT	1522	CAGCUUUUCCAGGGUCGCCdTdT	1693	GGCGACCCUGGAAAAGCUG	1180
AD-953738.1	UGGAAAAGCUGAUGAAGGCdTdT	1523	GCCUUCAUCAGCUUUUCCAdTdT	1694	UGGAAAAGCUGAUGAAGGC	1181
AD-953746.1	CUGAUGAAGGCCUUCGAGUdTdT	1524	ACUCGAAGGCCUUCAUCAGdTdT	1695	CUGAUGAAGGCCUUCGAGU	1182
AD-953754.1	GGCCUUCGAGUCCCUCAAGdTdT	1525	CUUGAGGGACUCGAAGGCCdTdT	1696	GGCCUUCGAGUCCCUCAAG	1183
AD-953762.1	AGUCCCUCAAGUCCUUCCAdTdT	1526	UGGAAGGACUUGAGGGACUdTdT	1697	AGUCCCUCAAGUCCUUCCA	1184
AD-953684.1	GGCCCGAGGCCUCCGGGGAdTdT	1527	UCCCCGGAGGCCUCGGGCCdTdT	1698	GGCCCGAGGCCUCCGGGGA	1185
AD-953692.1	GCCUCCGGGGACUGCCGUGdTdT	1528	CACGGCAGUCCCCGGAGGCdTdT	1699	GCCUCCGGGGACUGCCGUG	1186
AD-953700.1	GGACUGCCGUGCCGGGCGGdTdT	1529	CCGCCCGGCACGGCAGUCCdTdT	1700	GGACUGCCGUGCCGGGCGG	1187
AD-953708.1	GUGCCGGGCGGGAGACCGCdTdT	1530	GCGGUCUCCCGCCCGGCACdTdT	1701	GUGCCGGGCGGGAGACCGC	1188
AD-953716.1	CGGGAGACCGCCAUGGCGAdTdT	1531	UCGCCAUGGCGGUCUCCCGdTdT	1702	CGGGAGACCGCCAUGGCGA	1189
AD-953731.1	GCGACCCUGGAAAAGCUGAdTdT	1532	UCAGCUUUUCCAGGGUCGCdTdT	1703	GCGACCCUGGAAAAGCUGA	1190
AD-953739.1	GGAAAAGCUGAUGAAGGCCdTdT	1533	GGCCUUCAUCAGCUUUUCCdTdT	1704	GGAAAAGCUGAUGAAGGCC	1191
AD-953747.1	UGAUGAAGGCCUUCGAGUCdTdT	1534	GACUCGAAGGCCUUCAUCAdTdT	1705	UGAUGAAGGCCUUCGAGUC	1192
AD-953755.1	GCCUUCGAGUCCCUCAAGUdTdT	1535	ACUUGAGGGACUCGAAGGCdTdT	1706	GCCUUCGAGUCCCUCAAGU	1193

Table 8. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953857.1	UCAUAAUCACAUUCGUUUGUA	1707	4405-4425	UACAAACGAAUGUGAUUAUGAAU	1867	4403-4425
AD-953865.1	UUCAGUUACGGGUUAAUUACA	1708	4518-4538	UGUAAUUAACCCGUAACUGAACC	1868	4516-4538
AD-953873.1	ACUGUCUCGACAGAUAGCUGA	1709	4966-4986	UCAGCUAUCUGUCGAGACAGUCG	1869	4964-4986
AD-953881.1	UUACGGAGUAUGUUCGUCACA	1710	5108-5128	UGUGACGAACAUACUCCGUAAAA	1870	5106-5128
AD-953889.1	GCAACAUACUUUCUAUUGCCA	187	5452-5472	UGGCAAUAGAAAGUAUGUUGCUG	1871	5450-5472
AD-953897.1	ACUCCGAGCACUUAACGUGGA	1711	5886-5906	UCCACGUUAAGUGCUCGGAGUCA	1872	5884-5906
AD-953904.1	GCAAUUCAGUCUCGUUGUGAA	1712	6017-6037	UUCACAACGAGACUGAAUUGCCU	1873	6015-6037
AD-953912.1	UGCCUUCAUGAUGAACUCGGA	1713	6547-6567	UCCGAGUUCAUCAUGAAGGCAUU	1874	6545-6567
AD-953920.1	CAACAGCUACACACGUGUGCA	1714	7366-7386	UGCACACGUGUGUAGCUGUUGAC	1875	7364-7386
AD-953928.1	GACGCUGACAGAACUGCGAAA	1715	8317-8337	UUUCGCAGUUCUGUCAGCGUCAC	1876	8315-8337
AD-953936.1	CUGACUUGUUUACGAAAUGUA	1716	9539-9559	UACAUUUCGUAAACAAGUCAGCA	1877	9537-9559
AD-953858.1	AUCACAUUCGUUUGUUUGAAA	1717	4410-4430	UUUCAAACAAACGAAUGUGAUUA	1878	4408-4430
AD-953866.1	CAGUUACGGGUUAAUUACUGA	1718	4520-4540	UCAGUAAUUAACCCGUAACUGAA	1879	4518-4540
AD-953874.1	AAGCCCUUGGAGUGUUAAAUA	1719	5037-5057	UAUUUAACACUCCAAGGGCUUCA	1880	5035-5057
AD-953882.1	UCUGAUUUCCCAGUCAACUGA	1720	5197-5217	UCAGUUGACUGGGAAAUCAGAAC	1881	5195-5217
AD-953890.1	AUCUUCAAGUCUGGAAUGUUA	1721	5507-5527	UAACAUUCCAGACUUGAAGAUGU	1882	5505-5527
AD-953898.1	AUCCAGGCAAUUCAGUCUCGA	1722	6011-6031	UCGAGACUGAAUUGCCUGGAUGA	1883	6009-6031
AD-953905.1	AUGGUCGACAUCCUUGCUUGA	1723	6170-6190	UCAAGCAAGGAUGUCGACCAUGC	1884	6168-6190
AD-953913.1	CUUCAUGAUGAACUCGGAGUA	1724	6550-6570	UACUCCGAGUUCAUCAUGAAGGC	1885	6548-6570
AD-953921.1	GACCAGUCGUACUCAGUUUGA	1725	7525-7545	UCAAACUGAGUACGACUGGUCCA	1886	7523-7545
AD-953929.1	ACGCUGACAGAACUGCGAAGA	1726	8318-8338	UCUUCGCAGUUCUGUCAGCGUCA	1887	8316-8338
AD-953937.1	UGACUUGUUUACGAAAUGUCA	1727	9540-9560	UGACAUUUCGUAAACAAGUCAGC	1888	9538-9560
AD-953859.1	UGUUUGAACCUCUUGUUAUAA	127	4422-4442	UUAUAACAAGAGGUUCAAACAAA	328	4420-4442
AD-953867.1	UCAGAUCAGGUGUUUAUUGGA	1728	4550-4570	UCCAAUAAACACCUGAUCUGAAU	1889	4548-4570
AD-953875.1	GCCCUUGGAGUGUUAAAUACA	1729	5039-5059	UGUAUUUAACACUCCAAGGGCUU	1890	5037-5059
AD-953883.1	AAGAUAUUGUUCUUUCUCGUA	113	5217-5237	UACGAGAAAGAACAAUAUCUUCA	314	5215-5237

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953891.1	UCAAGUCUGGAAUGUUCCGGA	1730	5511-5531	UCCGGAACAUUCCAGACUUGAAG	1891	5509-5531
AD-953899.1	UCCAGGCAAUUCAGUCUCGUA	1731	6012-6032	UACGAGACUGAAUUGCCUGGAUG	1892	6010-6032
AD-953906.1	GUCGACAUCCUUGCUUGUCGA	1732	6173-6193	UCGACAAGCAAGGAUGUCGACCA	1893	6171-6193
AD-953914.1	CUGCUAGCUCCAUGCUUAAGA	1733	6581-6601	UCUUAAGCAUGGAGCUAGCAGGC	1894	6579-6601
AD-953922.1	ACCAGUCGUACUCAGUUUGAA	1734	7526-7546	UUCAAACUGAGUACGACUGGUCC	1895	7524-7546
AD-953930.1	GAAAGGAGAAAGUCAGUCCGA	1735	8937-8957	UCGGACUGACUUUCUCCUUUCCU	1896	8935-8957
AD-953938.1	UAACGUAACUCUUUCUAUGCA	1736	10173-10193	UGCAUAGAAAGAGUUACGUUAAA	1897	10171-10193
AD-953860.1	GUUUGAACCUCUUGUUAUAAA	123	4423-4443	UUUAUAACAAGAGGUUCAAACAA	324	4421-4443
AD-953868.1	UUGGCUUUGUAUUGAAACAGA	1737	4566-4586	UCUGUUUCAAUACAAAGCCAAUA	1898	4564-4586
AD-953876.1	UAGACAUGCUUUUACGGAGUA	1738	5097-5117	UACUCCGUAAAAGCAUGUCUACC	1899	5095-5117
AD-953884.1	GAUAUUGUUCUUUCUCGUAUA	1739	5219-5239	UAUACGAGAAAGAACAAUAUCUU	1900	5217-5239
AD-953892.1	CAAGUCUGGAAUGUUCCGGAA	1740	5512-5532	UUCCGGAACAUUCCAGACUUGAA	1901	5510-5532
AD-953900.1	CCAGGCAAUUCAGUCUCGUUA	1741	6013-6033	UAACGAGACUGAAUUGCCUGGAU	1902	6011-6033
AD-953907.1	CAUGCAAGACUCACUUAGUCA	1742	6349-6369	UGACUAAGUGAGUCUUGCAUGGU	1903	6347-6369
AD-953915.1	UGCUAGCUCCAUGCUUAAGCA	1743	6582-6602	UGCUUAAGCAUGGAGCUAGCAGG	1904	6580-6602
AD-953923.1	CCAGUCGUACUCAGUUUGAAA	1744	7527-7547	UUUCAAACUGAGUACGACUGGUC	1905	7525-7547
AD-953931.1	AGAACUUCAGACCCUAAUCCA	1745	8960-8980	UGGAUUAGGGUCUGAAGUUCUAC	1906	8958-8980
AD-953939.1	UCUAUGCCCGUGUAAAGUAUA	1746	10186-10206	UAUACUUUACACGGGCAUAGAAA	1907	10184-10206
AD-953861.1	UUUGAACCUCUUGUUAUAAAA	122	4424-4444	UUUUAUAACAAGAGGUUCAAACA	323	4422-4444
AD-953869.1	UUAUGAACGCUAUCAUUCAAA	1747	4666-4686	UUUGAAUGAUAGCGUUCAUAAGA	1908	4664-4686
AD-953877.1	ACAUGCUUUUACGGAGUAUGA	1748	5100-5120	UCAUACUCCGUAAAAGCAUGUCU	1909	5098-5120
AD-953885.1	UUGUUCUUUCUCGUAUUCAGA	1749	5223-5243	UCUGAAUACGAGAAAGAACAAUA	1910	5221-5243
AD-953893.1	AGCACAAAGUUACUUAGUCCA	1750	5744-5764	UGGACUAAGUAACUUUGUGCUGG	1911	5742-5764
AD-953901.1	CAGGCAAUUCAGUCUCGUUGA	1751	6014-6034	UCAACGAGACUGAAUUGCCUGGA	1912	6012-6034
AD-953908.1	AUGCAAGACUCACUUAGUCCA	1752	6350-6370	UGGACUAAGUGAGUCUUGCAUGG	1913	6348-6370
AD-953916.1	ACUGGAGCAAGUUGAAUGAUA	1753	6753-6773	UAUCAUUCAACUUGCUCCAGUAG	1914	6751-6773
AD-953924.1	CAGUCGUACUCAGUUUGAAGA	120	7528-7548	UCUUCAAACUGAGUACGACUGGU	321	7526-7548

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953932.1	UCAUGAACAAAGUCAUCGGAA	1754	9129-9149	UUCCGAUGACUUUGUUCAUGAUG	1915	9127-9149
AD-953940.1	CUAUGCCCGUGUAAAGUAUGA	1755	10187-10207	UCAUACUUUACACGGGCAUAGAA	1916	10185-10207
AD-953862.1	AAGCUUUAAAACAGUACACGA	1756	4443-4463	UCGUGUACUGUUUUAAAGCUUUU	1917	4441-4463
AD-953870.1	AACGCUAUCAUUCAAAACAGA	1757	4671-4691	UCUGUUUUGAAUGAUAGCGUUCA	1918	4669-4691
AD-953878.1	CUUUUACGGAGUAUGUUCGUA	1758	5105-5125	UACGAACAUACUCCGUAAAAGCA	1919	5103-5125
AD-953886.1	UGUUCUUUCUCGUAUUCAGGA	125	5224-5244	UCCUGAAUACGAGAAAGAACAAU	326	5222-5244
AD-953894.1	AGAGGAGGAUUCUGACUUGGA	1759	5779-5799	UCCAAGUCAGAAUCCUCCUCUUC	1920	5777-5799
AD-953902.1	AGGCAAUUCAGUCUCGUUGUA	1760	6015-6035	UACAACGAGACUGAAUUGCCUGG	1921	6013-6035
AD-953909.1	CACUGGAAACAGUGAGUCCGA	1761	6417-6437	UCGGACUCACUGUUUCCAGUGAC	1922	6415-6437
AD-953917.1	UGUCAACAGCUACACACGUGA	1762	7363-7383	UCACGUGUGUAGCUGUUGACAAG	1923	7361-7383
AD-953925.1	AAGCUGAGCAUUAUCAGAGGA	1763	7787-7807	UCCUCUGAUAAUGCUCAGCUUCC	1924	7785-7807
AD-953933.1	CGGCUGCUGACUUGUUUACGA	1764	9533-9553	UCGUAAACAAGUCAGCAGCCGGU	1925	9531-9553
AD-953941.1	CCGCUGACAUUUCCGUUGUAA	1765	10311-10331	UUACAACGGAAAUGUCAGCGGGU	1926	10309-10331
AD-953863.1	AGCUGGUUCAGUUACGGGUUA	1766	4512-4532	UAACCCGUAACUGAACCAGCUGC	1927	4510-4532
AD-953871.1	GUGGAAGCGACUGUCUCGACA	1767	4957-4977	UGUCGAGACAGUCGCUUCCACUU	1928	4955-4977
AD-953879.1	UUUUACGGAGUAUGUUCGUCA	1768	5106-5126	UGACGAACAUACUCCGUAAAAGC	1929	5104-5126
AD-953887.1	AUUUUCAAGGUUUCUAUUACA	137	5368-5388	UGUAAUAGAAACCUUGAAAAUGU	338	5366-5388
AD-953895.1	CAAUAGAGAAAUAGUACGAAA	1769	5818-5838	UUUCGUACUAUUUCUCUAUUGCA	1930	5816-5838
AD-953903.1	GGCAAUUCAGUCUCGUUGUGA	1770	6016-6036	UCACAACGAGACUGAAUUGCCUG	1931	6014-6036
AD-953910.1	AGCUGGUGAAUCGGAUUCCUA	1771	6513-6533	UAGGAAUCCGAUUCACCAGCUCU	1932	6511-6533
AD-953918.1	GUCAACAGCUACACACGUGUA	1772	7364-7384	UACACGUGUGUAGCUGUUGACAA	1933	7362-7384
AD-953926.1	UUGAGCUGAUGUAUGUGACGA	1773	8301-8321	UCGUCACAUACAUCAGCUCAAAC	1934	8299-8321
AD-953934.1	GGCUGCUGACUUGUUUACGAA	1774	9534-9554	UUCGUAAACAAGUCAGCAGCCGG	1935	9532-9554
AD-953864.1	GUUCAGUUACGGGUUAAUUAA	1775	4517-4537	UUAAUUAACCCGUAACUGAACCA	1936	4515-4537
AD-953872.1	GACUGUCUCGACAGAUAGCUA	1776	4965-4985	UAGCUAUCUGUCGAGACAGUCGC	1937	4963-4985
AD-953880.1	UUUACGGAGUAUGUUCGUCAA	1777	5107-5127	UUGACGAACAUACUCCGUAAAAG	1938	5105-5127
AD-953888.1	AAGGUUUCUAUUACAACUGGA	1778	5374-5394	UCCAGUUGUAAUAGAAACCUUGA	1939	5372-5394

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953896.1	GACUCCGAGCACUUAACGUGA	1779	5885-5905	UCACGUUAAGUGCUCGGAGUCAU	1940	5883-5905
AD-953911.1	GCUGGUGAAUCGGAUUCCUGA	1780	6514-6534	UCAGGAAUCCGAUUCACCAGCUC	1941	6512-6534
AD-953919.1	UCAACAGCUACACACGUGUGA	1781	7365-7385	UCACACGUGUGUAGCUGUUGACA	1942	7363-7385
AD-953927.1	GAGCUGAUGUAUGUGACGCUA	1782	8303-8323	UAGCGUCACAUACAUCAGCUCAA	1943	8301-8323
AD-953935.1	CUGCUGACUUGUUUACGAAAA	1783	9536-9556	UUUUCGUAAACAAGUCAGCAGCC	1944	9534-9556
AD-953763.1	AGCUACCAAGAAAGACCGUGA	1784	430-450	UCACGGUCUUUCUUGGUAGCUGA	1945	428-450
AD-953771.1	AUUCUAAUCUUCCAAGGUUAA	1785	630-650	UUAACCUUGGAAGAUUAGAAUCC	1946	628-650
AD-953779.1	AGGUUUAUGAACUGACGUUAA	1786	1218-1238	UUAACGUCAGUUCAUAAACCUGG	1947	1216-1238
AD-953787.1	AGUAUUGUGGAACUUAUAGCA	1787	1406-1426	UGCUAUAAGUUCCACAAUACUCC	1948	1404-1426
AD-953795.1	GACUCUGAAUCGAGAUCGGAA	1788	1511-1531	UUCCGAUCUCGAUUCAGAGUCAU	1949	1509-1531
AD-953803.1	ACAGCAGUGUUGAUAAAUUUA	1789	2073-2093	UAAAUUUAUCAACACUGCUGUCA	1950	2071-2093
AD-953810.1	CGCCUUUUAUCUGCUUCGUUA	1790	2207-2227	UAACGAAGCAGAUAAAAGGCGGA	1951	2205-2227
AD-953818.1	CUGAGGAACAGUUCCUAUUGA	1791	2717-2737	UCAAUAGGAACUGUUCCUCAGAG	1952	2715-2737
AD-953834.1	UAGGAAGAGCUGUACCGUUGA	1792	3325-3345	UCAACGGUACAGCUCUUCCUAGA	1953	3323-3345
AD-953842.1	UUCUCUAAGUCCCAUCCGACA	1793	3679-3699	UGUCGGAUGGGACUUAGAGAAGG	1954	3677-3699
AD-953764.1	CUACCAAGAAAGACCGUGUGA	1794	432-452	UCACACGGUCUUUCUUGGUAGCU	1955	430-452
AD-953772.1	UUCCAAGGUUACAGCUCGAGA	1795	639-659	UCUCGAGCUGUAACCUUGGAAGA	1956	637-659
AD-953780.1	GGUUUAUGAACUGACGUUACA	1796	1219-1239	UGUAACGUCAGUUCAUAAACCUG	1957	1217-1239
AD-953788.1	GUAUUGUGGAACUUAUAGCUA	1797	1407-1427	UAGCUAUAAGUUCCACAAUACUC	1958	1405-1427
AD-953796.1	ACUCUGAAUCGAGAUCGGAUA	1798	1512-1532	UAUCCGAUCUCGAUUCAGAGUCA	1959	1510-1532
AD-953804.1	UGAUAAAUUUGUGUUGAGAGA	1799	2083-2103	UCUCUCAACACAAAUUUAUCAAC	1960	2081-2103
AD-953811.1	UCUAUAAAGUUCCUCUUGACA	181	2352-2372	UGUCAAGAGGAACUUUAUAGAGU	382	2350-2372
AD-953819.1	UGAGGAACAGUUCCUAUUGGA	1800	2718-2738	UCCAAUAGGAACUGUUCCUCAGA	1961	2716-2738
AD-953827.1	UCUCCGUCAGCACAAUAACCA	1801	3075-3095	UGGUUAUUGUGCUGACGGAGAAA	1962	3073-3095
AD-953835.1	AGGAAGAGCUGUACCGUUGGA	1802	3326-3346	UCCAACGGUACAGCUCUUCCUAG	1963	3324-3346
AD-953843.1	GAGAACAAGCAUCUGUACCGA	1803	3723-3743	UCGGUACAGAUGCUUGUUCUCCU	1964	3721-3743
AD-953851.1	GAGUGUCACAAAGAACCGUGA	1804	4369-4389	UCACGGUUCUUUGUGACACUCGU	1965	4367-4389

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953765.1	AAUCAUUGUCUGACAAUAUGA	1805	452-472	UCAUAUUGUCAGACAAUGAUUCA	1966	450-472
AD-953773.1	UCCAAGGUUACAGCUCGAGCA	1806	640-660	UGCUCGAGCUGUAACCUUGGAAG	1967	638-660
AD-953781.1	UUUAUGAACUGACGUUACAUA	1807	1221-1241	UAUGUAACGUCAGUUCAUAAACC	1968	1219-1241
AD-953789.1	UAUUGUGGAACUUAUAGCUGA	1808	1408-1428	UCAGCUAUAAGUUCCACAAUACU	1969	1406-1428
AD-953797.1	CUCUGAAUCGAGAUCGGAUGA	1809	1513-1533	UCAUCCGAUCUCGAUUCAGAGUC	1970	1511-1533
AD-953805.1	AGAUGAAGCUACUGAACCGGA	1810	2101-2121	UCCGGUUCAGUAGCUUCAUCUCU	1971	2099-2121
AD-953812.1	CAUCUUGAACUACAUCGAUCA	1811	2407-2427	UGAUCGAUGUAGUUCAAGAUGUC	1972	2405-2427
AD-953828.1	UCCGUCAGCACAAUAACCAGA	1812	3077-3097	UCUGGUUAUUGUGCUGACGGAGA	1973	3075-3097
AD-953836.1	GGAAGAGCUGUACCGUUGGGA	1813	3327-3347	UCCCAACGGUACAGCUCUUCCUA	1974	3325-3347
AD-953852.1	UGUCACAAAGAACCGUGCAGA	1814	4372-4392	UCUGCACGGUUCUUUGUGACACU	1975	4370-4392
AD-953766.1	CAUUGUCUGACAAUAUGUGAA	119	455-475	UUCACAUAUUGUCAGACAAUGAU	1976	453-475
AD-953774.1	CUGUUCCCAAAAUUAUGGCUA	1815	843-863	UAGCCAUAAUUUUGGGAACAGCU	1977	841-863
AD-953782.1	CAGCACCAAGACCACAAUGUA	1816	1247-1267	UACAUUGUGGUCUUGGUGCUGUG	1978	1245-1267
AD-953790.1	AUUGUGGAACUUAUAGCUGGA	1817	1409-1429	UCCAGCUAUAAGUUCCACAAUAC	1979	1407-1429
AD-953798.1	UUCUGAAAUUGUGUUAGACGA	1818	1885-1905	UCGUCUAACACAAUUUCAGAACU	1980	1883-1905
AD-953806.1	CCUCUUGUCCAUUGUGUCCGA	1819	2189-2209	UCGGACACAAUGGACAAGAGGUG	1981	2187-2209
AD-953813.1	CUUGAACUACAUCGAUCAUGA	1820	2410-2430	UCAUGAUCGAUGUAGUUCAAGAU	1982	2408-2430
AD-953821.1	AAGAACGAGUGCUCAAUAAUA	1821	2862-2882	UAUUAUUGAGCACUCGUUCUUGC	1983	2860-2882
AD-953829.1	AACCUUUCAAGAGUUAUUGCA	1822	3152-3172	UGCAAUAACUCUUGAAAGGUUAU	1984	3150-3172
AD-953837.1	GUCAGCUUGGUUCCCAUUGGA	1823	3376-3396	UCCAAUGGGAACCAAGCUGACGA	1985	3374-3396
AD-953845.1	CCUGAAAUCCUGCUUUAGUCA	1824	4039-4059	UGACUAAAGCAGGAUUUCAGGUA	1986	4037-4059
AD-953853.1	UAAGAAUGCUAUUCAUAAUCA	1825	4393-4413	UGAUUAUGAAUAGCAUUCUUAUC	1987	4391-4413
AD-953767.1	AAUGCCUCAACAAAGUUAUCA	1826	597-617	UGAUAACUUUGUUGAGGCAUUCG	1988	595-617
AD-953775.1	AGGCCUUCAUAGCGAACCUGA	1827	909-929	UCAGGUUCGCUAUGAAGGCCUUU	1989	907-929
AD-953783.1	GCACCAAGACCACAAUGUUGA	1828	1249-1269	UCAACAUUGUGGUCUUGGUGCUG	1990	1247-1269
AD-953791.1	UGGAGGAUGACUCUGAAUCGA	1829	1503-1523	UCGAUUCAGAGUCAUCCUCCAAG	1991	1501-1523
AD-953799.1	UCUGAAAUUGUGUUAGACGGA	1830	1886-1906	UCCGUCUAACACAAUUUCAGAAC	1992	1884-1906

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953807.1	CUCUUGUCCAUUGUGUCCGCA	1831	2190-2210	UGCGGACACAAUGGACAAGAGGU	1993	2188-2210
AD-953822.1	GAGUGCUCAAUAAUGUUGUCA	1832	2868-2888	UGACAACAUUAUUGAGCACUCGU	1994	2866-2888
AD-953830.1	AGUUUGCAUUUGGAGUUUAGA	1833	3262-3282	UCUAAACUCCAAAUGCAAACUGG	1995	3260-3282
AD-953838.1	AGCUUGGUUCCCAUUGGAUCA	1834	3379-3399	UGAUCCAAUGGGAACCAAGCUGA	1996	3377-3399
AD-953846.1	CUGAAAUCCUGCUUUAGUCGA	1835	4040-4060	UCGACUAAAGCAGGAUUUCAGGU	1997	4038-4060
AD-953854.1	AGAAUGCUAUUCAUAAUCACA	115	4395-4415	UGUGAUUAUGAAUAGCAUUCUUA	1998	4393-4415
AD-953768.1	UUAUCAAAGCUUUGAUGGAUA	1836	612-632	UAUCCAUCAAAGCUUUGAUAACU	1999	610-632
AD-953776.1	CUCUGCUGAUUCUUGGCGUGA	1837	1074-1094	UCACGCCAAGAAUCAGCAGAGUG	2000	1072-1094
AD-953784.1	CACCAAGACCACAAUGUUGUA	1838	1250-1270	UACAACAUUGUGGUCUUGGUGCU	2001	1248-1270
AD-953792.1	GAGGAUGACUCUGAAUCGAGA	1839	1505-1525	UCUCGAUUCAGAGUCAUCCUCCA	2002	1503-1525
AD-953800.1	CUGAAAUUGUGUUAGACGGUA	165	1887-1907	UACCGUCUAACACAAUUUCAGAA	366	1885-1907
AD-953808.1	UCCGCCUUUUAUCUGCUUCGA	1840	2205-2225	UCGAAGCAGAUAAAAGGCGGACA	2003	2203-2225
AD-953815.1	GAACUACAUCGAUCAUGGAGA	1841	2413-2433	UCUCCAUGAUCGAUGUAGUUCAA	2004	2411-2433
AD-953823.1	GCCUCCAUCUCAUUUCUCCGA	1842	3061-3081	UCGGAGAAAUGAGAUGGAGGCUG	2005	3059-3081
AD-953831.1	GUUUGCAUUUGGAGUUUAGGA	1843	3263-3283	UCCUAAACUCCAAAUGCAAACUG	2006	3261-3283
AD-953839.1	AGAUGCUUUGAUUUUGGCCGA	1844	3412-3432	UCGGCCAAAAUCAAAGCAUCUUG	2007	3410-3432
AD-953847.1	GAAAUCCUGCUUUAGUCGAGA	1845	4042-4062	UCUCGACUAAAGCAGGAUUUCAG	2008	4040-4062
AD-953855.1	GCUAUUCAUAAUCACAUUCGA	1846	4400-4420	UCGAAUGUGAUUAUGAAUAGCAU	2009	4398-4420
AD-953769.1	GCUUUGAUGGAUUCUAAUCUA	1847	620-640	UAGAUUAGAAUCCAUCAAAGCUU	2010	618-640
AD-953777.1	GCAGCUUGUCCAGGUUUAUGA	1848	1207-1227	UCAUAAACCUGGACAAGCUGCUC	2011	1205-1227
AD-953785.1	ACCAAGACCACAAUGUUGUGA	1849	1251-1271	UCACAACAUUGUGGUCUUGGUGC	2012	1249-1271
AD-953793.1	AGGAUGACUCUGAAUCGAGAA	1850	1506-1526	UUCUCGAUUCAGAGUCAUCCUCC	2013	1504-1526
AD-953801.1	UGAAAUUGUGUUAGACGGUAA	1851	1888-1908	UUACCGUCUAACACAAUUUCAGA	2014	1886-1908
AD-953809.1	CCGCCUUUUAUCUGCUUCGUA	1852	2206-2226	UACGAAGCAGAUAAAAGGCGGAC	2015	2204-2226
AD-953816.1	CUUUGGCGGAUUGCAUUCCUA	1853	2559-2579	UAGGAAUGCAAUCCGCCAAAGAA	2016	2557-2579
AD-953824.1	CCUCCAUCUCAUUUCUCCGUA	1854	3062-3082	UACGGAGAAAUGAGAUGGAGGCU	2017	3060-3082
AD-953832.1	GUCUAGGAAGAGCUGUACCGA	1855	3322-3342	UCGGUACAGCUCUUCCUAGACUC	2018	3320-3342

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953840.1	GGCCGGAAACUUGCUUGCAGA	1856	3427-3447	UCUGCAAGCAAGUUUCCGGCCAA	2019	3425-3447
AD-953848.1	UUUAGUCGAGAACCAAUGAUA	1857	4052-4072	UAUCAUUGGUUCUCGACUAAAGC	2020	4050-4072
AD-953856.1	UUCAUAAUCACAUUCGUUUGA	1858	4404-4424	UCAAACGAAUGUGAUUAUGAAUA	2021	4402-4424
AD-953770.1	GAUUCUAAUCUUCCAAGGUUA	146	629-649	UAACCUUGGAAGAUUAGAAUCCA	2022	627-649
AD-953778.1	CAGGUUUAUGAACUGACGUUA	158	1217-1237	UAACGUCAGUUCAUAAACCUGGA	359	1215-1237
AD-953786.1	GAGUAUUGUGGAACUUAUAGA	1859	1405-1425	UCUAUAAGUUCCACAAUACUCCC	2023	1403-1425
AD-953794.1	GGAUGACUCUGAAUCGAGAUA	1860	1507-1527	UAUCUCGAUUCAGAGUCAUCCUC	2024	1505-1527
AD-953802.1	GAAAUUGUGUUAGACGGUACA	1861	1889-1909	UGUACCGUCUAACACAAUUUCAG	2025	1887-1909
AD-953817.1	UUUGGCGGAUUGCAUUCCUUA	1862	2560-2580	UAAGGAAUGCAAUCCGCCAAAGA	2026	2558-2580
AD-953825.1	CUCCAUCUCAUUUCUCCGUCA	1863	3063-3083	UGACGGAGAAAUGAGAUGGAGGC	2027	3061-3083
AD-953833.1	UCUAGGAAGAGCUGUACCGUA	1864	3323-3343	UACGGUACAGCUCUUCCUAGACU	2028	3321-3343
AD-953841.1	CUUCUCUAAGUCCCAUCCGAA	1865	3678-3698	UUCGGAUGGGACUUAGAGAAGGG	2029	3676-3698
AD-953849.1	UUAGUCGAGAACCAAUGAUGA	1866	4053-4073	UCAUCAUUGGUUCUCGACUAAAG	2030	4051-4073

Table 9. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-953857.1	uscsaua(Ahd)UfcAfCfAfuucguuuguaL96	2031	VPusAfscaaAfcGfAfauguGfaUfuaugasasu	2205	AUUCAUAAUCACAUUCGUUUGUU	984
AD-953865.1	ususcag(Uhd)UfaCfGfGfguuaauuacaL96	2032	VPusGfsuaaUfuAfAfcccgUfaAfcugaascsc	2206	GGUUCAGUUACGGGUUAAUUACU	1007
AD-953873.1	ascsugu(Chd)UfcGfAfCfagauagcugaL96	2033	VPusCfsagcUfaUfCfugucGfaGfacaguscsg	2207	CGACUGUCUCGACAGAUAGCUGA	2379
AD-953881.1	ususacg(Ghd)AfgUfAfUfguucgucacaL96	2034	VPusGfsugaCfgAfAfcauaCfuCfcguaasasa	2208	UUUUACGGAGUAUGUUCGUCACU	2380
AD-953889.1	gscsaac(Ahd)UfaCfUfUfucuauugccaL96	2035	VPusGfsgcaAfuAfGfaaagUfaUfguugcsusg	2209	CAGCAACAUACUUUCUAUUGCCA	993
AD-953897.1	ascsucc(Ghd)AfgCfAfCfuuaacguggaL96	2036	VPusCfscacGfuUfAfagugCfuCfggaguscsa	2210	UGACUCCGAGCACUUAACGUGGC	2381

Duplex ID	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-953904.1	gscsaau(Uhd)CfaGfUfCfucguugugaaL96	2037	VPusUfscacAfaCfGfagacUfgAfauugcscsu	2211	AGGCAAUUCAGUCUCGUUGUGAA	2382
AD-953912.1	usgsccu(Uhd)CfaUfGfAfugaacucggaL96	2038	VPusCfscgaGfuUfCfaucaUfgAfaggcasusu	2212	AAUGCCUUCAUGAUGAACUCGGA	2383
AD-953920.1	csasaca(Ghd)CfuAfCfAfcacgugugcaL96	2039	VPusGfscacAfcGfUfguguAfgCfuguugsasc	2213	GUCAACAGCUACACACGUGUGCC	2384
AD-953928.1	gsascgc(Uhd)GfaCfAfGfaacugcgaaaL96	2040	VPusUfsucgCfaGfUfucugUfcAfgcgucsasc	2214	GUGACGCUGACAGAACUGCGAAG	2385
AD-953936.1	csusgac(Uhd)UfgUfUfUfacgaaauguaL96	2041	VPusAfscauUfuCfGfuaaaCfaAfgucagscsa	2215	UGCUGACUUGUUUACGAAAUGUC	2386
AD-953858.1	asuscac(Ahd)UfuCfGfUfuuguuugaaaL96	2042	VPusUfsucaAfaCfAfaacgAfaUfgugaususa	2216	UAAUCACAUUCGUUUGUUUGAAC	2387
AD-953866.1	csasguu(Ahd)CfgGfGfUfuaauuacugaL96	2043	VPusCfsaguAfaUfUfaaccCfgUfaacugsasa	2217	UUCAGUUACGGGUUAAUUACUGU	2388
AD-953874.1	asasgcc(Chd)UfuGfGfAfguguuaaauaL96	2044	VPusAfsuuuAfaCfAfcuccAfaGfggcuuscsa	2218	UGAAGCCCUUGGAGUGUUAAAUA	2389
AD-953882.1	uscsuga(Uhd)UfuCfCfCfagucaacugaL96	2045	VPusCfsaguUfgAfCfugggAfaAfucagasasc	2219	GUUCUGAUUUCCCAGUCAACUGA	2390
AD-953890.1	asuscuu(Chd)AfaGfUfCfuggaauguuaL96	2046	VPusAfsacaUfuCfCfagacUfuGfaagausgsu	2220	ACAUCUUCAAGUCUGGAAUGUUC	1004
AD-953898.1	asuscca(Ghd)GfcAfAfUfucagucucgaL96	2047	VPusCfsgagAfcUfGfaauuGfcCfuggausgsa	2221	UCAUCCAGGCAAUUCAGUCUCGU	2391
AD-953905.1	asusggu(Chd)GfaCfAfUfccuugcuugaL96	2048	VPusCfsaagCfaAfGfgaugUfcGfaccausgsc	2222	GCAUGGUCGACAUCCUUGCUUGU	2392
AD-953913.1	csusuca(Uhd)GfaUfGfAfacucggaguaL96	2049	VPusAfscucCfgAfGfuucaUfcAfugaagsgsc	2223	GCCUUCAUGAUGAACUCGGAGUU	2393
AD-953921.1	gsascca(Ghd)UfcGfUfAfcucaguuugaL96	2050	VPusCfsaaaCfuGfAfguacGfaCfuggucscsa	2224	UGGACCAGUCGUACUCAGUUUGA	2394
AD-953929.1	ascsgcu(Ghd)AfcAfGfAfacugcgaagaL96	2051	VPusCfsuucGfcAfGfuucuGfuCfagcguscsa	2225	UGACGCUGACAGAACUGCGAAGG	2395
AD-953937.1	usgsacu(Uhd)GfuUfUfAfcgaaaugucaL96	2052	VPusGfsacaUfuUfCfguaaAfcAfagucasgsc	2226	GCUGACUUGUUUACGAAAUGUCC	950
AD-953859.1	usgsuuu(Ghd)AfaCfCfUfcuuguuauaaL96	2053	VPusUfsauaAfcAfAfgaggUfuCfaaacasasa	2227	UUUGUUUGAACCUCUUGUUAUAA	933
AD-953867.1	uscsaga(Uhd)CfaGfGfUfguuuauuggaL96	2054	VPusCfscaaUfaAfAfcaccUfgAfucugasasu	2228	AUUCAGAUCAGGUGUUUAUUGGC	2396
AD-953875.1	gscsccu(Uhd)GfgAfGfUfguuaaauacaL96	2055	VPusGfsuauUfuAfAfcacuCfcAfagggcsusu	2229	AAGCCCUUGGAGUGUUAAAUACA	2397
AD-953883.1	asasgau(Ahd)UfuGfUfUfcuuucucguaL96	2056	VPusAfscgaGfaAfAfgaacAfaUfaucuuscsa	2230	UGAAGAUAUUGUUCUUUCUCGUA	919

Duplex ID	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-953891.1	uscsaag(Uhd)CfuGfGfAfauguuccggaL96	2057	VPusCfscggAfaCfAfuuccAfgAfcuugasasg	2231	CUUCAAGUCUGGAAUGUUCCGGA	2398
AD-953899.1	uscscag(Ghd)CfaAfUfUfcagucucguaL96	2058	VPusAfscgaGfaCfUfgaauUfgCfcuggasusg	2232	CAUCCAGGCAAUUCAGUCUCGUU	2399
AD-953906.1	gsuscga(Chd)AfuCfCfUfugcuugucgaL96	2059	VPusCfsgacAfaGfCfaaggAfuGfucgacscsa	2233	UGGUCGACAUCCUUGCUUGUCGC	2400
AD-953914.1	csusgcu(Ahd)GfcUfCfCfaugcuuaagaL96	2060	VPusCfsuuaAfgCfAfuggaGfcUfagcagsgsc	2234	GCCUGCUAGCUCCAUGCUUAAGC	2401
AD-953922.1	ascscag(Uhd)CfgUfAfCfucaguuugaaL96	2061	VPusUfscaaAfcUfGfaguaCfgAfcugguscsc	2235	GGACCAGUCGUACUCAGUUUGAA	2402
AD-953930.1	gsasaag(Ghd)AfgAfAfAfgucaguccgaL96	2062	VPusCfsggaCfuGfAfcuuuCfuCfcuuucscsu	2236	AGGAAAGGAGAAAGUCAGUCCGG	2403
AD-953938.1	usasacg(Uhd)AfaCfUfCfuuucuaugcaL96	2063	VPusGfscauAfgAfAfagagUfuAfcguuasasa	2237	UUUAACGUAACUCUUUCUAUGCC	982
AD-953860.1	gsusuug(Ahd)AfcCfUfCfuuguuauaaaL96	2064	VPusUfsuauAfaCfAfagagGfuUfcaaacsasa	2238	UUGUUUGAACCUCUUGUUAUAAA	929
AD-953868.1	ususggc(Uhd)UfuGfUfAfuugaaacagaL96	2065	VPusCfsuguUfuCfAfauacAfaAfgccaasusa	2239	UAUUGGCUUUGUAUUGAAACAGU	2404
AD-953876.1	usasgac(Ahd)UfgCfUfUfuuacggaguaL96	2066	VPusAfscucCfgUfAfaaagCfaUfgucuascsc	2240	GGUAGACAUGCUUUUACGGAGUA	2405
AD-953884.1	gsasuau(Uhd)GfuUfCfUfuucucguauaL96	2067	VPusAfsuacGfaGfAfaagaAfcAfauaucsusu	2241	AAGAUAUUGUUCUUUCUCGUAUU	999
AD-953892.1	csasagu(Chd)UfgGfAfAfuguuccggaaL96	2068	VPusUfsccgGfaAfCfauucCfaGfacuugsasa	2242	UUCAAGUCUGGAAUGUUCCGGAG	2406
AD-953900.1	cscsagg(Chd)AfaUfUfCfagucucguuaL96	2069	VPusAfsacgAfgAfCfugaaUfuGfccuggsasu	2243	AUCCAGGCAAUUCAGUCUCGUUG	2407
AD-953907.1	csasugc(Ahd)AfgAfCfUfcacuuagucaL96	2070	VPusGfsacuAfaGfUfgaguCfuUfgcaugsgsu	2244	ACCAUGCAAGACUCACUUAGUCC	1008
AD-953915.1	usgscua(Ghd)CfuCfCfAfugcuuaagcaL96	2071	VPusGfscuuAfaGfCfauggAfgCfuagcasgsg	2245	CCUGCUAGCUCCAUGCUUAAGCC	2408
AD-953923.1	cscsagu(Chd)GfuAfCfUfcaguuugaaaL96	2072	VPusUfsucaAfaCfUfgaguAfcGfacuggsusc	2246	GACCAGUCGUACUCAGUUUGAAG	958
AD-953931.1	asgsaac(Uhd)UfcAfGfAfcccuaauccaL96	2073	VPusGfsgauUfaGfGfgucuGfaAfguucusasc	2247	GUAGAACUUCAGACCCUAAUCCU	2409
AD-953939.1	uscsuau(Ghd)CfcCfGfUfguaaaguauaL96	2074	VPusAfsuacUfuUfAfcacgGfgCfauagasasa	2248	UUUCUAUGCCCGUGUAAAGUAUG	2410
AD-953861.1	ususuga(Ahd)CfcUfCfUfuguuauaaaaL96	2075	VPusUfsuuaUfaAfCfaagaGfgUfucaaascsa	2249	UGUUUGAACCUCUUGUUAUAAAA	928
AD-953869.1	ususaug(Ahd)AfcGfCfUfaucauucaaaL96	2076	VPusUfsugaAfuGfAfuagcGfuUfcauaasgsa	2250	UCUUAUGAACGCUAUCAUUCAAA	2411

Duplex ID	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-953877.1	ascsaug(Chd)UfuUfUfAfcggaguaugaL96	2077	VPusCfsauaCfuCfCfguaaAfaGfcauguscsu	2251	AGACAUGCUUUUACGGAGUAUGU	2412
AD-953885.1	ususguu(Chd)UfuUfCfUfcguauucagaL96	2078	VPusCfsugaAfuAfCfgagaAfaGfaacaasusa	2252	UAUUGUUCUUUCUCGUAUUCAGG	916
AD-953893.1	asgscac(Ahd)AfaGfUfUfacuuaguccaL96	2079	VPusGfsgacUfaAfGfuaacUfuUfgugcusgsg	2253	CCAGCACAAAGUUACUUAGUCCC	2413
AD-953901.1	csasggc(Ahd)AfuUfCfAfgucucguugaL96	2080	VPusCfsaacGfaGfAfcugaAfuUfgccugsgsa	2254	UCCAGGCAAUUCAGUCUCGUUGU	2414
AD-953908.1	asusgca(Ahd)GfaCfUfCfacuuaguccaL96	2081	VPusGfsgacUfaAfGfugagUfcUfugcausgsg	2255	CCAUGCAAGACUCACUUAGUCCC	2415
AD-953916.1	ascsugg(Ahd)GfcAfAfGfuugaaugauaL96	2082	VPusAfsucaUfuCfAfacuuGfcUfccagusasg	2256	CUACUGGAGCAAGUUGAAUGAUC	2416
AD-953924.1	csasguc(Ghd)UfaCfUfCfaguuugaagaL96	2083	VPusCfsuucAfaAfCfugagUfaCfgacugsgsu	2257	ACCAGUCGUACUCAGUUUGAAGA	926
AD-953932.1	uscsaug(Ahd)AfcAfAfAfgucaucggaaL96	2084	VPusUfsccgAfuGfAfcuuuGfuUfcaugasusg	2258	CAUCAUGAACAAAGUCAUCGGAG	2417
AD-953940.1	csusaug(Chd)CfcGfUfGfuaaaguaugaL96	2085	VPusCfsauaCfuUfUfacacGfgGfcauagsasa	2259	UUCUAUGCCCGUGUAAAGUAUGU	2418
AD-953862.1	asasgcu(Uhd)UfaAfAfAfcaguacacgaL96	2086	VPusCfsgugUfaCfUfguuuUfaAfagcuususu	2260	AAAAGCUUUAAAACAGUACACGA	2419
AD-953870.1	asascgc(Uhd)AfuCfAfUfucaaaacagaL96	2087	VPusCfsuguUfuUfGfaaugAfuAfgcguuscsa	2261	UGAACGCUAUCAUUCAAAACAGA	2420
AD-953878.1	csususuu(Ahd)CfgGfAfGfuauguucguaL96	2088	VPusAfscgaAfcAfUfacucCfgUfaaaagscsa	2262	UGCUUUUACGGAGUAUGUUCGUC	2421
AD-953886.1	usgsuuc(Uhd)UfuCfUfCfguauucaggaL96	2089	VPusCfscugAfaUfAfcgagAfaAfgaacasasu	2263	AUUGUUCUUUCUCGUAUUCAGGA	931
AD-953894.1	asgsagg(Ahd)GfgAfUfUfcugacuuggaL96	2090	VPusCfscaaGfuCfAfgaauCfcUfccucususc	2264	GAAGAGGAGGAUUCUGACUUGGC	2422
AD-953902.1	asgsgca(Ahd)UfuCfAfGfucucguuguaL96	2091	VPusAfscaaCfgAfGfacugAfaUfugccusgsg	2265	CCAGGCAAUUCAGUCUCGUUGUG	2423
AD-953909.1	csascug(Ghd)AfaAfCfAfgugaguccgaL96	2092	VPusCfsggaCfuCfAfcuguUfuCfcagugsasc	2266	GUCACUGGAAACAGUGAGUCCGG	2424
AD-953917.1	usgsuca(Ahd)CfaGfCfUfacacacgugaL96	2093	VPusCfsacgUfgUfGfuagcUfgUfugacasasg	2267	CUUGUCAACAGCUACACACGUGU	2425
AD-953925.1	asasgcu(Ghd)AfgCfAfUfuaucagaggaL96	2094	VPusCfscucUfgAfUfaaugCfuCfagcuuscsc	2268	GGAAGCUGAGCAUUAUCAGAGGG	2426
AD-953933.1	csgsgcu(Ghd)CfuGfAfCfuuguuuacgaL96	2095	VPusCfsguaAfaCfAfagucAfgCfagccgsgsu	2269	ACCGGCUGCUGACUUGUUUACGA	2427
AD-953941.1	cscsgcu(Ghd)AfcAfUfUfuccguuguaaL96	2096	VPusUfsacaAfcGfGfaaauGfuCfagcggsgsu	2270	ACCCGCUGACAUUUCCGUUGUAC	2428

Duplex ID	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-953863.1	asgscug(Ghd)UfuCfAfGfuuacggguuaL96	2097	VPusAfsaccCfgUfAfacugAfaCfcagcusgsc	2271	GCAGCUGGUUCAGUUACGGGUUA	2429
AD-953871.1	gsusgga(Ahd)GfcGfAfCfugucucgacaL96	2098	VPusGfsucgAfgAfCfagucGfcUfuccacsusu	2272	AAGUGGAAGCGACUGUCUCGACA	2430
AD-953879.1	ususuua(Chd)GfgAfGfUfauguucgucaL96	2099	VPusGfsacgAfaCfAfuacuCfcGfuaaaasgsc	2273	GCUUUUACGGAGUAUGUUCGUCA	2431
AD-953887.1	asususuu(Chd)AfaGfGfUfuucuauuacaL96	2100	VPusGfsuaaUfaGfAfaaccUfuGfaaaausgsu	2274	ACAUUUUCAAGGUUUCUAUUACA	943
AD-953895.1	csasaua(Ghd)AfgAfAfAfuaguacgaaaL96	2101	VPusUfsucgUfaCfUfauuuCfuCfuauugscsa	2275	UGCAAUAGAGAAAUAGUACGAAG	2432
AD-953903.1	gsgscaa(Uhd)UfcAfGfUfcucguugugaL96	2102	VPusCfsacaAfcGfAfgacuGfaAfuugccsusg	2276	CAGGCAAUUCAGUCUCGUUGUGA	2433
AD-953910.1	asgscug(Ghd)UfgAfAfUfcggauuccuaL96	2103	VPusAfsggaAfuCfCfgauuCfaCfcagcuscsu	2277	AGAGCUGGUGAAUCGGAUUCCUG	2434
AD-953918.1	gsuscaa(Chd)AfgCfUfAfcacacguguaL96	2104	VPusAfscacGfuGfUfguagCfuGfuugacsasa	2278	UUGUCAACAGCUACACACGUGUG	2435
AD-953926.1	ususgag(Chd)UfgAfUfGfuaugugacgaL96	2105	VPusCfsgucAfcAfUfacauCfaGfcucaasasc	2279	GUUUGAGCUGAUGUAUGUGACGC	2436
AD-953934.1	gsgscug(Chd)UfgAfCfUfuguuuacgaaL96	2106	VPusUfscguAfaAfCfaaguCfaGfcagccsgsg	2280	CCGGCUGCUGACUUGUUUACGAA	2437
AD-953864.1	gsusuca(Ghd)UfuAfCfGfgguuaauuaaL96	2107	VPusUfsaauUfaAfCfccguAfaCfugaacscsa	2281	UGGUUCAGUUACGGGUUAAUUAC	957
AD-953872.1	gsascug(Uhd)CfuCfGfAfcagauagcuaL96	2108	VPusAfsgcuAfuCfUfgucgAfgAfcagucsgsc	2282	GCGACUGUCUCGACAGAUAGCUG	2438
AD-953880.1	ususuac(Ghd)GfaGfUfAfuguucgucaaL96	2109	VPusUfsgacGfaAfCfauacUfcCfguaaasasg	2283	CUUUUACGGAGUAUGUUCGUCAC	2439
AD-953888.1	asasggu(Uhd)UfcUfAfUfuacaacuggaL96	2110	VPusCfscagUfuGfUfaauaGfaAfaccuusgsa	2284	UCAAGGUUUCUAUUACAACUGGU	2440
AD-953896.1	gsascuc(Chd)GfaGfCfAfcuuaacgugaL96	2111	VPusCfsacgUfuAfAfgugcUfcGfgagucsasu	2285	AUGACUCCGAGCACUUAACGUGG	2441
AD-953911.1	gscsugg(Uhd)GfaAfUfCfggauuccugaL96	2112	VPusCfsaggAfaUfCfcgauUfcAfccagcsusc	2286	GAGCUGGUGAAUCGGAUUCCUGC	2442
AD-953919.1	uscsaac(Ahd)GfcUfAfCfacacgugugaL96	2113	VPusCfsacaCfgUfGfuguaGfcUfguugascsa	2287	UGUCAACAGCUACACACGUGUGC	2443
AD-953927.1	gsasgcu(Ghd)AfuGfUfAfugugacgcuaL96	2114	VPusAfsgcgUfcAfCfauacAfuCfagcucsasa	2288	UUGAGCUGAUGUAUGUGACGCUG	2444
AD-953935.1	csusgcu(Ghd)AfcUfUfGfuuuacgaaaaL96	2115	VPusUfsuucGfuAfAfacaaGfuCfagcagscsc	2289	GGCUGCUGACUUGUUUACGAAAU	938
AD-953763.1	asgscua(Chd)CfaAfGfAfaagaccgugaL96	2116	VPusCfsacgGfuCfUfuucuUfgGfuagcusgsa	2290	UCAGCUACCAAGAAAGACCGUGU	2445

Duplex ID	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-953771.1	asusucu(Ahd)AfuCfUfUfccaagguuaaL96	2117	VPusUfsaacCfuUfGfgaagAfuUfagaauscsc	2291	GGAUUCUAAUCUUCCAAGGUUAC	965
AD-953779.1	asgsguu(Uhd)AfuGfAfAfcugacguuaaL96	2118	VPusUfsaacGfuCfAfguucAfuAfaaccusgsg	2292	CCAGGUUUAUGAACUGACGUUAC	991
AD-953787.1	asgsuau(Uhd)GfuGfGfAfacuuauagcaL96	2119	VPusGfscuaUfaAfGfuuccAfcAfauacuscsc	2293	GGAGUAUUGUGGAACUUAUAGCU	2446
AD-953795.1	gsascuc(Uhd)GfaAfUfCfgagaucggaaL96	2120	VPusUfsccgAfuCfUfcgauUfcAfgagucsasu	2294	AUGACUCUGAAUCGAGAUCGGAU	2447
AD-953803.1	ascsagc(Ahd)GfuGfUfUfgauaaauuuaL96	2121	VPusAfsaauUfuAfUfcaacAfcUfgcuguscsa	2295	UGACAGCAGUGUUGAUAAAUUUG	1015
AD-953810.1	csgsccu(Uhd)UfuAfUfCfugcuucguuaL96	2122	VPusAfsacgAfaGfCfagauAfaAfaggcgsgsa	2296	UCCGCCUUUUAUCUGCUUCGUUU	1001
AD-953818.1	csusgag(Ghd)AfaCfAfGfuuccuauugaL96	2123	VPusCfsaauAfgGfAfacugUfuCfcucagsasg	2297	CUCUGAGGAACAGUUCCUAUUGG	1021
AD-953834.1	usasgga(Ahd)GfaGfCfUfguaccguugaL96	2124	VPusCfsaacGfgUfAfcagcUfcUfuccuasgsa	2298	UCUAGGAAGAGCUGUACCGUUGG	2448
AD-953842.1	ususcuc(Uhd)AfaGfUfCfccauccgacaL96	2125	VPusGfsucgGfaUfGfggacUfuAfgagaasgsg	2299	CCUUCUCUAAGUCCCAUCCGACG	2449
AD-953764.1	csusacc(Ahd)AfgAfAfAfgaccgugugaL96	2126	VPusCfsacaCfgGfUfcuuuCfuUfgguagscsu	2300	AGCUACCAAGAAAGACCGUGUGA	2450
AD-953772.1	ususcca(Ahd)GfgUfUfAfcagcucgagaL96	2127	VPusCfsucgAfgCfUfguaaCfcUfuggaasgsa	2301	UCUUCCAAGGUUACAGCUCGAGC	2451
AD-953780.1	gsgsuuu(Ahd)UfgAfAfCfugacguuacaL96	2128	VPusGfsuaaCfgUfCfaguuCfaUfaaaccsusg	2302	CAGGUUUAUGAACUGACGUUACA	2452
AD-953788.1	gsusauu(Ghd)UfgGfAfAfcuuauagcuaL96	2129	VPusAfsgcuAfuAfAfguucCfaCfaauacsusc	2303	GAGUAUUGUGGAACUUAUAGCUG	2453
AD-953796.1	ascsucu(Ghd)AfaUfCfGfagaucggauaL96	2130	VPusAfsuccGfaUfCfucgaUfuCfagaguscsa	2304	UGACUCUGAAUCGAGAUCGGAUG	1011
AD-953804.1	usgsaua(Ahd)AfuUfUfGfuguugagagaL96	2131	VPusCfsucuCfaAfCfacaaAfuUfuaucasasc	2305	GUUGAUAAAUUUGUGUUGAGAGA	2454
AD-953811.1	uscsuau(Ahd)AfaGfUfUfccucuugacaL96	2132	VPusGfsucaAfgAfGfgaacUfuUfauagasgsu	2306	ACUCUAUAAAGUUCCUCUUGACA	987
AD-953819.1	usgsagg(Ahd)AfcAfGfUfuccuauuggaL96	2133	VPusCfscaaUfaGfGfaacuGfuUfccucasgsa	2307	UCUGAGGAACAGUUCCUAUUGGC	2455
AD-953827.1	uscsucc(Ghd)UfcAfGfCfacaauaaccaL96	2134	VPusGfsguuAfuUfGfugcuGfaCfggagasasa	2308	UUUCUCCGUCAGCACAAUAACCA	2456
AD-953835.1	asgsgaa(Ghd)AfgCfUfGfuaccguuggaL96	2135	VPusCfscaaCfgGfUfacagCfuCfuuccusasg	2309	CUAGGAAGAGCUGUACCGUUGGG	2457
AD-953843.1	gsasgaa(Chd)AfaGfCfAfucuguaccgaL96	2136	VPusCfsgguAfcAfGfaugcUfuGfuucucscsu	2310	AGGAGAACAAGCAUCUGUACCGU	2458

Duplex ID	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-953851.1	gsasgug(Uhd)CfaCfAfAfagaaccgugaL96	2137	VPusCfsacgGfuUfCfuuugUfgAfcacucsgsu	2311	ACGAGUGUCACAAAGAACCGUGC	2459
AD-953765.1	asasuca(Uhd)UfgUfCfUfgacaauaugaL96	2138	VPusCfsauaUfuGfUfcagaCfaAfugauuscsa	2312	UGAAUCAUUGUCUGACAAUAUGU	2460
AD-953773.1	uscscaa(Ghd)GfuUfAfCfagcucgagcaL96	2139	VPusGfscucGfaGfCfuguaAfcCfuuggasasg	2313	CUUCCAAGGUUACAGCUCGAGCU	2461
AD-953781.1	ususuau(Ghd)AfaCfUfGfacguuacauaL96	2140	VPusAfsuguAfaCfGfucagUfuCfauaaascsc	2314	GGUUUAUGAACUGACGUUACAUC	2462
AD-953789.1	usasuug(Uhd)GfgAfAfCfuuauagcugaL96	2141	VPusCfsagcUfaUfAfaguuCfcAfcaauascsu	2315	AGUAUUGUGGAACUUAUAGCUGG	2463
AD-953797.1	csuscug(Ahd)AfuCfGfAfgaucggaugaL96	2142	VPusCfsaucCfgAfUfcucgAfuUfcagagsusc	2316	GACUCUGAAUCGAGAUCGGAUGU	2464
AD-953805.1	asgsaug(Ahd)AfgCfUfAfcugaaccggaL96	2143	VPusCfscggUfuCfAfguagCfuUfcaucuscsu	2317	AGAGAUGAAGCUACUGAACCGGG	2465
AD-953812.1	csasucu(Uhd)GfaAfCfUfacaucgaucaL96	2144	VPusGfsaucGfaUfGfuaguUfcAfagaugsusc	2318	GACAUCUUGAACUACAUCGAUCA	2466
AD-953828.1	uscscgu(Chd)AfgCfAfCfaauaaccagaL96	2145	VPusCfsuggUfuAfUfugugCfuGfacggasgsa	2319	UCUCCGUCAGCACAAUAACCAGA	2467
AD-953836.1	gsgsaag(Ahd)GfcUfGfUfaccguugggaL96	2146	VPusCfsccaAfcGfGfuacaGfcUfcuuccsusa	2320	UAGGAAGAGCUGUACCGUUGGGA	2468
AD-953852.1	usgsuca(Chd)AfaAfGfAfaccgugcagaL96	2147	VPusCfsugcAfcGfGfuucuUfuGfugacascsu	2321	AGUGUCACAAAGAACCGUGCAGA	2469
AD-953766.1	csasuug(Uhd)CfuGfAfCfaauaugugaaL96	2148	VPusUfscacAfuAfUfugucAfgAfcaaugsasu	2322	AUCAUUGUCUGACAAUAUGUGAA	925
AD-953774.1	csusguu(Chd)CfcAfAfAfauuauggcuaL96	2149	VPusAfsgccAfuAfAfuuuuGfgGfaacagscsu	2323	AGCUGUUCCCAAAAUUAUGGCUU	2470
AD-953782.1	csasgca(Chd)CfaAfGfAfccacaauguaL96	2150	VPusAfscauUfgUfGfgucuUfgGfugcugsusg	2324	CACAGCACCAAGACCACAAUGUU	2471
AD-953790.1	asusugu(Ghd)GfaAfCfUfuauagcuggaL96	2151	VPusCfscagCfuAfUfaaguUfcCfacaausasc	2325	GUAUUGUGGAACUUAUAGCUGGA	2472
AD-953798.1	ususcug(Ahd)AfaUfUfGfuguuagacgaL96	2152	VPusCfsgucUfaAfCfacaaUfuUfcagaascsu	2326	AGUUCUGAAAUUGUGUUAGACGG	2473
AD-953806.1	cscsucu(Uhd)GfuCfCfAfuuguguccgaL96	2153	VPusCfsggaCfaCfAfauggAfcAfagaggsusg	2327	CACCUCUUGUCCAUUGUGUCCGC	2474
AD-953813.1	csusuga(Ahd)CfuAfCfAfucgaucaugaL96	2154	VPusCfsaugAfuCfGfauguAfgUfucaagsasu	2328	AUCUUGAACUACAUCGAUCAUGG	930
AD-953821.1	asasgaa(Chd)GfaGfUfGfcucaauaauaL96	2155	VPusAfsuuaUfuGfAfgcacUfcGfuucuusgsc	2329	GCAAGAACGAGUGCUCAAUAAUG	2475
AD-953829.1	asasccu(Uhd)UfcAfAfGfaguuauugcaL96	2156	VPusGfscaaUfaAfCfucuuGfaAfagguusasu	2330	AUAACCUUUCAAGAGUUAUUGCA	2476

Duplex ID	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-953837.1	gsuscag(Chd)UfuGfGfUfucccauuggaL96	2157	VPusCfscaaUfgGfGfaaccAfaGfcugacsgsa	2331	UCGUCAGCUUGGUUCCCAUUGGA	2477
AD-953845.1	cscsuga(Ahd)AfuCfCfUfgcuuuagucaL96	2158	VPusGfsacuAfaAfGfcaggAfuUfucaggsusa	2332	UACCUGAAAUCCUGCUUUAGUCG	924
AD-953853.1	usasaga(Ahd)UfgCfUfAfuucauaaucaL96	2159	VPusGfsauuAfuGfAfauagCfaUfucuuasusc	2333	GAUAAGAAUGCUAUUCAUAAUCA	2478
AD-953767.1	asasugc(Chd)UfcAfAfCfaaaguuaucaL96	2160	VPusGfsauaAfcUfUfuguuGfaGfgcauuscsg	2334	CGAAUGCCUCAACAAAGUUAUCA	2479
AD-953775.1	asgsgcc(Uhd)UfcAfUfAfgcgaaccugaL96	2161	VPusCfsaggUfuCfGfcuauGfaAfggccususu	2335	AAAGGCCUUCAUAGCGAACCUGA	2480
AD-953783.1	gscsacc(Ahd)AfgAfCfCfacaauguugaL96	2162	VPusCfsaacAfuUfGfugguCfuUfggugcsusg	2336	CAGCACCAAGACCACAAUGUUGU	2481
AD-953791.1	usgsgag(Ghd)AfuGfAfCfucugaaucgaL96	2163	VPusCfsgauUfcAfGfagucAfuCfcuccasasg	2337	CUUGGAGGAUGACUCUGAAUCGA	2482
AD-953799.1	uscsuga(Ahd)AfuUfGfUfguuagacggaL96	2164	VPusCfscguCfuAfAfcacaAfuUfucagasasc	2338	GUUCUGAAAUUGUGUUAGACGGU	959
AD-953807.1	csuscuu(Ghd)UfcCfAfUfuguguccgcaL96	2165	VPusGfscggAfcAfCfaaugGfaCfaagagsgsu	2339	ACCUCUUGUCCAUUGUGUCCGCC	2483
AD-953822.1	gsasgug(Chd)UfcAfAfUfaauguugucaL96	2166	VPusGfsacaAfcAfUfuauuGfaGfcacucsgsu	2340	ACGAGUGCUCAAUAAUGUUGUCA	2484
AD-953830.1	asgsuuu(Ghd)CfaUfUfUfggaguuuagaL96	2167	VPusCfsuaaAfcUfCfcaaaUfgCfaaacusgsg	2341	CCAGUUUGCAUUUGGAGUUUAGG	2485
AD-953838.1	asgscuu(Ghd)GfuUfCfCfcauuggaucaL96	2168	VPusGfsaucCfaAfUfgggaAfcCfaagcusgsa	2342	UCAGCUUGGUUCCCAUUGGAUCU	2486
AD-953846.1	csusgaa(Ahd)UfcCfUfGfcuuuagucgaL96	2169	VPusCfsgacUfaAfAfgcagGfaUfuucagsgsu	2343	ACCUGAAAUCCUGCUUUAGUCGA	2487
AD-953854.1	asgsaau(Ghd)CfuAfUfUfcauaaucacaL96	2170	VPusGfsugaUfuAfUfgaauAfgCfauucususa	2344	UAAGAAUGCUAUUCAUAAUCACA	921
AD-953768.1	ususauc(Ahd)AfaGfCfUfuugauggauaL96	2171	VPusAfsuccAfuCfAfaagcUfuUfgauaascsu	2345	AGUUAUCAAAGCUUUGAUGGAUU	2488
AD-953776.1	csuscug(Chd)UfgAfUfUfcuuggcgugaL96	2172	VPusCfsacgCfcAfAfgaauCfaGfcagagsusg	2346	CACUCUGCUGAUUCUUGGCGUGC	2489
AD-953784.1	csascca(Ahd)GfaCfCfAfcaauguuguaL96	2173	VPusAfscaaCfaUfUfguggUfcUfuggugscsu	2347	AGCACCAAGACCACAAUGUUGUG	2490
AD-953792.1	gsasgga(Uhd)GfaCfUfCfugaaucgagaL96	2174	VPusCfsucgAfuUfCfagagUfcAfuccucscsa	2348	UGGAGGAUGACUCUGAAUCGAGA	2491
AD-953800.1	csusgaa(Ahd)UfuGfUfGfuuagacgguaL96	2175	VPusAfsccgUfcUfAfacacAfaUfuucagsasa	2349	UUCUGAAAUUGUGUUAGACGGUA	971
AD-953808.1	uscscgc(Chd)UfuUfUfAfucugcuucgaL96	2176	VPusCfsgaaGfcAfGfauaaAfaGfgcggascsa	2350	UGUCCGCCUUUUAUCUGCUUCGU	2492

Duplex ID	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-953815.1	gsasacu(Ahd)CfaUfCfGfaucauggagaL96	2177	VPusCfsuccAfuGfAfucgaUfgUfaguucsasa	2351	UUGAACUACAUCGAUCAUGGAGA	2493
AD-953823.1	gscscuc(Chd)AfuCfUfCfauuucuccgaL96	2178	VPusCfsggaGfaAfAfugagAfuGfgaggcsusg	2352	CAGCCUCCAUCUCAUUUCUCCGU	2494
AD-953831.1	gsusuug(Chd)AfuUfUfGfgaguuuaggaL96	2179	VPusCfscuaAfaCfUfccaaAfuGfcaaacsusg	2353	CAGUUUGCAUUUGGAGUUUAGGU	2495
AD-953839.1	asgsaug(Chd)UfuUfGfAfuuuuggccgaL96	2180	VPusCfsggcCfaAfAfaucaAfaGfcaucususg	2354	CAAGAUGCUUUGAUUUUGGCCGG	2496
AD-953847.1	gsasaau(Chd)CfuGfCfUfuuagucgagaL96	2181	VPusCfsucgAfcUfAfaagcAfgGfauuucsasg	2355	CUGAAAUCCUGCUUUAGUCGAGA	2497
AD-953855.1	gscsuau(Uhd)CfaUfAfAfucacauucgaL96	2182	VPusCfsgaaUfgUfGfauuaUfgAfauagcsasu	2356	AUGCUAUUCAUAAUCACAUUCGU	988
AD-953769.1	gscsuuu(Ghd)AfuGfGfAfuucuaaucuaL96	2183	VPusAfsgauUfaGfAfauccAfuCfaaagcsusu	2357	AAGCUUUGAUGGAUUCUAAUCUU	946
AD-953777.1	gscsagc(Uhd)UfgUfCfCfagguuuaugaL96	2184	VPusCfsauaAfaCfCfuggaCfaAfgcugcsusc	2358	GAGCAGCUUGUCCAGGUUUAUGA	2498
AD-953785.1	ascscaa(Ghd)AfcCfAfCfaauguugugaL96	2185	VPusCfsacaAfcAfUfugugGfuCfuuggusgsc	2359	GCACCAAGACCACAAUGUUGUGA	2499
AD-953793.1	asgsgau(Ghd)AfcUfCfUfgaaucgagaaL96	2186	VPusUfscucGfaUfUfcagaGfuCfauccuscsc	2360	GGAGGAUGACUCUGAAUCGAGAU	2500
AD-953801.1	usgsaaa(Uhd)UfgUfGfUfuagacgguaaL96	2187	VPusUfsaccGfuCfUfaacaCfaAfuuucasgsa	2361	UCUGAAAUUGUGUUAGACGGUAC	1003
AD-953809.1	cscsgcc(Uhd)UfuUfAfUfcugcuucguaL96	2188	VPusAfscgaAfgCfAfgauaAfaAfggcggsasc	2362	GUCCGCCUUUUAUCUGCUUCGUU	2501
AD-953816.1	csusuug(Ghd)CfgGfAfUfugcauuccuaL96	2189	VPusAfsggaAfuGfCfaaucCfgCfcaaagsasa	2363	UUCUUUGGCGGAUUGCAUUCCUU	2502
AD-953824.1	cscsucc(Ahd)UfcUfCfAfuuucuccguaL96	2190	VPusAfscggAfgAfAfaugaGfaUfggaggscsu	2364	AGCCUCCAUCUCAUUUCUCCGUC	2503
AD-953832.1	gsuscua(Ghd)GfaAfGfAfgcuguaccgaL96	2191	VPusCfsgguAfcAfGfcucuUfcCfuagacsusc	2365	GAGUCUAGGAAGAGCUGUACCGU	2504
AD-953840.1	gsgsccg(Ghd)AfaAfCfUfugcuugcagaL96	2192	VPusCfsugcAfaGfCfaaguUfuCfcggccsasa	2366	UUGGCCGGAAACUUGCUUGCAGC	2505
AD-953848.1	ususuag(Uhd)CfgAfGfAfaccaaugauaL96	2193	VPusAfsucaUfuGfGfuucuCfgAfcuaaasgsc	2367	GCUUUAGUCGAGAACCAAUGAUG	2506
AD-953856.1	ususcau(Ahd)AfuCfAfCfauucguuugaL96	2194	VPusCfsaaaCfgAfAfugugAfuUfaugaasusa	2368	UAUUCAUAAUCACAUUCGUUUGU	972
AD-953770.1	gsasuuc(Uhd)AfaUfCfUfuccaagguuaL96	2195	VPusAfsaccUfuGfGfaagaUfuAfgaaucscsa	2369	UGGAUUCUAAUCUUCCAAGGUUA	952
AD-953778.1	csasggu(Uhd)UfaUfGfAfacugacguuaL96	2196	VPusAfsacgUfcAfGfuucaUfaAfaccugsgsa	2370	UCCAGGUUUAUGAACUGACGUUA	964

Duplex ID	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-953786.1	gsasgua(Uhd)UfgUfGfGfaacuuauagaL96	2197	VPusCfsuauAfaGfUfuccaCfaAfuacucscsc	2371	GGGAGUAUUGUGGAACUUAUAGC	998
AD-953794.1	gsgsaug(Ahd)CfuCfUfGfaaucgagauaL96	2198	VPusAfsucuCfgAfUfucagAfgUfcauccsusc	2372	GAGGAUGACUCUGAAUCGAGAUC	2507
AD-953802.1	gsasaau(Uhd)GfuGfUfUfagacgguacaL96	2199	VPusGfsuacCfgUfCfuaacAfcAfauuucsasg	2373	CUGAAAUUGUGUUAGACGGUACC	2508
AD-953817.1	ususugg(Chd)GfgAfUfUfgcauuccuuaL96	2200	VPusAfsaggAfaUfGfcaauCfcGfccaaasgsa	2374	UCUUUGGCGGAUUGCAUUCCUUU	2509
AD-953825.1	csuscca(Uhd)CfuCfAfUfuucuccgucaL96	2201	VPusGfsacgGfaGfAfaaugAfgAfuggagsgsc	2375	GCCUCCAUCUCAUUUCUCCGUCA	2510
AD-953833.1	uscsuag(Ghd)AfaGfAfGfcuguaccguaL96	2202	VPusAfscggUfaCfAfgcucUfuCfcuagascsu	2376	AGUCUAGGAAGAGCUGUACCGUU	2511
AD-953841.1	csusucu(Chd)UfaAfGfUfcccauccgaaL96	2203	VPusUfscggAfuGfGfgacuUfaGfagaagsgsg	2377	CCCUUCUCUAAGUCCCAUCCGAC	2512
AD-953849.1	ususagu(Chd)GfaGfAfAfccaaugaugaL96	2204	VPusCfsaucAfuUfGfguucUfcGfacuaasasg	2378	CUUUAGUCGAGAACCAAUGAUGG	2513

Table 11. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953943.1	AGCUACCAAGAAAGACCGUGA	1784	430-450	UCACGGTCUUUCUUGGUAGCUGA	2574	428-450
AD-953944.1	CUACCAAGAAAGACCGUGUGA	1794	432-452	UCACACGGUCUUUCUUGGUAGCU	1955	430-452
AD-953945.1	UACCAAGAAAGACCGUGUGAA	2514	433-453	UUCACACGGUCUUUCUUGGUAGC	2575	431-453
AD-953946.1	CAUUGUCUGACAAUAUGUGAA	119	455-475	UUCACATAUUGUCAGACAAUGAU	320	453-475
AD-953947.1	AAUGCCUCAACAAAGUUAUCA	1826	597-617	UGAUAACUUUGUUGAGGCAUUCG	1988	595-617
AD-953948.1	UCAACAAAGUUAUCAAAGCUA	2515	603-623	UAGCUUTGAUAACUUUGUUGAGG	2576	601-623
AD-953949.1	CAACAAAGUUAUCAAAGCUUA	2516	604-624	UAAGCUTUGAUAACUUUGUUGAG	2577	602-624
AD-953950.1	GCUUUGAUGGAUUCUAAUCUA	1847	620-640	UAGAUUAGAAUCCAUCAAAGCUU	2010	618-640
AD-953951.1	UUGAUGGAUUCUAAUCUUCCA	161	623-643	UGGAAGAUUAGAAUCCAUCAAAG	362	621-643
AD-953952.1	AUGGAUUCUAAUCUUCCAAGA	2517	626-646	UCUUGGAAGAUUAGAAUCCAUCA	2578	624-646
AD-953953.1	GAUUCUAAUCUUCCAAGGUUA	146	629-649	UAACCUTGGAAGAUUAGAAUCCA	347	627-649

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953954.1	AUUCUAAUCUUCCAAGGUUAA	1785	630-650	UUAACCTUGGAAGAUUAGAAUCC	2579	628-650
AD-953955.1	UUCUAAUCUUCCAAGGUUACA	191	631-651	UGUAACCUUGGAAGAUUAGAAUC	392	629-651
AD-953956.1	UUCCAAGGUUACAGCUCGAGA	1795	639-659	UCUCGAGCUGUAACCUUGGAAGA	1956	637-659
AD-953957.1	UGUUCCCAAAAUUAUGGCUUA	2518	844-864	UAAGCCAUAAUUUUGGGAACAGC	2580	842-864
AD-953958.1	AGGCCUUCAUAGCGAACCUGA	1827	909-929	UCAGGUTCGCUAUGAAGGCCUUU	2581	907-929
AD-953959.1	CCAGGUUUAUGAACUGACGUA	2519	1216-1236	UACGUCAGUUCAUAAACCUGGAC	2582	1214-1236
AD-953960.1	CAGGUUUAUGAACUGACGUUA	158	1217-1237	UAACGUCAGUUCAUAAACCUGGA	359	1215-1237
AD-953961.1	AGGUUUAUGAACUGACGUUAA	1786	1218-1238	UUAACGTCAGUUCAUAAACCUGG	2583	1216-1238
AD-953962.1	GUUUAUGAACUGACGUUACAA	2520	1220-1240	UUGUAACGUCAGUUCAUAAACCU	2584	1218-1240
AD-953963.1	UUUAUGAACUGACGUUACAUA	1807	1221-1241	UAUGUAACGUCAGUUCAUAAACC	1968	1219-1241
AD-953964.1	ACUGACGUUACAUCAUACACA	129	1228-1248	UGUGUATGAUGUAACGUCAGUUC	330	1226-1248
AD-953965.1	CAGCACCAAGACCACAAUGUA	1816	1247-1267	UACAUUGUGGUCUUGGUGCUGUG	1978	1245-1267
AD-953966.1	GCACCAAGACCACAAUGUUGA	1828	1249-1269	UCAACATUGUGGUCUUGGUGCUG	2585	1247-1269
AD-953967.1	GCAGCAGCUCUUCAGAACGCA	2521	1291-1311	UGCGUUCUGAAGAGCUGCUGCAA	2586	1289-1311
AD-953968.1	GAGUAUUGUGGAACUUAUAGA	1859	1405-1425	UCUAUAAGUUCCACAAUACUCCC	2023	1403-1425
AD-953969.1	AGUAUUGUGGAACUUAUAGCA	1787	1406-1426	UGCUAUAAGUUCCACAAUACUCC	1948	1404-1426
AD-953970.1	GUAUUGUGGAACUUAUAGCUA	1797	1407-1427	UAGCUATAAGUUCCACAAUACUC	2587	1405-1427
AD-953971.1	UGGAGGAUGACUCUGAAUCGA	1829	1503-1523	UCGAUUCAGAGUCAUCCUCCAAG	1991	1501-1523
AD-953972.1	GAGGAUGACUCUGAAUCGAGA	1839	1505-1525	UCUCGATUCAGAGUCAUCCUCCA	2588	1503-1525
AD-953973.1	AGGAUGACUCUGAAUCGAGAA	1850	1506-1526	UUCUCGAUUCAGAGUCAUCCUCC	2013	1504-1526
AD-953974.1	GGAUGACUCUGAAUCGAGAUA	1860	1507-1527	UAUCUCGAUUCAGAGUCAUCCUC	2024	1505-1527
AD-953975.1	GACUCUGAAUCGAGAUCGGAA	1788	1511-1531	UUCCGATCUCGAUUCAGAGUCAU	2589	1509-1531
AD-953976.1	ACUCUGAAUCGAGAUCGGAUA	1798	1512-1532	UAUCCGAUCUCGAUUCAGAGUCA	1959	1510-1532
AD-953977.1	CUCUGAAUCGAGAUCGGAUGA	1809	1513-1533	UCAUCCGAUCUCGAUUCAGAGUC	1970	1511-1533
AD-953978.1	UCUGAAUCGAGAUCGGAUGUA	2522	1514-1534	UACAUCCGAUCUCGAUUCAGAGU	2590	1512-1534
AD-953979.1	UUCUGAAAUUGUGUUAGACGA	1818	1885-1905	UCGUCUAACACAAUUUCAGAACU	1980	1883-1905
AD-953980.1	UCUGAAAUUGUGUUAGACGGA	1830	1886-1906	UCCGUCTAACACAAUUUCAGAAC	2591	1884-1906

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-953981.1	CUGAAAUUGUGUUAGACGGUA	165	1887-1907	UACCGUCUAACACAAUUUCAGAA	366	1885-1907
AD-953982.1	UGAAAUUGUGUUAGACGGUAA	1851	1888-1908	UUACCGTCUAACACAAUUUCAGA	2592	1886-1908
AD-953983.1	GAAAUUGUGUUAGACGGUACA	1861	1889-1909	UGUACCGUCUAACACAAUUUCAG	2025	1887-1909
AD-953984.1	CGGUACCGACAACCAGUAUUA	2523	1903-1923	UAAUACTGGUUGUCGGUACCGUC	2593	1901-1923
AD-953985.1	ACAGCAGUGUUGAUAAAUUUA	1789	2073-2093	UAAAUUTAUCAACACUGCUGUCA	2594	2071-2093
AD-953986.1	CCUCUUGUCCAUUGUGUCCGA	1819	2189-2209	UCGGACACAAUGGACAAGAGGUG	1981	2187-2209
AD-953987.1	UCCGCCUUUUAUCUGCUUCGA	1840	2205-2225	UCGAAGCAGAUAAAAGGCGGACA	2003	2203-2225
AD-953988.1	CCGCCUUUUAUCUGCUUCGUA	1852	2206-2226	UACGAAGCAGAUAAAAGGCGGAC	2015	2204-2226
AD-953989.1	CGCCUUUUAUCUGCUUCGUUA	1790	2207-2227	UAACGAAGCAGAUAAAAGGCGGA	1951	2205-2227
AD-953990.1	CAAACUCUAUAAAGUUCCUCA	2524	2347-2367	UGAGGAACUUUAUAGAGUUUGCU	2595	2345-2367
AD-953991.1	UCUAUAAAGUUCCUCUUGACA	181	2352-2372	UGUCAAGAGGAACUUUAUAGAGU	382	2350-2372
AD-953992.1	CAUCUUGAACUACAUCGAUCA	1811	2407-2427	UGAUCGAUGUAGUUCAAGAUGUC	1972	2405-2427
AD-953993.1	AUCUUGAACUACAUCGAUCAA	2525	2408-2428	UUGAUCGAUGUAGUUCAAGAUGU	2596	2406-2428
AD-953994.1	UCUUGAACUACAUCGAUCAUA	2526	2409-2429	UAUGAUCGAUGUAGUUCAAGAUG	2597	2407-2429
AD-953995.1	CUUGAACUACAUCGAUCAUGA	1820	2410-2430	UCAUGATCGAUGUAGUUCAAGAU	2598	2408-2430
AD-953996.1	UUGAACUACAUCGAUCAUGGA	211	2411-2431	UCCAUGAUCGAUGUAGUUCAAGA	412	2409-2431
AD-953997.1	GAACUACAUCGAUCAUGGAGA	1841	2413-2433	UCUCCATGAUCGAUGUAGUUCAA	2599	2411-2433
AD-953998.1	UUUGGCGGAUUGCAUUCCUUA	1862	2560-2580	UAAGGAAUGCAAUCCGCCAAAGA	2026	2558-2580
AD-953999.1	UUGGCGGAUUGCAUUCCUUUA	2527	2561-2581	UAAAGGAAUGCAAUCCGCCAAAG	2600	2559-2581
AD-954000.1	GCUACAGUGAGUUAGGACUGA	2528	2673-2693	UCAGUCCUAACUCACUGUAGCUG	2601	2671-2693
AD-954001.1	CUCUGAGGAACAGUUCCUAUA	2529	2715-2735	UAUAGGAACUGUUCCUCAGAGUC	2602	2713-2735
AD-954002.1	CUGAGGAACAGUUCCUAUUGA	1791	2717-2737	UCAAUAGGAACUGUUCCUCAGAG	1952	2715-2737
AD-954003.1	UGAGGAACAGUUCCUAUUGGA	1800	2718-2738	UCCAAUAGGAACUGUUCCUCAGA	1961	2716-2738
AD-954004.1	GAGGAACAGUUCCUAUUGGCA	2530	2719-2739	UGCCAATAGGAACUGUUCCUCAG	2603	2717-2739
AD-954005.1	GAGUGCUCAAUAAUGUUGUCA	1832	2868-2888	UGACAACAUUAUUGAGCACUCGU	1994	2866-2888
AD-954006.1	GCCUCCAUCUCAUUUCUCCGA	1842	3061-3081	UCGGAGAAAUGAGAUGGAGGCUG	2005	3059-3081
AD-954007.1	CCUCCAUCUCAUUUCUCCGUA	1854	3062-3082	UACGGAGAAAUGAGAUGGAGGCU	2017	3060-3082

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954008.1	CUCCAUCUCAUUUCUCCGUCA	1863	3063-3083	UGACGGAGAAAUGAGAUGGAGGC	2027	3061-3083
AD-954009.1	UCUCCGUCAGCACAAUAACCA	1801	3075-3095	UGGUUATUGUGCUGACGGAGAAA	2604	3073-3095
AD-954010.1	CUCCGUCAGCACAAUAACCAA	2531	3076-3096	UUGGUUAUUGUGCUGACGGAGAA	2605	3074-3096
AD-954011.1	UCCGUCAGCACAAUAACCAGA	1812	3077-3097	UCUGGUTAUUGUGCUGACGGAGA	2606	3075-3097
AD-954012.1	AGAGGCUAUAACCUACUACCA	2532	3104-3124	UGGUAGTAGGUUAUAGCCUCUAU	2607	3102-3124
AD-954013.1	ACCUACUACCAAGCAUAACAA	2533	3114-3134	UUGUUATGCUUGGUAGUAGGUUA	2608	3112-3134
AD-954014.1	AACCUUUCAAGAGUUAUUGCA	1822	3152-3172	UGCAAUAACUCUUGAAAGGUUAU	1984	3150-3172
AD-954015.1	AGUUUGCAUUUGGAGUUUAGA	1833	3262-3282	UCUAAACUCCAAAUGCAAACUGG	1995	3260-3282
AD-954016.1	CAGAUGAGUCUAGGAAGAGCA	2534	3315-3335	UGCUCUTCCUAGACUCAUCUGAG	2609	3313-3335
AD-954017.1	GUCUAGGAAGAGCUGUACCGA	1855	3322-3342	UCGGUACAGCUCUUCCUAGACUC	2018	3320-3342
AD-954018.1	UAGGAAGAGCUGUACCGUUGA	1792	3325-3345	UCAACGGUACAGCUCUUCCUAGA	1953	3323-3345
AD-954019.1	GUCAGCUUGGUUCCCAUUGGA	1823	3376-3396	UCCAAUGGGAACCAAGCUGACGA	1985	3374-3396
AD-954020.1	GGCCGGAAACUUGCUUGCAGA	1856	3427-3447	UCUGCAAGCAAGUUUCCGGCCAA	2019	3425-3447
AD-954021.1	CUUCUCUAAGUCCCAUCCGAA	1865	3678-3698	UUCGGATGGGACUUAGAGAAGGG	2610	3676-3698
AD-954022.1	GAGAACAAGCAUCUGUACCGA	1803	3723-3743	UCGGUACAGAUGCUUGUUCUCCU	1964	3721-3743
AD-954023.1	AACAAGCAUCUGUACCGUUGA	2535	3726-3746	UCAACGGUACAGAUGCUUGUUCU	2611	3724-3746
AD-954024.1	AGCAUCUGUACCGUUGAGUCA	2536	3730-3750	UGACUCAACGGUACAGAUGCUUG	2612	3728-3750
AD-954025.1	GCAGCUUCUAGACAAUCUGAA	2537	3773-3793	UUCAGATUGUCUAGAAGCUGCAC	2613	3771-3793
AD-954026.1	UCUAGACAAUCUGAUACCUCA	148	3779-3799	UGAGGUAUCAGAUUGUCUAGAAG	349	3777-3799
AD-954027.1	UCAGGUCCUGUUACAACAAGA	2538	3797-3817	UCUUGUTGUAACAGGACCUGAGG	2614	3795-3817
AD-954028.1	GGUCCUGUUACAACAAGUAAA	210	3800-3820	UUUACUTGUUGUAACAGGACCUG	411	3798-3820
AD-954029.1	CAAGUAAAUCCUCAUCACUGA	2539	3813-3833	UCAGUGAUGAGGAUUUACUUGUU	2615	3811-3833
AD-954030.1	UUUCUAUCAUCUUCCUUCAUA	172	3838-3858	UAUGAAGGAAGAUGAUAGAAACU	373	3836-3858
AD-954031.1	UUCAUACCUCAAACUGCAUGA	2540	3853-3873	UCAUGCAGUUUGAGGUAUGAAGG	2616	3851-3873
AD-954032.1	ACCUCAAACUGCAUGAUGUCA	2541	3858-3878	UGACAUCAUGCAGUUUGAGGUAU	2617	3856-3878
AD-954033.1	CAGGACAUUGGGAAGUGUGUA	2542	4001-4021	UACACACUUCCCAAUGUCCUGCA	2618	3999-4021
AD-954034.1	CCUGAAAUCCUGCUUUAGUCA	1824	4039-4059	UGACUAAAGCAGGAUUUCAGGUA	1986	4037-4059

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954035.1	CUGAAAUCCUGCUUUAGUCGA	1835	4040-4060	UCGACUAAAGCAGGAUUUCAGGU	1997	4038-4060
AD-954036.1	GAAAUCCUGCUUUAGUCGAGA	1845	4042-4062	UCUCGACUAAAGCAGGAUUUCAG	2008	4040-4062
AD-954037.1	AAUCCUGCUUUAGUCGAGAAA	2543	4044-4064	UUUCUCGACUAAAGCAGGAUUUC	2619	4042-4064
AD-954038.1	UUUAGUCGAGAACCAAUGAUA	1857	4052-4072	UAUCAUTGGUUCUCGACUAAAGC	2620	4050-4072
AD-954039.1	UUAGUCGAGAACCAAUGAUGA	1866	4053-4073	UCAUCATUGGUUCUCGACUAAAG	2621	4051-4073
AD-954040.1	GAUGGCAACUGUUUGUGUUCA	2544	4069-4089	UGAACACAAACAGUUGCCAUCAU	2622	4067-4089
AD-954041.1	GAGUGUCACAAAGAACCGUGA	1804	4369-4389	UCACGGTUCUUUGUGACACUCGU	2623	4367-4389
AD-954042.1	AGUGUCACAAAGAACCGUGCA	2545	4370-4390	UGCACGGUUCUUUGUGACACUCG	2624	4368-4390
AD-954043.1	UGCAGAUAAGAAUGCUAUUCA	111	4387-4407	UGAAUAGCAUUCUUAUCUGCACG	312	4385-4407
AD-954044.1	AGAAUGCUAUUCAUAAUCACA	115	4395-4415	UGUGAUTAUGAAUAGCAUUCUUA	316	4393-4415
AD-954045.1	GCUAUUCAUAAUCACAUUCGA	1846	4400-4420	UCGAAUGUGAUUAUGAAUAGCAU	2009	4398-4420
AD-954046.1	AUCACAUUCGUUUGUUUGAAA	1717	4410-4430	UUUCAAACAAACGAAUGUGAUUA	1878	4408-4430
AD-954047.1	UGUUUGAACCUCUUGUUAUAA	127	4422-4442	UUAUAACAAGAGGUUCAAACAAA	328	4420-4442
AD-954048.1	GUUUGAACCUCUUGUUAUAAA	123	4423-4443	UUUAUAACAAGAGGUUCAAACAA	324	4421-4443
AD-954049.1	UUUGAACCUCUUGUUAUAAAA	122	4424-4444	UUUUAUAACAAGAGGUUCAAACA	323	4422-4444
AD-954050.1	GCUUUAAAACAGUACACGACA	2546	4445-4465	UGUCGUGUACUGUUUUAAAGCUU	2625	4443-4465
AD-954051.1	AGCUGGUUCAGUUACGGGUUA	1766	4512-4532	UAACCCGUAACUGAACCAGCUGC	1927	4510-4532
AD-954052.1	GCUGGUUCAGUUACGGGUUAA	2547	4513-4533	UUAACCCGUAACUGAACCAGCUG	2626	4511-4533
AD-954053.1	UGGUUCAGUUACGGGUUAAUA	2548	4515-4535	UAUUAACCCGUAACUGAACCAGC	2627	4513-4535
AD-954054.1	GUUCAGUUACGGGUUAAUUAA	1775	4517-4537	UUAAUUAACCCGUAACUGAACCA	1936	4515-4537
AD-954055.1	CAGUUACGGGUUAAUUACUGA	1718	4520-4540	UCAGUAAUUAACCCGUAACUGAA	1879	4518-4540
AD-954056.1	UUACGGGUUAAUUACUGUCUA	2549	4523-4543	UAGACAGUAAUUAACCCGUAACU	2628	4521-4543
AD-954057.1	UGGAUUCAGAUCAGGUGUUUA	131	4545-4565	UAAACACCUGAUCUGAAUCCAGA	332	4543-4565
AD-954058.1	UAUGAACGCUAUCAUUCAAAA	196	4667-4687	UUUUGAAUGAUAGCGUUCAUAAG	397	4665-4687
AD-954059.1	GCGACUGUCUCGACAGAUAGA	2550	4963-4983	UCUAUCTGUCGAGACAGUCGCUU	2629	4961-4983
AD-954060.1	CGACUGUCUCGACAGAUAGCA	2551	4964-4984	UGCUAUCUGUCGAGACAGUCGCU	2630	4962-4984
AD-954061.1	GACUGUCUCGACAGAUAGCUA	1776	4965-4985	UAGCUATCUGUCGAGACAGUCGC	2631	4963-4985

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954062.1	ACUGUCUCGACAGAUAGCUGA	1709	4966-4986	UCAGCUAUCUGUCGAGACAGUCG	1869	4964-4986
AD-954063.1	CCCAAUGUUAGCCAAACAGCA	2552	4996-5016	UGCUGUTUGGCUAACAUUGGGAG	2632	4994-5016
AD-954065.1	CACAUUGACUCUCAUGAAGCA	2553	5021-5041	UGCUUCAUGAGAGUCAAUGUGCA	2633	5019-5041
AD-954066.1	GCCCUUGGAGUGUUAAAUACA	1729	5039-5059	UGUAUUTAACACUCCAAGGGCUU	2634	5037-5059
AD-954067.1	ACAUGCUUUUACGGAGUAUGA	1748	5100-5120	UCAUACTCCGUAAAAGCAUGUCU	2635	5098-5120
AD-954068.1	UUUUACGGAGUAUGUUCGUCA	1768	5106-5126	UGACGAACAUACUCCGUAAAAGC	1929	5104-5126
AD-954069.1	UUUACGGAGUAUGUUCGUCAA	1777	5107-5127	UUGACGAACAUACUCCGUAAAAG	1938	5105-5127
AD-954070.1	GAGCACUGUUCAACUGUGGAA	2554	5149-5169	UUCCACAGUUGAACAGUGCUCAC	2636	5147-5169
AD-954071.1	AAGAUAUUGUUCUUUCUCGUA	113	5217-5237	UACGAGAAAGAACAAUAUCUUCA	314	5215-5237
AD-954072.1	GAUAUUGUUCUUUCUCGUAUA	1739	5219-5239	UAUACGAGAAAGAACAAUAUCUU	1900	5217-5239
AD-954073.1	UUGUUCUUUCUCGUAUUCAGA	1749	5223-5243	UCUGAATACGAGAAAGAACAAUA	2637	5221-5243
AD-954074.1	UGUUCUUUCUCGUAUUCAGGA	125	5224-5244	UCCUGAAUACGAGAAAGAACAAU	326	5222-5244
AD-954075.1	AUUUUCAAGGUUUCUAUUACA	137	5368-5388	UGUAAUAGAAACCUUGAAAAUGU	338	5366-5388
AD-954076.1	GUGAGCAGCAACAUACUUUCA	2555	5445-5465	UGAAAGTAUGUUGCUGCUCACUC	2638	5443-5465
AD-954077.1	GCAACAUACUUUCUAUUGCCA	187	5452-5472	UGGCAATAGAAAGUAUGUUGCUG	388	5450-5472
AD-954078.1	AUCUUCAAGUCUGGAAUGUUA	1721	5507-5527	UAACAUTCCAGACUUGAAGAUGU	2639	5505-5527
AD-954079.1	CUGCUUGUCAACCACACCGAA	2556	5672-5692	UUCGGUGUGGUUGACAAGCAGCA	2640	5670-5692
AD-954080.1	UCCGAGCACUUAACGUGGCUA	2557	5888-5908	UAGCCACGUUAAGUGCUCGGAGU	2641	5886-5908
AD-954081.1	CCUCCAGUACAGGACUUCAUA	2558	5951-5971	UAUGAAGUCCUGUACUGGAGGCU	2642	5949-5971
AD-954082.1	CAGGCAAUUCAGUCUCGUUGA	1751	6014-6034	UCAACGAGACUGAAUUGCCUGGA	1912	6012-6034
AD-954083.1	AGGCAAUUCAGUCUCGUUGUA	1760	6015-6035	UACAACGAGACUGAAUUGCCUGG	1921	6013-6035
AD-954084.1	GGCAAUUCAGUCUCGUUGUGA	1770	6016-6036	UCACAACGAGACUGAAUUGCCUG	1931	6014-6036
AD-954085.1	GCAAUUCAGUCUCGUUGUGAA	1712	6017-6037	UUCACAACGAGACUGAAUUGCCU	1873	6015-6037
AD-954086.1	CAAUUCAGUCUCGUUGUGAAA	167	6018-6038	UUUCACAACGAGACUGAAUUGCC	368	6016-6038
AD-954087.1	AUGGUCGACAUCCUUGCUUGA	1723	6170-6190	UCAAGCAAGGAUGUCGACCAUGC	1884	6168-6190
AD-954088.1	GGUCGACAUCCUUGCUUGUCA	2559	6172-6192	UGACAAGCAAGGAUGUCGACCAU	2643	6170-6192
AD-954089.1	GUCGACAUCCUUGCUUGUCGA	1732	6173-6193	UCGACAAGCAAGGAUGUCGACCA	1893	6171-6193

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954090.1	CUGGACAGGUUUCGUCUCUCA	2560	6326-6346	UGAGAGACGAAACCUGUCCAGCA	2644	6324-6346
AD-954091.1	CAUGCAAGACUCACUUAGUCA	1742	6349-6369	UGACUAAGUGAGUCUUGCAUGGU	1903	6347-6369
AD-954092.1	AUGCAAGACUCACUUAGUCCA	1752	6350-6370	UGGACUAAGUGAGUCUUGCAUGG	1913	6348-6370
AD-954093.1	UGUCACUGGAAACAGUGAGUA	2561	6414-6434	UACUCACUGUUUCCAGUGACACG	2645	6412-6434
AD-954094.1	CACUGGAAACAGUGAGUCCGA	1761	6417-6437	UCGGACTCACUGUUUCCAGUGAC	2646	6415-6437
AD-954095.1	GCUGGUGAAUCGGAUUCCUGA	1780	6514-6534	UCAGGAAUCCGAUUCACCAGCUC	1941	6512-6534
AD-954096.1	AACUCGGAGUUCAACCUAAGA	2562	6560-6580	UCUUAGGUUGAACUCCGAGUUCA	2647	6558-6580
AD-954097.1	ACUCGGAGUUCAACCUAAGCA	2563	6561-6581	UGCUUAGGUUGAACUCCGAGUUC	2648	6559-6581
AD-954098.1	CUCGGAGUUCAACCUAAGCCA	2564	6562-6582	UGGCUUAGGUUGAACUCCGAGUU	2649	6560-6582
AD-954099.1	CUGGAGCAAGUUGAAUGAUCA	2565	6754-6774	UGAUCATUCAACUUGCUCCAGUA	2650	6752-6774
AD-954100.1	AGAGCAGCUUCUUAGUCCAGA	2566	7120-7140	UCUGGACUAAGAAGCUGCUCUCC	2651	7118-7140
AD-954101.1	CUUGUCAACAGCUACACACGA	2567	7361-7381	UCGUGUGUAGCUGUUGACAAGGG	2652	7359-7381
AD-954102.1	UCAACAGCUACACACGUGUGA	1781	7365-7385	UCACACGUGUGUAGCUGUUGACA	1942	7363-7385
AD-954103.1	CAACAGCUACACACGUGUGCA	1714	7366-7386	UGCACACGUGUGUAGCUGUUGAC	1875	7364-7386
AD-954104.1	CUUUAAGGAGUUCAUCUACCA	2568	7486-7506	UGGUAGAUGAACUCCUUAAAGAC	2653	7484-7506
AD-954105.1	GGACCAGUCGUACUCAGUUUA	2569	7524-7544	UAAACUGAGUACGACUGGUCCAG	2654	7522-7544
AD-954106.1	GACCAGUCGUACUCAGUUUGA	1725	7525-7545	UCAAACTGAGUACGACUGGUCCA	2655	7523-7545
AD-954107.1	ACCAGUCGUACUCAGUUUGAA	1734	7526-7546	UUCAAACUGAGUACGACUGGUCC	1895	7524-7546
AD-954108.1	CCAGUCGUACUCAGUUUGAAA	1744	7527-7547	UUUCAAACUGAGUACGACUGGUC	1905	7525-7547
AD-954109.1	CAGUCGUACUCAGUUUGAAGA	120	7528-7548	UCUUCAAACUGAGUACGACUGGU	321	7526-7548
AD-954110.1	GACGCUGACAGAACUGCGAAA	1715	8317-8337	UUUCGCAGUUCUGUCAGCGUCAC	1876	8315-8337
AD-954111.1	ACGCUGACAGAACUGCGAAGA	1726	8318-8338	UCUUCGCAGUUCUGUCAGCGUCA	1887	8316-8338
AD-954112.1	UCAUUGAGAACUAUCCUCUGA	2570	8667-8687	UCAGAGGAUAGUUCUCAAUGAGG	2656	8665-8687
AD-954113.1	CGGCUGCUGACUUGUUUACGA	1764	9533-9553	UCGUAAACAAGUCAGCAGCCGGU	1925	9531-9553
AD-954114.1	GGCUGCUGACUUGUUUACGAA	1774	9534-9554	UUCGUAAACAAGUCAGCAGCCGG	1935	9532-9554
AD-954115.1	CUGCUGACUUGUUUACGAAAA	1783	9536-9556	UUUUCGTAAACAAGUCAGCAGCC	2657	9534-9556
AD-954116.1	UGCUGACUUGUUUACGAAAUA	2571	9537-9557	UAUUUCGUAAACAAGUCAGCAGC	2658	9535-9557

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954117.1	CUGACUUGUUUACGAAAUGUA	1716	9539-9559	UACAUUTCGUAAACAAGUCAGCA	2659	9537-9559
AD-954118.1	UGACUUGUUUACGAAAUGUCA	1727	9540-9560	UGACAUTUCGUAAACAAGUCAGC	2660	9538-9560
AD-954119.1	UAACGUAACUCUUUCUAUGCA	1736	10173-10193	UGCAUAGAAAGAGUUACGUUAAA	1897	10171-10193
AD-954120.1	CCGCUGACAUUUCCGUUGUAA	1765	10311-10331	UUACAACGGAAAUGUCAGCGGGU	1926	10309-10331
AD-954121.1	CUGACAUUUCCGUUGUACAUA	2572	10314-10334	UAUGUACAACGGAAAUGUCAGCG	2661	10312-10334
AD-954122.1	UCCGUUGUACAUGUUCCUGUA	2573	10322-10342	UACAGGAACAUGUACAACGGAAA	2662	10320-10342

Table 12. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-953943.1	asgscua(Chd)CfaAfGfAfaagaccgugaL96	2116	VPusCfsacgg(Tgn)cuuucuUfgGfuagcusgsa	2734	UCAGCUACCAAGAAAGACCGUGU	2445
AD-953944.1	csusacc(Ahd)AfgAfAfAfgaccgugugaL96	2126	VPusCfsacac(Ggn)gucuuuCfuUfgguagscsu	2735	AGCUACCAAGAAAGACCGUGUGA	2450
AD-953945.1	usascca(Ahd)GfaAfAfGfaccgugugaaL96	2663	VPusUfscaca(Cgn)ggucuuUfcUfugguasgsc	2736	GCUACCAAGAAAGACCGUGUGAA	2913
AD-953946.1	csasuug(Uhd)CfuGfAfCfaauaugugaaL96	2148	VPusUfscaca(Tgn)auugucAfgAfcaaugsasu	2737	AUCAUUGUCUGACAAUAUGUGAA	925
AD-953947.1	asasugc(Chd)UfcAfAfCfaaaguuaucaL96	2160	VPusGfsauaa(Cgn)uuuguuGfaGfgcauuscsg	2738	CGAAUGCCUCAACAAAGUUAUCA	2479
AD-953948.1	uscsaac(Ahd)AfaGfUfUfaucaaagcuaL96	2664	VPusAfsgcuu(Tgn)gauaacUfuUfguugasgsg	2739	CCUCAACAAAGUUAUCAAAGCUU	922
AD-953949.1	csasaca(Ahd)AfgUfUfAfucaaagcuuaL96	2665	VPusAfsagcu(Tgn)ugauaaCfuUfuguugsasg	2740	CUCAACAAAGUUAUCAAAGCUUU	955
AD-953950.1	gscsuuu(Ghd)AfuGfGfAfuucuaaucuaL96	2183	VPusAfsgauu(Agn)gaauccAfuCfaaagcsusu	2741	AAGCUUUGAUGGAUUCUAAUCUU	946
AD-953951.1	ususgau(Ghd)GfaUfUfCfuaaucuuccaL96	2666	VPusGfsgaag(Agn)uuagaaUfcCfaucaasasg	2742	CUUUGAUGGAUUCUAAUCUUCCA	967
AD-953952.1	asusgga(Uhd)UfcUfAfAfucuuccaagaL96	2667	VPusCfsuugg(Agn)agauuaGfaAfuccauscsa	2743	UGAUGGAUUCUAAUCUUCCAAGG	985
AD-953953.1	gsasuuc(Uhd)AfaUfCfUfuccaagguuaL96	2195	VPusAfsaccu(Tgn)ggaagaUfuAfgaaucscsa	2744	UGGAUUCUAAUCUUCCAAGGUUA	952
AD-953954.1	asusucu(Ahd)AfuCfUfUfccaagguuaaL96	2117	VPusUfsaacc(Tgn)uggaagAfuUfagaauscsc	2745	GGAUUCUAAUCUUCCAAGGUUAC	965

Duplex ID	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-953955.1	ususcua(Ahd)UfcUfUfCfcaagguuacaL96	2668	VPusGfsuaac(Cgn)uuggaaGfaUfuagaasusc	2746	GAUUCUAAUCUUCCAAGGUUACA	997
AD-953956.1	ususcca(Ahd)GfgUfUfAfcagcucgagaL96	2127	VPusCfsucga(Ggn)cuguaaCfcUfuggaasgsa	2747	UCUUCCAAGGUUACAGCUCGAGC	2451
AD-953957.1	usgsuuc(Chd)CfaAfAfAfuuauggcuuaL96	2669	VPusAfsagcc(Agn)uaauuuUfgGfgaacasgsc	2748	GCUGUUCCCAAAAUUAUGGCUUC	977
AD-953958.1	asgsgcc(Uhd)UfcAfUfAfgcgaaccugaL96	2161	VPusCfsaggu(Tgn)cgcuauGfaAfggccususu	2749	AAAGGCCUUCAUAGCGAACCUGA	2480
AD-953959.1	cscsagg(Uhd)UfuAfUfGfaacugacguaL96	2670	VPusAfscguc(Agn)guucauAfaAfccuggsasc	2750	GUCCAGGUUUAUGAACUGACGUU	974
AD-953960.1	csasggu(Uhd)UfaUfGfAfacugacguuaL96	2196	VPusAfsacgu(Cgn)aguucaUfaAfaccugsgsa	2751	UCCAGGUUUAUGAACUGACGUUA	964
AD-953961.1	asgsguu(Uhd)AfuGfAfAfcugacguuaaL96	2118	VPusUfsaacg(Tgn)caguucAfuAfaaccusgsg	2752	CCAGGUUUAUGAACUGACGUUAC	991
AD-953962.1	gsusuua(Uhd)GfaAfCfUfgacguuacaaL96	2671	VPusUfsguaa(Cgn)gucaguUfcAfuaaacscsu	2753	AGGUUUAUGAACUGACGUUACAU	2914
AD-953963.1	ususuau(Ghd)AfaCfUfGfacguuacauaL96	2140	VPusAfsugua(Agn)cgucagUfuCfauaaascsc	2754	GGUUUAUGAACUGACGUUACAUC	2462
AD-953964.1	ascsuga(Chd)GfuUfAfCfaucauacacaL96	2672	VPusGfsugua(Tgn)gauguaAfcGfucagususc	2755	GAACUGACGUUACAUCAUACACA	935
AD-953965.1	csasgca(Chd)CfaAfGfAfccacaauguaL96	2150	VPusAfscauu(Ggn)uggucuUfgGfugcugsusg	2756	CACAGCACCAAGACCACAAUGUU	2471
AD-953966.1	gscsacc(Ahd)AfgAfCfCfacaauguugaL96	2162	VPusCfsaaca(Tgn)ugugguCfuUfggugcsusg	2757	CAGCACCAAGACCACAAUGUUGU	2481
AD-953967.1	gscsagc(Ahd)GfcUfCfUfucagaacgcaL96	2673	VPusGfscguu(Cgn)ugaagaGfcUfgcugcsasa	2758	UUGCAGCAGCUCUUCAGAACGCC	2915
AD-953968.1	gsasgua(Uhd)UfgUfGfGfaacuuauagaL96	2197	VPusCfsuaua(Agn)guuccaCfaAfuacucscsc	2759	GGGAGUAUUGUGGAACUUAUAGC	998
AD-953969.1	asgsuau(Uhd)GfuGfGfAfacuuauagcaL96	2119	VPusGfscuau(Agn)aguuccAfcAfauacuscsc	2760	GGAGUAUUGUGGAACUUAUAGCU	2446
AD-953970.1	gsusauu(Ghd)UfgGfAfAfcuuauagcuaL96	2129	VPusAfsgcua(Tgn)aaguucCfaCfaauacsusc	2761	GAGUAUUGUGGAACUUAUAGCUG	2453
AD-953971.1	usgsgag(Ghd)AfuGfAfCfucugaaucgaL96	2163	VPusCfsgauu(Cgn)agagucAfuCfcuccasasg	2762	CUUGGAGGAUGACUCUGAAUCGA	2482
AD-953972.1	gsasgga(Uhd)GfaCfUfCfugaaucgagaL96	2174	VPusCfsucga(Tgn)ucagagUfcAfuccucscsa	2763	UGGAGGAUGACUCUGAAUCGAGA	2491
AD-953973.1	asgsgau(Ghd)AfcUfCfUfgaaucgagaaL96	2186	VPusUfscucg(Agn)uucagaGfuCfauccuscsc	2764	GGAGGAUGACUCUGAAUCGAGAU	2500
AD-953974.1	gsgsaug(Ahd)CfuCfUfGfaaucgagauaL96	2198	VPusAfsucuc(Ggn)auucagAfgUfcauccsusc	2765	GAGGAUGACUCUGAAUCGAGAUC	2507

Duplex ID	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-953975.1	gsascuc(Uhd)GfaAfUfCfgagaucggaaL96	2120	VPusUfsccga(Tgn)cucgauUfcAfgagucsasu	2766	AUGACUCUGAAUCGAGAUCGGAU	2447
AD-953976.1	ascsucu(Ghd)AfaUfCfGfagaucggauaL96	2130	VPusAfsuccg(Agn)ucucgaUfuCfagaguscsa	2767	UGACUCUGAAUCGAGAUCGGAUG	1011
AD-953977.1	csuscug(Ahd)AfuCfGfAfgaucggaugaL96	2142	VPusCfsaucc(Ggn)aucucgAfuUfcagagsusc	2768	GACUCUGAAUCGAGAUCGGAUGU	2464
AD-953978.1	uscsuga(Ahd)UfcGfAfGfaucggauguaL96	2674	VPusAfscauc(Cgn)gaucucGfaUfucagasgsu	2769	ACUCUGAAUCGAGAUCGGAUGUC	1013
AD-953979.1	ususcug(Ahd)AfaUfUfGfuguuagacgaL96	2152	VPusCfsgucu(Agn)acacaaUfuUfcagaascsu	2770	AGUUCUGAAAUUGUGUUAGACGG	2473
AD-953980.1	uscsuga(Ahd)AfuUfGfUfguuagacggaL96	2164	VPusCfscguc(Tgn)aacacaAfuUfucagasasc	2771	GUUCUGAAAUUGUGUUAGACGGU	959
AD-953981.1	csusgaa(Ahd)UfuGfUfGfuuagacgguaL96	2175	VPusAfsccgu(Cgn)uaacacAfaUfuucagsasa	2772	UUCUGAAAUUGUGUUAGACGGUA	971
AD-953982.1	usgsaaa(Uhd)UfgUfGfUfuagacgguaaL96	2187	VPusUfsaccg(Tgn)cuaacaCfaAfuuucasgsa	2773	UCUGAAAUUGUGUUAGACGGUAC	1003
AD-953983.1	gsasaau(Uhd)GfuGfUfUfagacgguacaL96	2199	VPusGfsuacc(Ggn)ucuaacAfcAfauuucsasg	2774	CUGAAAUUGUGUUAGACGGUACC	2508
AD-953984.1	csgsgua(Chd)CfgAfCfAfaccaguauuaL96	2675	VPusAfsauac(Tgn)gguuguCfgGfuaccgsusc	2775	GACGGUACCGACAACCAGUAUUU	2916
AD-953985.1	ascsagc(Ahd)GfuGfUfUfgauaaauuuaL96	2121	VPusAfsaauu(Tgn)aucaacAfcUfgcuguscsa	2776	UGACAGCAGUGUUGAUAAAUUUG	1015
AD-953986.1	cscsucu(Uhd)GfuCfCfAfuuguguccgaL96	2153	VPusCfsggac(Agn)caauggAfcAfagaggsusg	2777	CACCUCUUGUCCAUUGUGUCCGC	2474
AD-953987.1	uscscgc(Chd)UfuUfUfAfucugcuucgaL96	2176	VPusCfsgaag(Cgn)agauaaAfaGfgcggascsa	2778	UGUCCGCCUUUUAUCUGCUUCGU	2492
AD-953988.1	cscsgcc(Uhd)UfuUfAfUfcugcuucguaL96	2188	VPusAfscgaa(Ggn)cagauaAfaAfggcggsasc	2779	GUCCGCCUUUUAUCUGCUUCGUU	2501
AD-953989.1	csgsccu(Uhd)UfuAfUfCfugcuucguuaL96	2122	VPusAfsacga(Agn)gcagauAfaAfaggcgsgsa	2780	UCCGCCUUUUAUCUGCUUCGUUU	1001
AD-953990.1	csasaac(Uhd)CfuAfUfAfaaguuccucaL96	2676	VPusGfsagga(Agn)cuuuauAfgAfguuugscsu	2781	AGCAAACUCUAUAAAGUUCCUCU	918
AD-953991.1	uscsuau(Ahd)AfaGfUfUfccucuugacaL96	2132	VPusGfsucaa(Ggn)aggaacUfuUfauagasgsu	2782	ACUCUAUAAAGUUCCUCUUGACA	987
AD-953992.1	csasucu(Uhd)GfaAfCfUfacaucgaucaL96	2144	VPusGfsaucg(Agn)uguaguUfcAfagaugsusc	2783	GACAUCUUGAACUACAUCGAUCA	2466
AD-953993.1	asuscuu(Ghd)AfaCfUfAfcaucgaucaaL96	2677	VPusUfsgauc(Ggn)auguagUfuCfaagausgsu	2784	ACAUCUUGAACUACAUCGAUCAU	2917
AD-953994.1	uscsuug(Ahd)AfcUfAfCfaucgaucauaL96	2678	VPusAfsugau(Cgn)gauguaGfuUfcaagasusg	2785	CAUCUUGAACUACAUCGAUCAUG	2918

Duplex ID	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-953995.1	csusuga(Ahd)CfuAfCfAfucgaucaugaL96	2154	VPusCfsauga(Tgn)cgauguAfgUfucaagsasu	2786	AUCUUGAACUACAUCGAUCAUGG	930
AD-953996.1	ususgaa(Chd)UfaCfAfUfcgaucauggaL96	2679	VPusCfscaug(Agn)ucgaugUfaGfuucaasgsa	2787	UCUUGAACUACAUCGAUCAUGGA	1017
AD-953997.1	gsasacu(Ahd)CfaUfCfGfaucauggagaL96	2177	VPusCfsucca(Tgn)gaucgaUfgUfaguucsasa	2788	UUGAACUACAUCGAUCAUGGAGA	2493
AD-953998.1	ususugg(Chd)GfgAfUfUfgcauuccuuaL96	2200	VPusAfsagga(Agn)ugcaauCfcGfccaaasgsa	2789	UCUUUGGCGGAUUGCAUUCCUUU	2509
AD-953999.1	ususggc(Ghd)GfaUfUfGfcauuccuuuaL96	2680	VPusAfsaagg(Agn)augcaaUfcCfgccaasasg	2790	CUUUGGCGGAUUGCAUUCCUUUG	2919
AD-954000.1	gscsuac(Ahd)GfuGfAfGfuuaggacugaL96	2681	VPusCfsaguc(Cgn)uaacucAfcUfguagcsusg	2791	CAGCUACAGUGAGUUAGGACUGC	2920
AD-954001.1	csuscug(Ahd)GfgAfAfCfaguuccuauaL96	2682	VPusAfsuagg(Agn)acuguuCfcUfcagagsusc	2792	GACUCUGAGGAACAGUUCCUAUU	1019
AD-954002.1	csusgag(Ghd)AfaCfAfGfuuccuauugaL96	2123	VPusCfsaaua(Ggn)gaacugUfuCfcucagsasg	2793	CUCUGAGGAACAGUUCCUAUUGG	1021
AD-954003.1	usgsagg(Ahd)AfcAfGfUfuccuauuggaL96	2133	VPusCfscaau(Agn)ggaacuGfuUfccucasgsa	2794	UCUGAGGAACAGUUCCUAUUGGC	2455
AD-954004.1	gsasgga(Ahd)CfaGfUfUfccuauuggcaL96	2683	VPusGfsccaa(Tgn)aggaacUfgUfuccucsasg	2795	CUGAGGAACAGUUCCUAUUGGCU	2921
AD-954005.1	gsasgug(Chd)UfcAfAfUfaauguugucaL96	2166	VPusGfsacaa(Cgn)auuauuGfaGfcacucsgsu	2796	ACGAGUGCUCAAUAAUGUUGUCA	2484
AD-954006.1	gscscuc(Chd)AfuCfUfCfauuucuccgaL96	2178	VPusCfsggag(Agn)aaugagAfuGfgaggcsusg	2797	CAGCCUCCAUCUCAUUUCUCCGU	2494
AD-954007.1	cscsucc(Ahd)UfcUfCfAfuuucuccguaL96	2190	VPusAfscgga(Ggn)aaaugaGfaUfggaggscsu	2798	AGCCUCCAUCUCAUUUCUCCGUC	2503
AD-954008.1	csuscca(Uhd)CfuCfAfUfuucuccgucaL96	2201	VPusGfsacgg(Agn)gaaaugAfgAfuggagsgsc	2799	GCCUCCAUCUCAUUUCUCCGUCA	2510
AD-954009.1	uscsucc(Ghd)UfcAfGfCfacaauaaccaL96	2134	VPusGfsguua(Tgn)ugugcuGfaCfggagasasa	2800	UUUCUCCGUCAGCACAAUAACCA	2456
AD-954010.1	csusccg(Uhd)CfaGfCfAfcaauaaccaaL96	2684	VPusUfsgguu(Agn)uugugcUfgAfcggagsasa	2801	UUCUCCGUCAGCACAAUAACCAG	995
AD-954011.1	uscscgu(Chd)AfgCfAfCfaauaaccagaL96	2145	VPusCfsuggu(Tgn)auugugCfuGfacggasgsa	2802	UCUCCGUCAGCACAAUAACCAGA	2467
AD-954012.1	asgsagg(Chd)UfaUfAfAfccuacuaccaL96	2685	VPusGfsguag(Tgn)agguuaUfaGfccucusasu	2803	AUAGAGGCUAUAACCUACUACCA	2922
AD-954013.1	ascscua(Chd)UfaCfCfAfagcauaacaaL96	2686	VPusUfsguua(Tgn)gcuuggUfaGfuaggususa	2804	UAACCUACUACCAAGCAUAACAG	1012
AD-954014.1	asasccu(Uhd)UfcAfAfGfaguuauugcaL96	2156	VPusGfscaau(Agn)acucuuGfaAfagguusasu	2805	AUAACCUUUCAAGAGUUAUUGCA	2476

Duplex ID	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-954015.1	asgsuuu(Ghd)CfaUfUfUfggaguuuagaL96	2167	VPusCfsuaaa(Cgn)uccaaaUfgCfaaacusgsg	2806	CCAGUUUGCAUUUGGAGUUUAGG	2485
AD-954016.1	csasgau(Ghd)AfgUfCfUfaggaagagcaL96	2687	VPusGfscucu(Tgn)ccuagaCfuCfaucugsasg	2807	CUCAGAUGAGUCUAGGAAGAGCU	2923
AD-954017.1	gsuscua(Ghd)GfaAfGfAfgcuguaccgaL96	2191	VPusCfsggua(Cgn)agcucuUfcCfuagacsusc	2808	GAGUCUAGGAAGAGCUGUACCGU	2504
AD-954018.1	usasgga(Ahd)GfaGfCfUfguaccguugaL96	2124	VPusCfsaacg(Ggn)uacagcUfcUfuccuasgsa	2809	UCUAGGAAGAGCUGUACCGUUGG	2448
AD-954019.1	gsuscag(Chd)UfuGfGfUfucccauuggaL96	2157	VPusCfscaau(Ggn)ggaaccAfaGfcugacsgsa	2810	UCGUCAGCUUGGUUCCCAUUGGA	2477
AD-954020.1	gsgsccg(Ghd)AfaAfCfUfugcuugcagaL96	2192	VPusCfsugca(Agn)gcaaguUfuCfcggccsasa	2811	UUGGCCGGAAACUUGCUUGCAGC	2505
AD-954021.1	csusucu(Chd)UfaAfGfUfcccauccgaaL96	2203	VPusUfscgga(Tgn)gggacuUfaGfagaagsgsg	2812	CCCUUCUCUAAGUCCCAUCCGAC	2512
AD-954022.1	gsasgaa(Chd)AfaGfCfAfucuguaccgaL96	2136	VPusCfsggua(Cgn)agaugcUfuGfuucucscsu	2813	AGGAGAACAAGCAUCUGUACCGU	2458
AD-954023.1	asascaa(Ghd)CfaUfCfUfguaccguugaL96	2688	VPusCfsaacg(Ggn)uacagaUfgCfuuguuscsu	2814	AGAACAAGCAUCUGUACCGUUGA	2924
AD-954024.1	asgscau(Chd)UfgUfAfCfcguugagucaL96	2689	VPusGfsacuc(Agn)acgguaCfaGfaugcususg	2815	CAAGCAUCUGUACCGUUGAGUCC	2925
AD-954025.1	gscsagc(Uhd)UfcUfAfGfacaaucugaaL96	2690	VPusUfscaga(Tgn)ugucuaGfaAfgcugcsasc	2816	GUGCAGCUUCUAGACAAUCUGAU	932
AD-954026.1	uscsuag(Ahd)CfaAfUfCfugauaccucaL96	2691	VPusGfsaggu(Agn)ucagauUfgUfcuagasasg	2817	CUUCUAGACAAUCUGAUACCUCA	954
AD-954027.1	uscsagg(Uhd)CfcUfGfUfuacaacaagaL96	2692	VPusCfsuugu(Tgn)guaacaGfgAfccugasgsg	2818	CCUCAGGUCCUGUUACAACAAGU	2926
AD-954028.1	gsgsucc(Uhd)GfuUfAfCfaacaaguaaaL96	2693	VPusUfsuacu(Tgn)guuguaAfcAfggaccsusg	2819	CAGGUCCUGUUACAACAAGUAAA	1016
AD-954029.1	csasagu(Ahd)AfaUfCfCfucaucacugaL96	2694	VPusCfsagug(Agn)ugaggaUfuUfacuugsusu	2820	AACAAGUAAAUCCUCAUCACUGG	966
AD-954030.1	ususucu(Ahd)UfcAfUfCfuuccuucauaL96	2695	VPusAfsugaa(Ggn)gaagauGfaUfagaaascsu	2821	AGUUUCUAUCAUCUUCCUUCAUA	978
AD-954031.1	ususcau(Ahd)CfcUfCfAfaacugcaugaL96	2696	VPusCfsaugc(Agn)guuugaGfgUfaugaasgsg	2822	CCUUCAUACCUCAAACUGCAUGA	2927
AD-954032.1	ascscuc(Ahd)AfaCfUfGfcaugaugucaL96	2697	VPusGfsacau(Cgn)augcagUfuUfgaggusasu	2823	AUACCUCAAACUGCAUGAUGUCC	2928
AD-954033.1	csasgga(Chd)AfuUfGfGfgaaguguguaL96	2698	VPusAfscaca(Cgn)uucccaAfuGfuccugscsa	2824	UGCAGGACAUUGGGAAGUGUGUU	2929
AD-954034.1	cscsuga(Ahd)AfuCfCfUfgcuuuagucaL96	2158	VPusGfsacua(Agn)agcaggAfuUfucaggsusa	2825	UACCUGAAAUCCUGCUUUAGUCG	924

Duplex ID	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-954035.1	csusgaa(Ahd)UfcCfUfGfcuuuagucgaL96	2169	VPusCfsgacu(Agn)aagcagGfaUfuucagsgsu	2826	ACCUGAAAUCCUGCUUUAGUCGA	2487
AD-954036.1	gsasaau(Chd)CfuGfCfUfuuagucgagaL96	2181	VPusCfsucga(Cgn)uaaagcAfgGfauuucsasg	2827	CUGAAAUCCUGCUUUAGUCGAGA	2497
AD-954037.1	asasucc(Uhd)GfcUfUfUfagucgagaaaL96	2699	VPusUfsucuc(Ggn)acuaaaGfcAfggauususc	2828	GAAAUCCUGCUUUAGUCGAGAAC	2930
AD-954038.1	ususuag(Uhd)CfgAfGfAfaccaaugauaL96	2193	VPusAfsucau(Tgn)gguucuCfgAfcuaaasgsc	2829	GCUUUAGUCGAGAACCAAUGAUG	2506
AD-954039.1	ususagu(Chd)GfaGfAfAfccaaugaugaL96	2204	VPusCfsauca(Tgn)ugguucUfcGfacuaasasg	2830	CUUUAGUCGAGAACCAAUGAUGG	2513
AD-954040.1	gsasugg(Chd)AfaCfUfGfuuuguguucaL96	2700	VPusGfsaaca(Cgn)aaacagUfuGfccaucsasu	2831	AUGAUGGCAACUGUUUGUGUUCA	2931
AD-954041.1	gsasgug(Uhd)CfaCfAfAfagaaccgugaL96	2137	VPusCfsacgg(Tgn)ucuuugUfgAfcacucsgsu	2832	ACGAGUGUCACAAAGAACCGUGC	2459
AD-954042.1	asgsugu(Chd)AfcAfAfAfgaaccgugcaL96	2701	VPusGfscacg(Ggn)uucuuuGfuGfacacuscsg	2833	CGAGUGUCACAAAGAACCGUGCA	2932
AD-954043.1	usgscag(Ahd)UfaAfGfAfaugcuauucaL96	2702	VPusGfsaaua(Ggn)cauucuUfaUfcugcascsg	2834	CGUGCAGAUAAGAAUGCUAUUCA	917
AD-954044.1	asgsaau(Ghd)CfuAfUfUfcauaaucacaL96	2170	VPusGfsugau(Tgn)augaauAfgCfauucususa	2835	UAAGAAUGCUAUUCAUAAUCACA	921
AD-954045.1	gscsuau(Uhd)CfaUfAfAfucacauucgaL96	2182	VPusCfsgaau(Ggn)ugauuaUfgAfauagcsasu	2836	AUGCUAUUCAUAAUCACAUUCGU	988
AD-954046.1	asuscac(Ahd)UfuCfGfUfuuguuugaaaL96	2042	VPusUfsucaa(Agn)caaacgAfaUfgugaususa	2837	UAAUCACAUUCGUUUGUUUGAAC	2387
AD-954047.1	usgsuuu(Ghd)AfaCfCfUfcuuguuauaaL96	2053	VPusUfsauaa(Cgn)aagaggUfuCfaaacasasa	2838	UUUGUUUGAACCUCUUGUUAUAA	933
AD-954048.1	gsususg(Ahd)AfcCfUfCfuuguuauaaaL96	2064	VPusUfsuaua(Agn)caagagGfuUfcaaacsasa	2839	UUGUUUGAACCUCUUGUUAUAAA	929
AD-954049.1	ususuga(Ahd)CfcUfCfUfuguuauaaaaL96	2075	VPusUfsuuau(Agn)acaagaGfgUfucaaascsa	2840	UGUUUGAACCUCUUGUUAUAAAA	928
AD-954050.1	gscsuuu(Ahd)AfaAfCfAfguacacgacaL96	2703	VPusGfsucgu(Ggn)uacuguUfuUfaaagcsusu	2841	AAGCUUUAAAACAGUACACGACU	990
AD-954051.1	asgscug(Ghd)UfuCfAfGfuuacggguuaL96	2097	VPusAfsaccc(Ggn)uaacugAfaCfcagcusgsc	2842	GCAGCUGGUUCAGUUACGGGUUA	2429
AD-954052.1	gscsugg(Uhd)UfcAfGfUfuacggguuaaL96	2704	VPusUfsaacc(Cgn)guaacuGfaAfccagcsusg	2843	CAGCUGGUUCAGUUACGGGUUAA	2933
AD-954053.1	usgsguu(Chd)AfgUfUfAfcggguuaauaL96	2705	VPusAfsuuaa(Cgn)ccguaaCfuGfaaccasgsc	2844	GCUGGUUCAGUUACGGGUUAAUU	996
AD-954054.1	gsusuca(Ghd)UfuAfCfGfgguuaauuaaL96	2107	VPusUfsaauu(Agn)acccguAfaCfugaacscsa	2845	UGGUUCAGUUACGGGUUAAUUAC	957

Duplex ID	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-954055.1	csasguu(Ahd)CfgGfGfUfuaauuacugaL96	2043	VPusCfsagua(Agn)uuaaccCfgUfaacugsasa	2846	UUCAGUUACGGGUUAAUUACUGU	2388
AD-954056.1	ususacg(Ghd)GfuUfAfAfuuacugucuaL96	2706	VPusAfsgaca(Ggn)uaauuaAfcCfcguaascsu	2847	AGUUACGGGUUAAUUACUGUCUU	2934
AD-954057.1	usgsgau(Uhd)CfaGfAfUfcagguguuuaL96	2707	VPusAfsaaca(Cgn)cugaucUfgAfauccasgsa	2848	UCUGGAUUCAGAUCAGGUGUUUA	937
AD-954058.1	usasuga(Ahd)CfgCfUfAfucauucaaaaL96	2708	VPusUfsuuga(Agn)ugauagCfgUfucauasasg	2849	CUUAUGAACGCUAUCAUUCAAAA	1002
AD-954059.1	gscsgac(Uhd)GfuCfUfCfgacagauagaL96	2709	VPusCfsuauc(Tgn)gucgagAfcAfgucgcsusu	2850	AAGCGACUGUCUCGACAGAUAGC	2935
AD-954060.1	csgsacu(Ghd)UfcUfCfGfacagauagcaL96	2710	VPusGfscuau(Cgn)ugucgaGfaCfagucgscsu	2851	AGCGACUGUCUCGACAGAUAGCU	2936
AD-954061.1	gsascug(Uhd)CfuCfGfAfcagauagcuaL96	2108	VPusAfsgcua(Tgn)cugucgAfgAfcagucsgsc	2852	GCGACUGUCUCGACAGAUAGCUG	2438
AD-954062.1	ascsugu(Chd)UfcGfAfCfagauagcugaL96	2033	VPusCfsagcu(Agn)ucugucGfaGfacaguscsg	2853	CGACUGUCUCGACAGAUAGCUGA	2379
AD-954063.1	cscscaa(Uhd)GfuUfAfGfccaaacagcaL96	2711	VPusGfscugu(Tgn)uggcuaAfcAfuugggsasg	2854	CUCCCAAUGUUAGCCAAACAGCA	2937
AD-954065.1	csascau(Uhd)GfaCfUfCfucaugaagcaL96	2712	VPusGfscuuc(Agn)ugagagUfcAfaugugscsa	2855	UGCACAUUGACUCUCAUGAAGCC	2938
AD-954066.1	gscsccu(Uhd)GfgAfGfUfguuaaauacaL96	2055	VPusGfsuauu(Tgn)aacacuCfcAfagggcsusu	2856	AAGCCCUUGGAGUGUUAAAUACA	2397
AD-954067.1	ascsaug(Chd)UfuUfUfAfcggaguaugaL96	2077	VPusCfsauac(Tgn)ccguaaAfaGfcauguscsu	2857	AGACAUGCUUUUACGGAGUAUGU	2412
AD-954068.1	ususuua(Chd)GfgAfGfUfauguucgucaL96	2099	VPusGfsacga(Agn)cauacuCfcGfuaaaasgsc	2858	GCUUUUACGGAGUAUGUUCGUCA	2431
AD-954069.1	ususuac(Ghd)GfaGfUfAfuguucgucaaL96	2109	VPusUfsgacg(Agn)acauacUfcCfguaaasasg	2859	CUUUUACGGAGUAUGUUCGUCAC	2439
AD-954070.1	gsasgca(Chd)UfgUfUfCfaacuguggaaL96	2713	VPusUfsccac(Agn)guugaaCfaGfugcucsasc	2860	GUGAGCACUGUUCAACUGUGGAU	2939
AD-954071.1	asasgau(Ahd)UfuGfUfUfcuuucucguaL96	2056	VPusAfscgag(Agn)aagaacAfaUfaucuuscsa	2861	UGAAGAUAUUGUUCUUUCUCGUA	919
AD-954072.1	gsasuau(Uhd)GfuUfCfUfuucucguauaL96	2067	VPusAfsuacg(Agn)gaaagaAfcAfauaucsusu	2862	AAGAUAUUGUUCUUUCUCGUAUU	999
AD-954073.1	ususguu(Chd)UfuUfCfUfcguauucagaL96	2078	VPusCfsugaa(Tgn)acgagaAfaGfaacaasusa	2863	UAUUGUUCUUUCUCGUAUUCAGG	916
AD-954074.1	usgsuuc(Uhd)UfuCfUfCfguauucaggaL96	2089	VPusCfscuga(Agn)uacgagAfaAfgaacasasu	2864	AUUGUUCUUUCUCGUAUUCAGGA	931
AD-954075.1	asususu(Chd)AfaGfGfUfuucuauuacaL96	2100	VPusGfsuaau(Agn)gaaaccUfuGfaaaausgsu	2865	ACAUUUUCAAGGUUUCUAUUACA	943

Duplex ID	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-954076.1	gsusgag(Chd)AfgCfAfAfcauacuuucaL96	2714	VPusGfsaaag(Tgn)auguugCfuGfcucacsusc	2866	GAGUGAGCAGCAACAUACUUUCU	2940
AD-954077.1	gscsaac(Ahd)UfaCfUfUfucuauugccaL96	2035	VPusGfsgcaa(Tgn)agaaagUfaUfguugcsusg	2867	CAGCAACAUACUUUCUAUUGCCA	993
AD-954078.1	asuscuu(Chd)AfaGfUfCfuggaauguuaL96	2046	VPusAfsacau(Tgn)ccagacUfuGfaagausgsu	2868	ACAUCUUCAAGUCUGGAAUGUUC	1004
AD-954079.1	csusgcu(Uhd)GfuCfAfAfccacaccgaaL96	2715	VPusUfscggu(Ggn)ugguugAfcAfagcagscsa	2869	UGCUGCUUGUCAACCACACCGAC	2941
AD-954080.1	uscscga(Ghd)CfaCfUfUfaacguggcuaL96	2716	VPusAfsgcca(Cgn)guuaagUfgCfucggasgsu	2870	ACUCCGAGCACUUAACGUGGCUC	2942
AD-954081.1	cscsucc(Ahd)GfuAfCfAfggacuucauaL96	2717	VPusAfsugaa(Ggn)uccuguAfcUfggaggscsu	2871	AGCCUCCAGUACAGGACUUCAUC	2943
AD-954082.1	csasggc(Ahd)AfuUfCfAfgucucguugaL96	2080	VPusCfsaacg(Agn)gacugaAfuUfgccugsgsa	2872	UCCAGGCAAUUCAGUCUCGUUGU	2414
AD-954083.1	asgsgca(Ahd)UfuCfAfGfucucguuguaL96	2091	VPusAfscaac(Ggn)agacugAfaUfugccusgsg	2873	CCAGGCAAUUCAGUCUCGUUGUG	2423
AD-954084.1	gsgscaa(Uhd)UfcAfGfUfcucguugugaL96	2102	VPusCfsacaa(Cgn)gagacuGfaAfuugccsusg	2874	CAGGCAAUUCAGUCUCGUUGUGA	2433
AD-954085.1	gscsaau(Uhd)CfaGfUfCfucguugugaaL96	2037	VPusUfscaca(Agn)cgagacUfgAfauugcscsu	2875	AGGCAAUUCAGUCUCGUUGUGAA	2382
AD-954086.1	csasauu(Chd)AfgUfCfUfcguugugaaaL96	2718	VPusUfsucac(Agn)acgagaCfuGfaauugscsc	2876	GGCAAUUCAGUCUCGUUGUGAAA	973
AD-954087.1	asusggu(Chd)GfaCfAfUfccuugcuugaL96	2048	VPusCfsaagc(Agn)aggaugUfcGfaccausgsc	2877	GCAUGGUCGACAUCCUUGCUUGU	2392
AD-954088.1	gsgsucg(Ahd)CfaUfCfCfuugcuugucaL96	2719	VPusGfsacaa(Ggn)caaggaUfgUfcgaccsasu	2878	AUGGUCGACAUCCUUGCUUGUCG	2944
AD-954089.1	gsuscga(Chd)AfuCfCfUfugcuugucgaL96	2059	VPusCfsgaca(Agn)gcaaggAfuGfucgacscsa	2879	UGGUCGACAUCCUUGCUUGUCGC	2400
AD-954090.1	csusgga(Chd)AfgGfUfUfucgucucucaL96	2720	VPusGfsagag(Agn)cgaaacCfuGfuccagscsa	2880	UGCUGGACAGGUUUCGUCUCUCC	2945
AD-954091.1	csasugc(Ahd)AfgAfCfUfcacuuagucaL96	2070	VPusGfsacua(Agn)gugaguCfuUfgcaugsgsu	2881	ACCAUGCAAGACUCACUUAGUCC	1008
AD-954092.1	asusgca(Ahd)GfaCfUfCfacuuaguccaL96	2081	VPusGfsgacu(Agn)agugagUfcUfugcausgsg	2882	CCAUGCAAGACUCACUUAGUCCC	2415
AD-954093.1	usgsuca(Chd)UfgGfAfAfacagugaguaL96	2721	VPusAfscuca(Cgn)uguuucCfaGfugacascsg	2883	CGUGUCACUGGAAACAGUGAGUC	2946
AD-954094.1	csascug(Ghd)AfaAfCfAfgugaguccgaL96	2092	VPusCfsggac(Tgn)cacuguUfuCfcagugsasc	2884	GUCACUGGAAACAGUGAGUCCGG	2424
AD-954095.1	gscsugg(Uhd)GfaAfUfCfggauuccugaL96	2112	VPusCfsagga(Agn)uccgauUfcAfccagcsusc	2885	GAGCUGGUGAAUCGGAUUCCUGC	2442

Duplex ID	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-954096.1	asascuc(Ghd)GfaGfUfUfcaaccuaagaL96	2722	VPusCfsuuag(Ggn)uugaacUfcCfgaguuscsa	2886	UGAACUCGGAGUUCAACCUAAGC	2947
AD-954097.1	ascsucg(Ghd)AfgUfUfCfaaccuaagcaL96	2723	VPusGfscuua(Ggn)guugaaCfuCfcgagususc	2887	GAACUCGGAGUUCAACCUAAGCC	1018
AD-954098.1	csuscgg(Ahd)GfuUfCfAfaccuaagccaL96	2724	VPusGfsgcuu(Agn)gguugaAfcUfccgagsusu	2888	AACUCGGAGUUCAACCUAAGCCU	1020
AD-954099.1	csusgga(Ghd)CfaAfGfUfugaaugaucaL96	2725	VPusGfsauca(Tgn)ucaacuUfgCfuccagsusa	2889	UACUGGAGCAAGUUGAAUGAUCU	2948
AD-954100.1	asgsagc(Ahd)GfcUfUfCfuuaguccagaL96	2726	VPusCfsugga(Cgn)uaagaaGfcUfgcucuscsc	2890	GGAGAGCAGCUUCUUAGUCCAGA	2949
AD-954101.1	csusugu(Chd)AfaCfAfGfcuacacacgaL96	2727	VPusCfsgugu(Ggn)uagcugUfuGfacaagsgsg	2891	CCCUUGUCAACAGCUACACACGU	2950
AD-954102.1	uscsaac(Ahd)GfcUfAfCfacacgugugaL96	2113	VPusCfsacac(Ggn)uguguaGfcUfguugascsa	2892	UGUCAACAGCUACACACGUGUGC	2443
AD-954103.1	csasaca(Ghd)CfuAfCfAfcacgugugcaL96	2039	VPusGfscaca(Cgn)guguguAfgCfuguugsasc	2893	GUCAACAGCUACACACGUGUGCC	2384
AD-954104.1	csusuua(Ahd)GfgAfGfUfucaucuaccaL96	2728	VPusGfsguag(Agn)ugaacuCfcUfuaaagsasc	2894	GUCUUUAAGGAGUUCAUCUACCG	979
AD-954105.1	gsgsacc(Ahd)GfuCfGfUfacucaguuuaL96	2729	VPusAfsaacu(Ggn)aguacgAfcUfgguccsasg	2895	CUGGACCAGUCGUACUCAGUUUG	2951
AD-954106.1	gsascca(Ghd)UfcGfUfAfcucaguuugaL96	2050	VPusCfsaaac(Tgn)gaguacGfaCfuggucscsa	2896	UGGACCAGUCGUACUCAGUUUGA	2394
AD-954107.1	ascscag(Uhd)CfgUfAfCfucaguuugaaL96	2061	VPusUfscaaa(Cgn)ugaguaCfgAfcuggcscsc	2897	GGACCAGUCGUACUCAGUUUGAA	2402
AD-954108.1	cscsagu(Chd)GfuAfCfUfcaguuugaaaL96	2072	VPusUfsucaa(Agn)cugaguAfcGfacuggsusc	2898	GACCAGUCGUACUCAGUUUGAAG	958
AD-954109.1	csasguc(Ghd)UfaCfUfCfaguuugaagaL96	2083	VPusCfsuuca(Agn)acugagUfaCfgacugsgsu	2899	ACCAGUCGUACUCAGUUUGAAGA	926
AD-954110.1	gsascgc(Uhd)GfaCfAfGfaacugcgaaaL96	2040	VPusUfsucgc(Agn)guucugUfcAfgcgucsasc	2900	GUGACGCUGACAGAACUGCGAAG	2385
AD-954111.1	ascsgcu(Ghd)AfcAfGfAfacugcgaagaL96	2051	VPusCfsuucg(Cgn)aguucuGfuCfagcguscsa	2901	UGACGCUGACAGAACUGCGAAGG	2395
AD-954112.1	uscsauu(Ghd)AfgAfAfCfuauccucugaL96	2730	VPusCfsagag(Ggn)auaguuCfuCfaaugasgsg	2902	CCUCAUUGAGAACUAUCCUCUGG	2952
AD-954113.1	csgsgcu(Ghd)CfuGfAfCfuuguuuacgaL96	2095	VPusCfsguaa(Agn)caagucAfgCfagccgsgsu	2903	ACCGGCUGCUGACUUGUUUACGA	2427
AD-954114.1	gsgscug(Chd)UfgAfCfUfuguuuacgaaL96	2106	VPusUfscgua(Agn)acaaguCfaGfcagccsgsg	2904	CCGGCUGCUGACUUGUUUACGAA	2437
AD-954115.1	csusgcu(Ghd)AfcUfUfGfuuuacgaaaaL96	2115	VPusUfsuucg(Tgn)aaacaaGfuCfagcagscsc	2905	GGCUGCUGACUUGUUUACGAAAU	938

Duplex ID	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-954116.1	usgscug(Ahd)CfuUfGfUfuuacgaaauaL96	2731	VPusAfsuuuc(Ggn)uaaacaAfgUfcagcasgsc	2906	GCUGCUGACUUGUUUACGAAAUG	970
AD-954117.1	csusgac(Uhd)UfgUfUfUfacgaaauguaL96	2041	VPusAfscauu(Tgn)cguaaaCfaAfgucagscsa	2907	UGCUGACUUGUUUACGAAAUGUC	2386
AD-954118.1	usgsacu(Uhd)GfuUfUfAfcgaaaugucaL96	2052	VPusGfsacau(Tgn)ucguaaAfcAfagucasgsc	2908	GCUGACUUGUUUACGAAAUGUCC	950
AD-954119.1	usasacg(Uhd)AfaCfUfCfuuucuaugcaL96	2063	VPusGfscaua(Ggn)aaagagUfuAfcguuasasa	2909	UUUAACGUAACUCUUUCUAUGCC	982
AD-954120.1	cscsgcu(Ghd)AfcAfUfUfuccguuguaaL96	2096	VPusUfsacaa(Cgn)ggaaauGfuCfagcggsgsu	2910	ACCCGCUGACAUUUCCGUUGUAC	2428
AD-954121.1	csusgac(Ahd)UfuUfCfCfguuguacauaL96	2732	VPusAfsugua(Cgn)aacggaAfaUfgucagscsg	2911	CGCUGACAUUUCCGUUGUACAUG	962
AD-954122.1	uscscgu(Uhd)GfuAfCfAfuguuccuguaL96	2733	VPusAfscagg(Agn)acauguAfcAfacggasasa	2912	UUUCCGUUGUACAUGUUCCUGUU	1005

Table 14. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954123.1	AGCUACCAAGAAAGACCGUGA	1784	430-450	UCACGGTCUUUCUTGGUAGCUGA	3046	428-450
AD-954131.1	AUUCUAAUCUTCCAAGGUUAA	2953	630-650	UTAACCTUGGAAGAUTAGAAUCC	3047	628-650
AD-954139.1	AGGUUUAUGAACUGACGUUAA	1786	1218-1238	UTAACGTCAGUTCAUAAACCUGG	3048	1216-1238
AD-954147.1	AGUAUUGUGGAACUUAUAGCA	1787	1406-1426	UGCUAUAAGUUCCACAAUACUCC	1948	1404-1426
AD-954155.1	GACUCUGAAUCGAGAUCGGAA	1788	1511-1531	UTCCGATCUCGAUTCAGAGUCAU	3049	1509-1531
AD-954163.1	ACAGCAGUGUTGAUAAAUUUA	2954	2073-2093	UAAATUTAUCAACACTGCUGUCA	3050	2071-2093
AD-954170.1	CGCCUUUUAUCUGCUUCGUUA	1790	2207-2227	UAACGAAGCAGAUAAAAGGCGGA	1951	2205-2227
AD-954178.1	CUGAGGAACAGUUCCUAUUGA	1791	2717-2737	UCAATAGGAACTGTUCCUCAGAG	3051	2715-2737
AD-954186.1	UUCUCCGUCAGCACAAUAACA	2955	3074-3094	UGUUAUTGUGCTGACGGAGAAAU	3052	3072-3094
AD-954194.1	UAGGAAGAGCTGUACCGUUGA	2956	3325-3345	UCAACGGUACAGCTCTUCCUAGA	3053	3323-3345
AD-954202.1	UUCUCUAAGUCCCAUCCGACA	1793	3679-3699	UGUCGGAUGGGACTUAGAGAAGG	3054	3677-3699
AD-954210.1	UUGUGUUCAACAAUUGUUGAA	2957	4081-4101	UTCAACAAUUGTUGAACACAAAC	3055	4079-4101
AD-954124.1	CUACCAAGAAAGACCGUGUGA	1794	432-452	UCACACGGUCUTUCUTGGUAGCU	3056	430-452
AD-954132.1	UUCCAAGGTUACAGCUCGAGA	2958	639-659	UCUCGAGCUGUAACCTUGGAAGA	3057	637-659

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954140.1	GGUUUAUGAACUGACGUUACA	1796	1219-1239	UGUAACGUCAGTUCATAAACCUG	3058	1217-1239
AD-954148.1	GUAUUGUGGAACUUAUAGCUA	1797	1407-1427	UAGCTATAAGUTCCACAAUACUC	3059	1405-1427
AD-954156.1	ACUCUGAATCGAGAUCGGAUA	2959	1512-1532	UAUCCGAUCUCGATUCAGAGUCA	3060	1510-1532
AD-954164.1	UGAUAAAUTUGUGUUGAGAGA	2960	2083-2103	UCUCTCAACACAAAUTUAUCAAC	3061	2081-2103
AD-954171.1	UCUAUAAAGUTCCUCUUGACA	2961	2352-2372	UGUCAAGAGGAACTUTAUAGAGU	3062	2350-2372
AD-954179.1	UGAGGAACAGTUCCUAUUGGA	2962	2718-2738	UCCAAUAGGAACUGUTCCUCAGA	3063	2716-2738
AD-954187.1	UCUCCGUCAGCACAAUAACCA	1801	3075-3095	UGGUTATUGUGCUGACGGAGAAA	3064	3073-3095
AD-954195.1	AGGAAGAGCUGUACCGUUGGA	1802	3326-3346	UCCAACGGUACAGCUCUUCCUAG	1963	3324-3346
AD-954203.1	GAGAACAAGCAUCUGUACCGA	1803	3723-3743	UCGGTACAGAUGCTUGUUCUCCU	3065	3721-3743
AD-954211.1	GAGUGUCACAAAGAACCGUGA	1804	4369-4389	UCACGGTUCUUTGTGACACUCGU	3066	4367-4389
AD-954125.1	AAUCAUUGTCTGACAAUAUGA	2963	452-472	UCAUAUTGUCAGACAAUGAUUCA	3067	450-472
AD-954133.1	UCCAAGGUTACAGCUCGAGCA	2964	640-660	UGCUCGAGCUGTAACCUUGGAAG	3068	638-660
AD-954141.1	UUUAUGAACUGACGUUACAUA	1807	1221-1241	UAUGTAACGUCAGTUCAUAAACC	3069	1219-1241
AD-954149.1	UAUUGUGGAACUUAUAGCUGA	1808	1408-1428	UCAGCUAUAAGTUCCACAAUACU	3070	1406-1428
AD-954157.1	CUCUGAAUCGAGAUCGGAUGA	1809	1513-1533	UCAUCCGAUCUCGAUTCAGAGUC	3071	1511-1533
AD-954165.1	AGAUGAAGCUACUGAACCGGA	1810	2101-2121	UCCGGUTCAGUAGCUTCAUCUCU	3072	2099-2121
AD-954172.1	CAUCUUGAACTACAUCGAUCA	2965	2407-2427	UGAUCGAUGUAGUTCAAGAUGUC	3073	2405-2427
AD-954180.1	GAGGAACAGUTCCUAUUGGCA	2966	2719-2739	UGCCAATAGGAACTGTUCCUCAG	3074	2717-2739
AD-954188.1	UCCGUCAGCACAAUAACCAGA	1812	3077-3097	UCUGGUTAUUGTGCUGACGGAGA	3075	3075-3097
AD-954196.1	GGAAGAGCTGTACCGUUGGGA	2967	3327-3347	UCCCAACGGUACAGCTCUUCCUA	3076	3325-3347
AD-954204.1	AACAAGCATCTGUACCGUUGA	2968	3726-3746	UCAACGGUACAGATGCUUGUUCU	3077	3724-3746
AD-954212.1	UGUCACAAAGAACCGUGCAGA	1814	4372-4392	UCUGCACGGUUCUTUGUGACACU	3078	4370-4392
AD-954126.1	CAUUGUCUGACAAUAUGUGAA	119	455-475	UTCACATAUUGTCAGACAAUGAU	3079	453-475
AD-954134.1	CUGUUCCCAAAAUUAUGGCUA	1815	843-863	UAGCCATAAUUTUGGGAACAGCU	3080	841-863
AD-954142.1	CAGCACCAAGACCACAAUGUA	1816	1247-1267	UACATUGUGGUCUTGGUGCUGUG	3081	1245-1267
AD-954150.1	AUUGUGGAACTUAUAGCUGGA	2969	1409-1429	UCCAGCTAUAAGUTCCACAAUAC	3082	1407-1429
AD-954158.1	UUCUGAAATUGUGUUAGACGA	2970	1885-1905	UCGUCUAACACAATUTCAGAACU	3083	1883-1905
AD-954166.1	CCUCUUGUCCAUUGUGUCCGA	1819	2189-2209	UCGGACACAAUGGACAAGAGGUG	1981	2187-2209

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954173.1	CUUGAACUACAUCGAUCAUGA	1820	2410-2430	UCAUGATCGAUGUAGTUCAAGAU	3084	2408-2430
AD-954181.1	AAGAACGAGUGCUCAAUAAUA	1821	2862-2882	UAUUAUTGAGCACTCGUUCUUGC	3085	2860-2882
AD-954189.1	AACCUUUCAAGAGUUAUUGCA	1822	3152-3172	UGCAAUAACUCTUGAAAGGUUAU	3086	3150-3172
AD-954197.1	GUCAGCUUGGTUCCCAUUGGA	2971	3376-3396	UCCAAUGGGAACCAAGCUGACGA	1985	3374-3396
AD-954205.1	CCUGAAAUCCTGCUUUAGUCA	2972	4039-4059	UGACTAAAGCAGGAUTUCAGGUA	3087	4037-4059
AD-954213.1	UAAGAAUGCUAUUCAUAAUCA	1825	4393-4413	UGAUTATGAAUAGCATUCUUAUC	3088	4391-4413
AD-954127.1	AAUGCCUCAACAAAGUUAUCA	1826	597-617	UGAUAACUUUGTUGAGGCAUUCG	3089	595-617
AD-954135.1	AGGCCUUCAUAGCGAACCUGA	1827	909-929	UCAGGUTCGCUAUGAAGGCCUUU	2581	907-929
AD-954143.1	GCACCAAGACCACAAUGUUGA	1828	1249-1269	UCAACATUGUGGUCUTGGUGCUG	3090	1247-1269
AD-954151.1	UGGAGGAUGACUCUGAAUCGA	1829	1503-1523	UCGATUCAGAGTCAUCCUCCAAG	3091	1501-1523
AD-954159.1	UCUGAAAUTGTGUUAGACGGA	2973	1886-1906	UCCGTCTAACACAAUTUCAGAAC	3092	1884-1906
AD-954167.1	CUCUUGUCCATUGUGUCCGCA	2974	2190-2210	UGCGGACACAATGGACAAGAGGU	3093	2188-2210
AD-954174.1	UUGAACUACATCGAUCAUGGA	2975	2411-2431	UCCATGAUCGATGTAGUUCAAGA	3094	2409-2431
AD-954182.1	GAGUGCUCAATAAUGUUGUCA	2976	2868-2888	UGACAACAUUATUGAGCACUCGU	3095	2866-2888
AD-954190.1	AGUUUGCATUTGGAGUUUAGA	2977	3262-3282	UCUAAACUCCAAATGCAAACUGG	3096	3260-3282
AD-954198.1	AGCUUGGUTCCCAUUGGAUCA	2978	3379-3399	UGAUCCAAUGGGAACCAAGCUGA	1996	3377-3399
AD-954206.1	CUGAAAUCCUGCUUUAGUCGA	1835	4040-4060	UCGACUAAAGCAGGATUUCAGGU	3097	4038-4060
AD-954214.1	AGAAUGCUAUTCAUAAUCACA	2979	4395-4415	UGUGAUTAUGAAUAGCAUUCUUA	316	4393-4415
AD-954128.1	UUAUCAAAGCTUUGAUGGAUA	2980	612-632	UAUCCATCAAAGCTUTGAUAACU	3098	610-632
AD-954136.1	CUCUGCUGAUTCUUGGCGUGA	2981	1074-1094	UCACGCCAAGAAUCAGCAGAGUG	2000	1072-1094
AD-954144.1	CACCAAGACCACAAUGUUGUA	1838	1250-1270	UACAACAUUGUGGTCTUGGUGCU	3099	1248-1270
AD-954152.1	GAGGAUGACUCUGAAUCGAGA	1839	1505-1525	UCUCGATUCAGAGTCAUCCUCCA	3100	1503-1525
AD-954160.1	CUGAAAUUGUGUUAGACGGUA	165	1887-1907	UACCGUCUAACACAATUUCAGAA	3101	1885-1907
AD-954168.1	UCCGCCUUTUAUCUGCUUCGA	2982	2205-2225	UCGAAGCAGAUAAAAGGCGGACA	2003	2203-2225
AD-954175.1	GAACUACATCGAUCAUGGAGA	2983	2413-2433	UCUCCATGAUCGATGTAGUUCAA	3102	2411-2433
AD-954183.1	GCCUCCAUCUCAUUUCUCCGA	1842	3061-3081	UCGGAGAAAUGAGAUGGAGGCUG	2005	3059-3081
AD-954191.1	GUUUGCAUTUGGAGUUUAGGA	2984	3263-3283	UCCUAAACUCCAAAUGCAAACUG	2006	3261-3283
AD-954199.1	AGAUGCUUTGAUUUUGGCCGA	2985	3412-3432	UCGGCCAAAAUCAAAGCAUCUUG	2007	3410-3432

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954207.1	GAAAUCCUGCTUUAGUCGAGA	2986	4042-4062	UCUCGACUAAAGCAGGAUUUCAG	2008	4040-4062
AD-954215.1	GCUAUUCATAAUCACAUUCGA	2987	4400-4420	UCGAAUGUGAUTATGAAUAGCAU	3103	4398-4420
AD-954129.1	GCUUUGAUGGAUUCUAAUCUA	1847	620-640	UAGATUAGAAUCCAUCAAAGCUU	3104	618-640
AD-954137.1	GCAGCUUGTCCAGGUUUAUGA	2988	1207-1227	UCAUAAACCUGGACAAGCUGCUC	2011	1205-1227
AD-954145.1	ACCAAGACCACAAUGUUGUGA	1849	1251-1271	UCACAACAUUGTGGUCUUGGUGC	3105	1249-1271
AD-954153.1	AGGAUGACTCTGAAUCGAGAA	2989	1506-1526	UTCUCGAUUCAGAGUCAUCCUCC	3106	1504-1526
AD-954161.1	UGAAAUUGTGTUAGACGGUAA	2990	1888-1908	UTACCGTCUAACACAAUUUCAGA	3107	1886-1908
AD-954169.1	CCGCCUUUTATCUGCUUCGUA	2991	2206-2226	UACGAAGCAGATAAAAGGCGGAC	3108	2204-2226
AD-954176.1	CUUUGGCGGATUGCAUUCCUA	2992	2559-2579	UAGGAATGCAATCCGCCAAAGAA	3109	2557-2579
AD-954184.1	CCUCCAUCTCAUUUCUCCGUA	2993	3062-3082	UACGGAGAAAUGAGATGGAGGCU	3110	3060-3082
AD-954192.1	GUCUAGGAAGAGCUGUACCGA	1855	3322-3342	UCGGTACAGCUCUTCCUAGACUC	3111	3320-3342
AD-954200.1	GGCCGGAAACTUGCUUGCAGA	2994	3427-3447	UCUGCAAGCAAGUTUCCGGCCAA	3112	3425-3447
AD-954208.1	UUUAGUCGAGAACCAAUGAUA	1857	4052-4072	UAUCAUTGGUUCUCGACUAAAGC	2620	4050-4072
AD-954216.1	UUCAUAAUCACAUUCGUUUGA	1858	4404-4424	UCAAACGAAUGTGAUTAUGAAUA	3113	4402-4424
AD-954130.1	GAUUCUAATCTUCCAAGGUUA	2995	629-649	UAACCUTGGAAGATUAGAAUCCA	3114	627-649
AD-954138.1	CAGGUUUATGAACUGACGUUA	2996	1217-1237	UAACGUCAGUUCATAAACCUGGA	3115	1215-1237
AD-954146.1	GAGUAUUGTGGAACUUAUAGA	2997	1405-1425	UCUATAAGUUCCACAAUACUCCC	3116	1403-1425
AD-954154.1	GGAUGACUCUGAAUCGAGAUA	1860	1507-1527	UAUCTCGAUUCAGAGTCAUCCUC	3117	1505-1527
AD-954162.1	GAAAUUGUGUTAGACGGUACA	2998	1889-1909	UGUACCGUCUAACACAAUUUCAG	2025	1887-1909
AD-954177.1	UUUGGCGGAUTGCAUUCCUUA	2999	2560-2580	UAAGGAAUGCAAUCCGCCAAAGA	2026	2558-2580
AD-954185.1	CUCCAUCUCATUUCUCCGUCA	3000	3063-3083	UGACGGAGAAATGAGAUGGAGGC	3118	3061-3083
AD-954193.1	UCUAGGAAGAGCUGUACCGUA	1864	3323-3343	UACGGUACAGCTCTUCCUAGACU	3119	3321-3343
AD-954201.1	CUUCUCUAAGTCCCAUCCGAA	3001	3678-3698	UTCGGATGGGACUTAGAGAAGGG	3120	3676-3698
AD-954209.1	UUAGUCGAGAACCAAUGAUGA	1866	4053-4073	UCAUCATUGGUTCTCGACUAAAG	3121	4051-4073
AD-954217.1	UCAUAAUCACAUUCGUUUGUA	1707	4405-4425	UACAAACGAAUGUGATUAUGAAU	3122	4403-4425
AD-954225.1	UUCAGUUACGGGUUAAUUACA	1708	4518-4538	UGUAAUTAACCCGTAACUGAACC	3123	4516-4538
AD-954233.1	ACUGUCUCGACAGAUAGCUGA	1709	4966-4986	UCAGCUAUCUGTCGAGACAGUCG	3124	4964-4986
AD-954241.1	UUACGGAGTATGUUCGUCACA	3002	5108-5128	UGUGACGAACATACUCCGUAAAA	3125	5106-5128

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954249.1	GCAACAUACUTUCUAUUGCCA	3003	5452-5472	UGGCAATAGAAAGTATGUUGCUG	3126	5450-5472
AD-954257.1	ACUCCGAGCACUUAACGUGGA	1711	5886-5906	UCCACGTUAAGTGCUCGGAGUCA	3127	5884-5906
AD-954264.1	GCAAUUCAGUCUCGUUGUGAA	1712	6017-6037	UTCACAACGAGACTGAAUUGCCU	3128	6015-6037
AD-954272.1	UGCCUUCATGAUGAACUCGGA	3004	6547-6567	UCCGAGTUCAUCATGAAGGCAUU	3129	6545-6567
AD-954280.1	CAACAGCUACACACGUGUGCA	1714	7366-7386	UGCACACGUGUGUAGCUGUUGAC	1875	7364-7386
AD-954288.1	GACGCUGACAGAACUGCGAAA	1715	8317-8337	UTUCGCAGUUCTGTCAGCGUCAC	3130	8315-8337
AD-954296.1	CUGACUUGTUTACGAAAUGUA	3005	9539-9559	UACATUTCGUAAACAAGUCAGCA	3131	9537-9559
AD-954218.1	AUCACAUUCGTUUGUUUGAAA	3006	4410-4430	UTUCAAACAAACGAATGUGAUUA	3132	4408-4430
AD-954226.1	CAGUUACGGGTUAAUUACUGA	3007	4520-4540	UCAGTAAUUAACCCGTAACUGAA	3133	4518-4540
AD-954234.1	AAGCCCUUGGAGUGUUAAAUA	1719	5037-5057	UAUUTAACACUCCAAGGGCUUCA	3134	5035-5057
AD-954242.1	UCUGAUUUCCCAGUCAACUGA	1720	5197-5217	UCAGTUGACUGGGAAAUCAGAAC	3135	5195-5217
AD-954250.1	AUCUUCAAGUCUGGAAUGUUA	1721	5507-5527	UAACAUTCCAGACTUGAAGAUGU	3136	5505-5527
AD-954258.1	AUCCAGGCAATUCAGUCUCGA	3008	6011-6031	UCGAGACUGAATUGCCUGGAUGA	3137	6009-6031
AD-954265.1	AUGGUCGACATCCUUGCUUGA	3009	6170-6190	UCAAGCAAGGATGTCGACCAUGC	3138	6168-6190
AD-954273.1	CUUCAUGATGAACUCGGAGUA	3010	6550-6570	UACUCCGAGUUCATCAUGAAGGC	3139	6548-6570
AD-954281.1	GACCAGUCGUACUCAGUUUGA	1725	7525-7545	UCAAACTGAGUACGACUGGUCCA	2655	7523-7545
AD-954289.1	ACGCUGACAGAACUGCGAAGA	1726	8318-8338	UCUUCGCAGUUCUGUCAGCGUCA	1887	8316-8338
AD-954297.1	UGACUUGUTUACGAAAUGUCA	3011	9540-9560	UGACAUTUCGUAAACAAGUCAGC	2660	9538-9560
AD-954219.1	UGUUUGAACCTCUUGUUAUAA	3012	4422-4442	UTAUAACAAGAGGTUCAAACAAA	3140	4420-4442
AD-954227.1	UCAGAUCAGGTGUUUAUUGGA	3013	4550-4570	UCCAAUAAACACCTGAUCUGAAU	3141	4548-4570
AD-954235.1	GCCCUUGGAGTGUUAAAUACA	3014	5039-5059	UGUATUTAACACUCCAAGGGCUU	3142	5037-5059
AD-954243.1	AAGAUAUUGUTCUUUCUCGUA	3015	5217-5237	UACGAGAAAGAACAATAUCUUCA	3143	5215-5237
AD-954251.1	UCAAGUCUGGAAUGUUCCGGA	1730	5511-5531	UCCGGAACAUUCCAGACUUGAAG	1891	5509-5531
AD-954259.1	UCCAGGCAAUTCAGUCUCGUA	3016	6012-6032	UACGAGACUGAAUTGCCUGGAUG	3144	6010-6032
AD-954266.1	GUCGACAUCCTUGCUUGUCGA	3017	6173-6193	UCGACAAGCAAGGAUGUCGACCA	1893	6171-6193
AD-954274.1	CUGCUAGCTCCAUGCUUAAGA	3018	6581-6601	UCUUAAGCAUGGAGCTAGCAGGC	3145	6579-6601
AD-954282.1	ACCAGUCGTACUCAGUUUGAA	3019	7526-7546	UTCAAACUGAGTACGACUGGUCC	3146	7524-7546
AD-954290.1	GAAAGGAGAAAGUCAGUCCGA	1735	8937-8957	UCGGACTGACUTUCUCCUUUCCU	3147	8935-8957

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954298.1	UAACGUAACUCUUUCUAUGCA	1736	10173-10193	UGCATAGAAAGAGTUACGUUAAA	3148	10171-10193
AD-954220.1	GUUUGAACCUCUUGUUAUAAA	123	4423-4443	UTUATAACAAGAGGUTCAAACAA	3149	4421-4443
AD-954228.1	UUGGCUUUGUAUUGAAACAGA	1737	4566-4586	UCUGTUTCAAUACAAAGCCAAUA	3150	4564-4586
AD-954236.1	UAGACAUGCUTUUACGGAGUA	3020	5097-5117	UACUCCGUAAAAGCATGUCUACC	3151	5095-5117
AD-954244.1	GAUAUUGUTCTUUCUCGUAUA	3021	5219-5239	UAUACGAGAAAGAACAAUAUCUU	1900	5217-5239
AD-954252.1	CAAGUCUGGAAUGUUCCGGAA	1740	5512-5532	UTCCGGAACAUTCCAGACUUGAA	3152	5510-5532
AD-954260.1	CCAGGCAATUCAGUCUCGUUA	3022	6013-6033	UAACGAGACUGAATUGCCUGGAU	3153	6011-6033
AD-954267.1	CAUGCAAGACTCACUUAGUCA	3023	6349-6369	UGACTAAGUGAGUCUTGCAUGGU	3154	6347-6369
AD-954275.1	UGCUAGCUCCAUGCUUAAGCA	1743	6582-6602	UGCUTAAGCAUGGAGCUAGCAGG	3155	6580-6602
AD-954283.1	CCAGUCGUACTCAGUUUGAAA	3024	7527-7547	UTUCAAACUGAGUACGACUGGUC	3156	7525-7547
AD-954291.1	AGAACUUCAGACCCUAAUCCA	1745	8960-8980	UGGATUAGGGUCUGAAGUUCUAC	3157	8958-8980
AD-954299.1	UCUAUGCCCGTGUAAAGUAUA	3025	10186-10206	UAUACUTUACACGGGCAUAGAAA	3158	10184-10206
AD-954221.1	UUUGAACCTCTUGUUAUAAAA	3026	4424-4444	UTUUAUAACAAGAGGTUCAAACA	3159	4422-4444
AD-954229.1	UUAUGAACGCTAUCAUUCAAA	3027	4666-4686	UTUGAATGAUAGCGUTCAUAAGA	3160	4664-4686
AD-954237.1	ACAUGCUUTUACGGAGUAUGA	3028	5100-5120	UCAUACTCCGUAAAAGCAUGUCU	2635	5098-5120
AD-954245.1	UUGUUCUUTCTCGUAUUCAGA	3029	5223-5243	UCUGAATACGAGAAAGAACAAUA	2637	5221-5243
AD-954253.1	AGCACAAAGUTACUUAGUCCA	3030	5744-5764	UGGACUAAGUAACTUTGUGCUGG	3161	5742-5764
AD-954261.1	CAGGCAAUTCAGUCUCGUUGA	3031	6014-6034	UCAACGAGACUGAAUTGCCUGGA	3162	6012-6034
AD-954268.1	AUGCAAGACUCACUUAGUCCA	1752	6350-6370	UGGACUAAGUGAGTCTUGCAUGG	3163	6348-6370
AD-954276.1	ACUGGAGCAAGUUGAAUGAUA	1753	6753-6773	UAUCAUTCAACTUGCTCCAGUAG	3164	6751-6773
AD-954284.1	CAGUCGUACUCAGUUUGAAGA	120	7528-7548	UCUUCAAACUGAGTACGACUGGU	3165	7526-7548
AD-954292.1	UCAUGAACAAAGUCAUCGGAA	1754	9129-9149	UTCCGATGACUTUGUTCAUGAUG	3166	9127-9149
AD-954300.1	CUAUGCCCGUGUAAAGUAUGA	1755	10187-10207	UCAUACTUUACACGGGCAUAGAA	3167	10185-10207
AD-954222.1	AAGCUUUAAAACAGUACACGA	1756	4443-4463	UCGUGUACUGUTUTAAAGCUUUU	3168	4441-4463
AD-954230.1	AACGCUAUCATUCAAAACAGA	3032	4671-4691	UCUGTUTUGAATGAUAGCGUUCA	3169	4669-4691
AD-954238.1	CUUUUACGGAGUAUGUUCGUA	1758	5105-5125	UACGAACAUACTCCGTAAAAGCA	3170	5103-5125
AD-954246.1	UGUUCUUUCUCGUAUUCAGGA	125	5224-5244	UCCUGAAUACGAGAAAGAACAAU	326	5222-5244
AD-954254.1	AGAGGAGGAUTCUGACUUGGA	3033	5779-5799	UCCAAGTCAGAAUCCTCCUCUUC	3171	5777-5799

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-954262.1	AGGCAAUUCAGUCUCGUUGUA	1760	6015-6035	UACAACGAGACTGAATUGCCUGG	3172	6013-6035
AD-954269.1	CACUGGAAACAGUGAGUCCGA	1761	6417-6437	UCGGACTCACUGUTUCCAGUGAC	3173	6415-6437
AD-954277.1	UGUCAACAGCTACACACGUGA	3034	7363-7383	UCACGUGUGUAGCTGTUGACAAG	3174	7361-7383
AD-954285.1	AAGCUGAGCATUAUCAGAGGA	3035	7787-7807	UCCUCUGAUAATGCUCAGCUUCC	3175	7785-7807
AD-954293.1	CGGCUGCUGACUUGUUUACGA	1764	9533-9553	UCGUAAACAAGTCAGCAGCCGGU	3176	9531-9553
AD-954301.1	CCGCUGACAUTUCCGUUGUAA	3036	10311-10331	UTACAACGGAAAUGUCAGCGGGU	3177	10309-10331
AD-954223.1	AGCUGGUUCAGUUACGGGUUA	1766	4512-4532	UAACCCGUAACTGAACCAGCUGC	3178	4510-4532
AD-954231.1	GUGGAAGCGACUGUCUCGACA	1767	4957-4977	UGUCGAGACAGTCGCTUCCACUU	3179	4955-4977
AD-954239.1	UUUUACGGAGTAUGUUCGUCA	3037	5106-5126	UGACGAACAUACUCCGUAAAAGC	1929	5104-5126
AD-954247.1	AUUUUCAAGGTUUCUAUUACA	3038	5368-5388	UGUAAUAGAAACCTUGAAAAUGU	3180	5366-5388
AD-954255.1	CAAUAGAGAAAUAGUACGAAA	1769	5818-5838	UTUCGUACUAUTUCUCUAUUGCA	3181	5816-5838
AD-954263.1	GGCAAUUCAGTCUCGUUGUGA	3039	6016-6036	UCACAACGAGACUGAAUUGCCUG	1931	6014-6036
AD-954270.1	AGCUGGUGAATCGGAUUCCUA	3040	6513-6533	UAGGAATCCGATUCACCAGCUCU	3182	6511-6533
AD-954278.1	GUCAACAGCUACACACGUGUA	1772	7364-7384	UACACGTGUGUAGCUGUUGACAA	3183	7362-7384
AD-954286.1	UUGAGCUGAUGUAUGUGACGA	1773	8301-8321	UCGUCACAUACAUCAGCUCAAAC	1934	8299-8321
AD-954294.1	GGCUGCUGACTUGUUUACGAA	3041	9534-9554	UTCGTAAACAAGUCAGCAGCCGG	3184	9532-9554
AD-954302.1	GACUGUCATGTGGCUUGGUUA	3042	11080-11100	UAACCAAGCCACATGACAGUCGC	3185	11078-11100
AD-954224.1	GUUCAGUUACGGGUUAAUUAA	1775	4517-4537	UTAATUAACCCGUAACUGAACCA	3186	4515-4537
AD-954232.1	GACUGUCUCGACAGAUAGCUA	1776	4965-4985	UAGCTATCUGUCGAGACAGUCGC	3187	4963-4985
AD-954240.1	UUUACGGAGUAUGUUCGUCAA	1777	5107-5127	UTGACGAACAUACTCCGUAAAAG	3188	5105-5127
AD-954248.1	AAGGUUUCTATUACAACUGGA	3043	5374-5394	UCCAGUTGUAATAGAAACCUUGA	3189	5372-5394
AD-954256.1	GACUCCGAGCACUUAACGUGA	1779	5885-5905	UCACGUTAAGUGCTCGGAGUCAU	3190	5883-5905
AD-954271.1	GCUGGUGAAUCGGAUUCCUGA	1780	6514-6534	UCAGGAAUCCGAUTCACCAGCUC	3191	6512-6534
AD-954279.1	UCAACAGCTACACACGUGUGA	3044	7365-7385	UCACACGUGUGTAGCTGUUGACA	3192	7363-7385
AD-954287.1	GAGCUGAUGUAUGUGACGCUA	1782	8303-8323	UAGCGUCACAUACAUCAGCUCAA	1943	8301-8323
AD-954295.1	CUGCUGACTUGUUUACGAAAA	3045	9536-9556	UTUUCGTAAACAAGUCAGCAGCC	3193	9534-9556

Table 15. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-954123.1	asgscua(Chd)cadAgdAaagaccgugaL96	3194	VPusdCsacdGgdTcuuudCudTgdGuagcusgsa	3374	UCAGCUACCAAGAAAGACCGUGU	2445
AD-954131.1	asusucu(Ahd)audCudTccaagguuaaL96	3195	VPusdTsaadCcdTuggadAgdAudTagaauscsc	3375	GGAUUCUAAUCUUCCAAGGUUAC	965
AD-954139.1	asgsguu(Uhd)audGadAcugacguuaaL96	3196	VPusdTsaadCgdTcagudTcdAudAaaccusggsg	3376	CCAGGUUUAUGAACUGACGUUAC	991
AD-954147.1	asgsuau(Uhd)gudGgdAacuuauagcaL96	3197	VPusdGscudAudAaguudCcdAcdAauacuscsc	3377	GGAGUAUUGUGGAACUUAUAGCU	2446
AD-954155.1	gsascuc(Uhd)gadAudCgagaucggaaL96	3198	VPusdTsccdGadTcucgdAudTcdAgagucsasu	3378	AUGACUCUGAAUCGAGAUCGGAU	2447
AD-954163.1	ascsagc(Ahd)gudGudTgauaaauuuaL96	3199	VPusdAsaadTudTaucadAcdAcdTgcuguscsa	3379	UGACAGCAGUGUUGAUAAAUUUG	1015
AD-954170.1	csgsccu(Uhd)uudAudCugcuucguuaL96	3200	VPusdAsacdGadAgcagdAudAadAaggcgsgsa	3380	UCCGCCUUUUAUCUGCUUCGUUU	1001
AD-954178.1	csusgag(Ghd)aadCadGuuccuauugaL96	3201	VPusdCsaadTadGgaacdTgdTudCcucagsasg	3381	CUCUGAGGAACAGUUCCUAUUGG	1021
AD-954186.1	ususcuc(Chd)gudCadGcacaauaacaL96	3202	VPusdGsuudAudTgugcdTgdAcdGgagaasasu	3382	AUUUCUCCGUCAGCACAAUAACC	3554
AD-954194.1	usasgga(Ahd)gadGcdTguaccguugaL96	3203	VPusdCsaadCgdGuacadGcdTcdTuccuasgsa	3383	UCUAGGAAGAGCUGUACCGUUGG	2448
AD-954202.1	ususcuc(Uhd)aadGudCccauccgacaL96	3204	VPusdGsucdGgdAugggdAcdTudAgagaasgsg	3384	CCUUCUCUAAGUCCCAUCCGACG	2449
AD-954210.1	ususgug(Uhd)ucdAadCaauuguugaaL96	3205	VPusdTscadAcdAauugdTudGadAcacaasasc	3385	GUUUGUGUUCAACAAUUGUUGAA	3555
AD-954124.1	csusacc(Ahd)agdAadAgaccgugugaL96	3206	VPusdCsacdAcdGgucudTudCudTgguagscsu	3386	AGCUACCAAGAAAGACCGUGUGA	2450
AD-954132.1	ususcca(Ahd)ggdTudAcagcucgagaL96	3207	VPusdCsucdGadGcugudAadCcdTuggaasgsa	3387	UCUUCCAAGGUUACAGCUCGAGC	2451
AD-954140.1	gsgsuuu(Ahd)ugdAadCugacguuacaL96	3208	VPusdGsuadAcdGucagdTudCadTaaaccsusg	3388	CAGGUUUAUGAACUGACGUUACA	2452
AD-954148.1	gsusauu(Ghd)ugdGadAcuuauagcuaL96	3209	VPusdAsgcdTadTaagudTcdCadCaauacsusc	3389	GAGUAUUGUGGAACUUAUAGCUG	2453
AD-954156.1	ascsucu(Ghd)aadTcdGagaucggauaL96	3210	VPusdAsucdCgdAucucdGadTudCagagucsasa	3390	UGACUCUGAAUCGAGAUCGGAUG	1011
AD-954164.1	usgsaua(Ahd)audTudGuguugagagaL96	3211	VPusdCsucdTcdAacacdAadAudTuaucasasc	3391	GUUGAUAAAUUUGUGUUGAGAGA	2454
AD-954171.1	uscsuau(Ahd)aadGudTccucuugacaL96	3212	VPusdGsucdAadGaggadAcdTudTauagasgsu	3392	ACUCUAUAAAGUUCCUCUUGACA	987

Duplex ID	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-954179.1	usgsagg(Ahd)acdAgdTuccuauuggaL96	3213	VPusdCscadAudAggaadCudGudTccucasgsa	3393	UCUGAGGAACAGUUCCUAUUGGC	2455
AD-954187.1	uscsucc(Ghd)ucdAgdCacaauaaccaL96	3214	VPusdGsgudTadTugugdCudGadCggagasasa	3394	UUUCUCCGUCAGCACAAUAACCA	2456
AD-954195.1	asgsgaa(Ghd)agdCudGuaccguuggaL96	3215	VPusdCscadAcdGguacdAgdCudCuuccusasg	3395	CUAGGAAGAGCUGUACCGUUGGG	2457
AD-954203.1	gsasgaa(Chd)aadGcdAucuguaccgaL96	3216	VPusdCsggdTadCagaudGcdTudGuucucscsu	3396	AGGAGAACAAGCAUCUGUACCGU	2458
AD-954211.1	gsasgug(Uhd)cadCadAagaaccgugaL96	3217	VPusdCsacdGgdTucuudTgdTgdAcacucsgsu	3397	ACGAGUGUCACAAAGAACCGUGC	2459
AD-954125.1	asasuca(Uhd)ugdTcdTgacaauaugaL96	3218	VPusdCsaudAudTgucadGadCadAugauuscsa	3398	UGAAUCAUUGUCUGACAAUAUGU	2460
AD-954133.1	uscscaa(Ghd)gudTadCagcucgagcaL96	3219	VPusdGscudCgdAgcugdTadAcdCuuggasasg	3399	CUUCCAAGGUUACAGCUCGAGCU	2461
AD-954141.1	ususuau(Ghd)aadCudGacguuacauaL96	3220	VPusdAsugdTadAcgucdAgdTudCauaaascsc	3400	GGUUUAUGAACUGACGUUACAUC	2462
AD-954149.1	usasuug(Uhd)ggdAadCuuauagcugaL96	3221	VPusdCsagdCudAuaagdTudCcdAcaauascsu	3401	AGUAUUGUGGAACUUAUAGCUGG	2463
AD-954157.1	csuscug(Ahd)audCgdAgaucggaugaL96	3222	VPusdCsaudCcdGaucudCgdAudTcagagsusc	3402	GACUCUGAAUCGAGAUCGGAUGU	2464
AD-954165.1	asgsaug(Ahd)agdCudAcugaaccggaL96	3223	VPusdCscgdGudTcagudAgdCudTcaucuscsu	3403	AGAGAUGAAGCUACUGAACCGGG	2465
AD-954172.1	csasucu(Uhd)gadAcdTacaucgaucaL96	3224	VPusdGsaudCgdAuguadGudTcdAagaugsusc	3404	GACAUCUUGAACUACAUCGAUCA	2466
AD-954180.1	gsasgga(Ahd)cadGudTccuauuggcaL96	3225	VPusdGsccdAadTaggadAcdTgdTuccucsasg	3405	CUGAGGAACAGUUCCUAUUGGCU	2921
AD-954188.1	uscscgu(Chd)agdCadCaauaaccagaL96	3226	VPusdCsugdGudTauugdTgdCudGacggasgsa	3406	UCUCCGUCAGCACAAUAACCAGA	2467
AD-954196.1	gsgsaag(Ahd)gcdTgdTaccguugggaL96	3227	VPusdCsccdAadCgguadCadGcdTcuuccsusa	3407	UAGGAAGAGCUGUACCGUUGGGA	2468
AD-954204.1	asascaa(Ghd)cadTcdTguaccguugaL96	3228	VPusdCsaadCgdGuacadGadTgdCuuguuscsu	3408	AGAACAAGCAUCUGUACCGUUGA	2924
AD-954212.1	usgsuca(Chd)aadAgdAaccgugcagaL96	3229	VPusdCsugdCadCgguudCudTudGugacascsu	3409	AGUGUCACAAAGAACCGUGCAGA	2469
AD-954126.1	csasuug(Uhd)cudGadCaauaugugaaL96	3230	VPusdTscadCadTauugdTcdAgdAcaaugsasu	3410	AUCAUUGUCUGACAAUAUGUGAA	925
AD-954134.1	csusguu(Chd)ccdAadAauuauggcuaL96	3231	VPusdAsgcdCadTaauudTudGgdGaacagscsu	3411	AGCUGUUCCCAAAAUUAUGGCUU	2470
AD-954142.1	csasgca(Chd)cadAgdAccacaauguaL96	3232	VPusdAscadTudGuggudCudTgdGugcugsusg	3412	CACAGCACCAAGACCACAAUGUU	2471

Duplex ID	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-954150.1	asusugu(Ghd)gadAcdTuauagcuggaL96	3233	VPusdCscadGcdTauaadGudTcdCacaausasc	3413	GUAUUGUGGAACUUAUAGCUGGA	2472
AD-954158.1	ususcug(Ahd)aadTudGuguuagacgaL96	3234	VPusdCsgudCudAacacdAadTudTcagaascsu	3414	AGUUCUGAAAUUGUGUUAGACGG	2473
AD-954166.1	cscsucu(Uhd)gudCcdAuuguguccgaL96	3235	VPusdCsggdAcdAcaaudGgdAcdAagaggsusg	3415	CACCUCUUGUCCAUUGUGUCCGC	2474
AD-954173.1	csusuga(Ahd)cudAcdAucgaucaugaL96	3236	VPusdCsaudGadTcgaudGudAgdTucaagsasu	3416	AUCUUGAACUACAUCGAUCAUGG	930
AD-954181.1	asasgaa(Chd)gadGudGcucaauaauaL96	3237	VPusdAsuudAudTgagcdAcdTcdGuucuusgsc	3417	GCAAGAACGAGUGCUCAAUAAUG	2475
AD-954189.1	asasccu(Uhd)ucdAadGaguuauugcaL96	3238	VPusdGscadAudAacucdTudGadAagguusasu	3418	AUAACCUUUCAAGAGUUAUUGCA	2476
AD-954197.1	gsuscag(Chd)uudGgdTucccauuggaL96	3239	VPusdCscadAudGggaadCcdAadGcugacsgsa	3419	UCGUCAGCUUGGUUCCCAUUGGA	2477
AD-954205.1	cscsuga(Ahd)audCcdTgcuuuagucaL96	3240	VPusdGsacdTadAagcadGgdAudTucaggsusa	3420	UACCUGAAAUCCUGCUUUAGUCG	924
AD-954213.1	usasaga(Ahd)ugdCudAuucauaaucaL96	3241	VPusdGsaudTadTgaaudAgdCadTucuuasusc	3421	GAUAAGAAUGCUAUUCAUAAUCA	2478
AD-954127.1	asasugc(Chd)ucdAadCaaaguuaucaL96	3242	VPusdGsaudAadCuuugdTudGadGgcauuscsg	3422	CGAAUGCCUCAACAAAGUUAUCA	2479
AD-954135.1	asgsgcc(Uhd)ucdAudAgcgaaccugaL96	3243	VPusdCsagdGudTcgcudAudGadAggccususu	3423	AAAGGCCUUCAUAGCGAACCUGA	2480
AD-954143.1	gscsacc(Ahd)agdAcdCacaauguugaL96	3244	VPusdCsaadCadTugugdGudCudTggugcsusg	3424	CAGCACCAAGACCACAAUGUUGU	2481
AD-954151.1	usgsgag(Ghd)audGadCucugaaucgaL96	3245	VPusdCsgadTudCagagdTcdAudCcuccasasg	3425	CUUGGAGGAUGACUCUGAAUCGA	2482
AD-954159.1	uscsuga(Ahd)audTgdTguuagacggaL96	3246	VPusdCscgdTcdTaacadCadAudTucagasasc	3426	GUUCUGAAAUUGUGUUAGACGGU	959
AD-954167.1	csuscuu(Ghd)ucdCadTuguguccgcaL96	3247	VPusdGscgdGadCacaadTgdGadCaagagsgsu	3427	ACCUCUUGUCCAUUGUGUCCGCC	2483
AD-954174.1	ususgaa(Chd)uadCadTcgaucauggaL96	3248	VPusdCscadTgdAucgadTgdTadGuucaasgsa	3428	UCUUGAACUACAUCGAUCAUGGA	1017
AD-954182.1	gsasgug(Chd)ucdAadTaauguugucaL96	3249	VPusdGsacdAadCauuadTudGadGcacucsgsu	3429	ACGAGUGCUCAAUAAUGUUGUCA	2484
AD-954190.1	asgsuuu(Ghd)cadTudTggaguuuagaL96	3250	VPusdCsuadAadCuccadAadTgdCaaacusgsg	3430	CCAGUUUGCAUUUGGAGUUUAGG	2485
AD-954198.1	asgscuu(Ghd)gudTcdCcauuggaucaL96	3251	VPusdGsaudCcdAauggdGadAcdCaagcusgsa	3431	UCAGCUUGGUUCCCAUUGGAUCU	2486
AD-954206.1	csusgaa(Ahd)ucdCudGcuuuagucgaL96	3252	VPusdCsgadCudAaagcdAgdGadTuucagsgsu	3432	ACCUGAAAUCCUGCUUUAGUCGA	2487

Duplex ID	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-954214.1	asgsaau(Ghd)cudAudTcauaaucacaL96	3253	VPusdGsugdAudTaugadAudAgdCauucsusa	3433	UAAGAAUGCUAUUCAUAAUCACA	921
AD-954128.1	ususauc(Ahd)aadGcdTuugauggauaL96	3254	VPusdAsucdCadTcaaadGcdTudTgauaascsu	3434	AGUUAUCAAAGCUUUGAUGGAUU	2488
AD-954136.1	csuscug(Chd)ugdAudTcuuggcgugaL96	3255	VPusdCsacdGcdCaagadAudCadGcagagsusg	3435	CACUCUGCUGAUUCUUGGCGUGC	2489
AD-954144.1	csascca(Ahd)gadCcdAcaauguuguaL96	3256	VPusdAscadAcdAuugudGgdTcdTuggugcsu	3436	AGCACCAAGACCACAAUGUUGUG	2490
AD-954152.1	gsasgga(Uhd)gadCudCugaaucgagaL96	3257	VPusdCsucdGadTucagdAgdTcdAuccucscsa	3437	UGGAGGAUGACUCUGAAUCGAGA	2491
AD-954160.1	csusgaa(Ahd)uudGudGuuagacgguaL96	3258	VPusdAsccdGudCuaacdAcdAadTuucagsasa	3438	UUCUGAAAUUGUGUUAGACGGUA	971
AD-954168.1	uscscgc(Chd)uudTudAucugcuucgaL96	3259	VPusdCsgadAgdCagaudAadAadGgcggascsa	3439	UGUCCGCCUUUUAUCUGCUUCGU	2492
AD-954175.1	gsasacu(Ahd)cadTcdGaucauggagaL96	3260	VPusdCsucdCadTgaucdGadTgdTaguucsasa	3440	UUGAACUACAUCGAUCAUGGAGA	2493
AD-954183.1	gscscuc(Chd)audCudCauuucuccgaL96	3261	VPusdCsggdAgdAaaugdAgdAudGgaggcsusg	3441	CAGCCUCCAUCUCAUUUCUCCGU	2494
AD-954191.1	gsusuug(Chd)audTudGgaguuuaggaL96	3262	VPusdCscudAadAcuccdAadAudGcaaacsusg	3442	CAGUUUGCAUUUGGAGUUUAGGU	2495
AD-954199.1	asgsaug(Chd)uudTgdAuuuuggccgaL96	3263	VPusdCsggdCcdAaaaudCadAadGcaucususg	3443	CAAGAUGCUUUGAUUUUGGCCGG	2496
AD-954207.1	gsasaau(Chd)cudGcdTuuagucgagaL96	3264	VPusdCsucdGadCuaaadGcdAgdGauuucsasg	3444	CUGAAAUCCUGCUUUAGUCGAGA	2497
AD-954215.1	gscsuau(Uhd)cadTadAucacauucgaL96	3265	VPusdCsgadAudGugaudTadTgdAauagcsasu	3445	AUGCUAUUCAUAAUCACAUUCGU	988
AD-954129.1	gscsuuu(Ghd)audGgdAuucuaaucuaL96	3266	VPusdAsgadTudAgaaudCcdAudCaaagcsusu	3446	AAGCUUUGAUGGAUUCUAAUCUU	946
AD-954137.1	gscsagc(Uhd)ugdTcdCagguuuaugaL96	3267	VPusdCsaudAadAccugdGadCadAgcugcsusc	3447	GAGCAGCUUGUCCAGGUUUAUGA	2498
AD-954145.1	ascscaa(Ghd)acdCadCaauguugugaL96	3268	VPusdCsacdAadCauugdTgdGudCuuggusgsc	3448	GCACCAAGACCACAAUGUUGUGA	2499
AD-954153.1	asgsgau(Ghd)acdTcdTgaaucgagaaL96	3269	VPusdTscudCgdAuucadGadGudCauccuscsc	3449	GGAGGAUGACUCUGAAUCGAGAU	2500
AD-954161.1	usgsaaa(Uhd)ugdTgdTuagacgguaaL96	3270	VPusdTsacdCgdTcuaadCadCadAuuucasgsa	3450	UCUGAAAUUGUGUUAGACGGUAC	1003
AD-954169.1	cscsgcc(Uhd)uudTadTcugcuucguaL96	3271	VPusdAscgdAadGcagadTadAadAggcggsasc	3451	GUCCGCCUUUUAUCUGCUUCGUU	2501
AD-954176.1	csusuug(Ghd)cgdGadTugcauuccuaL96	3272	VPusdAsggdAadTgcaadTcdCgdCcaaagsasa	3452	UUCUUUGGCGGAUUGCAUUCCUU	2502

Duplex ID	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-954184.1	cscsucc(Ahd)ucdTcdAuuucuccguaL96	3273	VPusdAscgdGadGaaaudGadGadTggaggscsu	3453	AGCCUCCAUCUCAUUUCUCCGUC	2503
AD-954192.1	gsuscua(Ghd)gadAgdAgcuguaccgaL96	3274	VPusdCsggdTadCagcudCudTcdCuagacsusc	3454	GAGUCUAGGAAGAGCUGUACCGU	2504
AD-954200.1	gsgsccg(Ghd)aadAcdTugcuugcagaL96	3275	VPusdCsugdCadAgcaadGudTudCcggccsasa	3455	UUGGCCGGAAACUUGCUUGCAGC	2505
AD-954208.1	ususuag(Uhd)cgdAgdAaccaaugauaL96	3276	VPusdAsucdAudTgguudCudCgdAcuaaasgsc	3456	GCUUUAGUCGAGAACCAAUGAUG	2506
AD-954216.1	ususcau(Ahd)audCadCauucguuugaL96	3277	VPusdCsaadAcdGaaugdTgdAudTaugaasusa	3457	UAUUCAUAAUCACAUUCGUUUGU	972
AD-954130.1	gsasuuc(Uhd)aadTcdTuccaagguuaL96	3278	VPusdAsacdCudTggaadGadTudAgaaucscsa	3458	UGGAUUCUAAUCUUCCAAGGUUA	952
AD-954138.1	csasggu(Uhd)uadTgdAacugacguuaL96	3279	VPusdAsacdGudCaguudCadTadAaccugsgsa	3459	UCCAGGUUUAUGAACUGACGUUA	964
AD-954146.1	gsasgua(Uhd)ugdTgdGaacuuauagaL96	3280	VPusdCsuadTadAguucdCadCadAuacucscsc	3460	GGGAGUAUUGUGGAACUUAUAGC	998
AD-954154.1	gsgsaug(Ahd)cudCudGaaucgagauaL96	3281	VPusdAsucdTcdGauucdAgdAgdTcauccsusc	3461	GAGGAUGACUCUGAAUCGAGAUC	2507
AD-954162.1	gsasaau(Uhd)gudGudTagacgguacaL96	3282	VPusdGsuadCcdGucuadAcdAcdAauuucsasg	3462	CUGAAAUUGUGUUAGACGGUACC	2508
AD-954177.1	ususugg(Chd)ggdAudTgcauuccuuaL96	3283	VPusdAsagdGadAugcadAudCcdGccaaasgsa	3463	UCUUUGGCGGAUUGCAUUCCUUU	2509
AD-954185.1	csuscca(Uhd)cudCadTuucuccgucaL96	3284	VPusdGsacdGgdAgaaadTgdAgdAuggagsgsc	3464	GCCUCCAUCUCAUUUCUCCGUCA	2510
AD-954193.1	uscsuag(Ghd)aadGadGcuguaccguaL96	3285	VPusdAscgdGudAcagcdTcdTudCcuagascsu	3465	AGUCUAGGAAGAGCUGUACCGUU	2511
AD-954201.1	csusucu(Chd)uadAgdTcccauccgaaL96	3286	VPusdTscgdGadTgggadCudTadGagaagsgsg	3466	CCCUUCUCUAAGUCCCAUCCGAC	2512
AD-954209.1	ususagu(Chd)gadGadAccaaugaugaL96	3287	VPusdCsaudCadTuggudTcdTcdGacuaasasg	3467	CUUUAGUCGAGAACCAAUGAUGG	2513
AD-954217.1	uscsaua(Ahd)ucdAcdAuucguuuguaL96	3288	VPusdAscadAadCgaaudGudGadTuaugasasu	3468	AUUCAUAAUCACAUUCGUUUGUU	984
AD-954225.1	ususcag(Uhd)uadCgdGguuaauuacaL96	3289	VPusdGsuadAudTaaccdCgdTadAcugaascsc	3469	GGUUCAGUUACGGGUUAAUUACU	1007
AD-954233.1	ascsugu(Chd)ucdGadCagauagcugaL96	3290	VPusdCsagdCudAucugdTcdGadGacaguscsg	3470	CGACUGUCUCGACAGAUAGCUGA	2379
AD-954241.1	ususacg(Ghd)agdTadTguucgucacaL96	3291	VPusdGsugdAcdGaacadTadCudCcguaasasa	3471	UUUUACGGAGUAUGUUCGUCACU	2380
AD-954249.1	gscsaac(Ahd)uadCudTucuauugccaL96	3292	VPusdGsgcdAadTagaadAgdTadTguugcsusg	3472	CAGCAACAUACUUUCUAUUGCCA	993

Duplex ID	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-954257.1	ascsucc(Ghd)agdCadCuuaacguggaL96	3293	VPusdCscadCgdTuaagdTgdCudCggagusc sa	3473	UGACUCCGAGCACUUAACGUGGC	2381
AD-954264.1	gscsaau(Uhd)cadGudCucguugugaaL96	3294	VPusdTscadCadAcgagdAcdTgdAauugcsc su	3474	AGGCAAUUCAGUCUCGUUGUGA A	2382
AD-954272.1	usgsccu(Uhd)cadTgdAugaacucggaL96	3295	VPusdCscgdAgdTucaudCadTgdAaggcasu su	3475	AAUGCCUUCAUGAUGAACUCGG A	2383
AD-954280.1	csasaca(Ghd)cudAcdAcacgugugcaL96	3296	VPusdGscadCadCgugudGudAgdCuguugs asc	3476	GUCAACAGCUACACACGUGUGCC	2384
AD-954288.1	gsascgc(Uhd)gadCadGaacugcgaaaL96	3297	VPusdTsucdGcdAguucdTgdTcdAgcgucsa sc	3477	GUGACGCUGACAGAACUGCGAA G	2385
AD-954296.1	csusgac(Uhd)ugdTudTacgaaauguaL96	3298	VPusdAscadTudTcguadAadCadAgucagsc sa	3478	UGCUGACUUGUUUACGAAAUGU C	2386
AD-954218.1	asuscac(Ahd)uudCgdTuuguuugaaaL96	3299	VPusdTsucdAadAcaaadCgdAadTgugausu sa	3479	UAAUCACAUUCGUUUGUUUGAA C	2387
AD-954226.1	csasguu(Ahd)cgdGgdTuaauuacugaL96	3300	VPusdCsagdTadAuuaadCcdCgdTaacugsas a	3480	UUCAGUUACGGGUUAAUUACUG U	2388
AD-954234.1	asasgcc(Chd)uudGgdAguguuaaauaL96	3301	VPusdAsuudTadAcacudCcdAadGggcuusc sa	3481	UGAAGCCCUUGGAGUGUUAAAU A	2389
AD-954242.1	uscsuga(Uhd)uudCcdCagucaacugaL96	3302	VPusdCsagdTudGacugdGgdAadAucagasa sc	3482	GUUCUGAUUUCCCAGUCAACUGA	2390
AD-954250.1	asuscuu(Chd)aadGudCuggaauguuaL96	3303	VPusdAsacdAudTccagdAcdTudGaagausg su	3483	ACAUCUUCAAGUCUGGAAUGUU C	1004
AD-954258.1	asuscca(Ghd)gcdAadTucagucucgaL96	3304	VPusdCsgadGadCugaadTudGcdCuggausg sa	3484	UCAUCCAGGCAAUUCAGUCUCGU	2391
AD-954265.1	asusggu(Chd)gadCadTccuugcuugaL96	3305	VPusdCsaadGcdAaggadTgdTcdGaccausg sc	3485	GCAUGGUCGACAUCCUUGCUUGU	2392
AD-954273.1	csusuca(Uhd)gadTgdAacucggaguaL96	3306	VPusdAscudCcdGaguudCadTcdAugaagsg sc	3486	GCCUUCAUGAUGAACUCGGAGU U	2393
AD-954281.1	gsascca(Ghd)ucdGudAcucaguuugaL96	3307	VPusdCsaadAcdTgagudAcdGadCuggucsc sa	3487	UGGACCAGUCGUACUCAGUUUG A	2394
AD-954289.1	ascsgcu(Ghd)acdAgdAacugcgaagaL96	3308	VPusdCsuudCgdCaguudCudGudCagcgusc sa	3488	UGACGCUGACAGAACUGCGAAG G	2395
AD-954297.1	usgsacu(Uhd)gudTudAcgaaaugucaL96	3309	VPusdGsacdAudTucgudAadAcdAagucasg sc	3489	GCUGACUUGUUUACGAAAUGUC C	950
AD-954219.1	usgsuuu(Ghd)aadCcdTcuuguuauaaL96	3310	VPusdTsaudAadCaagadGgdTudCaaacasas a	3490	UUUGUUUGAACCUCUUGUUAUA A	933
AD-954227.1	uscsaga(Uhd)cadGgdTguuuauuggaL96	3311	VPusdCscadAudAaacadCcdTgdAucugasa su	3491	AUUCAGAUCAGGUGUUUAUUGG C	2396
AD-954235.1	gscsccu(Uhd)ggdAgdTguuaaauacaL96	3312	VPusdGsuadTudTaacadCudCcdAagggcsu su	3492	AAGCCCUUGGAGUGUUAAAUAC A	2397

Duplex ID	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-954243.1	asasgau(Ahd)uudGudTcuuucucguaL96	3313	VPusdAscgdAgdAaagadAcdAadTaucuuscsa	3493	UGAAGAUAUUGUUCUUUCUCGUA	919
AD-954251.1	uscsaag(Uhd)cudGgdAauguuccggaL96	3314	VPusdCscgdGadAcauudCcdAgdAcuugasasg	3494	CUUCAAGUCUGGAAUGUUCCGGA	2398
AD-954259.1	uscscag(Ghd)cadAudTcagucucguaL96	3315	VPusdAscgdAgdAcugadAudTgdCcuggasusg	3495	CAUCCAGGCAAUUCAGUCUCGUU	2399
AD-954266.1	gsuscga(Chd)audCcdTugcuugucgaL96	3316	VPusdCsgadCadAgcaadGgdAudGucgacscsa	3496	UGGUCGACAUCCUUGCUUGUCGC	2400
AD-954274.1	csusgcu(Ahd)gcdTcdCaugcuuaagaL96	3317	VPusdCsuudAadGcaugdGadGcdTagcagsgsc	3497	GCCUGCUAGCUCCAUGCUUAAGC	2401
AD-954282.1	ascscag(Uhd)cgdTadCucaguuugaaL96	3318	VPusdTscadAadCugagdTadCgdAcugguscsc	3498	GGACCAGUCGUACUCAGUUUGAA	2402
AD-954290.1	gsasaag(Ghd)agdAadAgucaguccgaL96	3319	VPusdCsggdAcdTgacudTudCudCcuuucscsu	3499	AGGAAAGGAGAAAGUCAGUCCGG	2403
AD-954298.1	usasacg(Uhd)aadCudCuuucuaugcaL96	3320	VPusdGscadTadGaaagdAgdTudAcguuasasa	3500	UUUAACGUAACUCUUUCUAUGCC	982
AD-954220.1	gsusuug(Ahd)acdCudCuuguuauaaaL96	3321	VPusdTsuadTadAcaagdAgdGudTcaaacsasa	3501	UUGUUUGAACCUCUUGUUAUAAA	929
AD-954228.1	ususggc(Uhd)uudGudAuugaaacagaL96	3322	VPusdCsugdTudTcaaudAcdAadAgccaasusa	3502	UAUUGGCUUUGUAUUGAAACAGU	2404
AD-954236.1	usasgac(Ahd)ugdCudTuuacggaguaL96	3323	VPusdAscudCcdGuaaadAgdCadTgucuascsc	3503	GGUAGACAUGCUUUUACGGAGUA	2405
AD-954244.1	gsasuau(Uhd)gudTcdTuucucguauaL96	3324	VPusdAsuadCgdAgaaadGadAcdAauaucsusu	3504	AAGAUAUUGUUCUUUCUCGUAUU	999
AD-954252.1	csasagu(Chd)ugdGadAuguuccggaaL96	3325	VPusdTsccdGgdAacaudTcdCadGacuugsasa	3505	UUCAAGUCUGGAAUGUUCCGGAG	2406
AD-954260.1	cscsagg(Chd)aadTudCagucucguuaL96	3326	VPusdAsacdGadGacugdAadTudGccuggsasu	3506	AUCCAGGCAAUUCAGUCUCGUUG	2407
AD-954267.1	csasugc(Ahd)agdAcdTcacuuagucaL96	3327	VPusdGsacdTadAgugadGudCudTgcaugsgsu	3507	ACCAUGCAAGACUCACUUAGUCC	1008
AD-954275.1	usgscua(Ghd)cudCcdAugcuuaagcaL96	3328	VPusdGscudTadAgcaudGgdAgdCuagcasgsg	3508	CCUGCUAGCUCCAUGCUUAAGCC	2408
AD-954283.1	cscsagu(Chd)gudAcdTcaguuugaaaL96	3329	VPusdTsucdAadAcugadGudAcdGacuggsusc	3509	GACCAGUCGUACUCAGUUUGAAG	958
AD-954291.1	asgsaac(Uhd)ucdAgdAcccuaauccaL96	3330	VPusdGsgadTudAgggudCudGadAguucusasc	3510	GUAGAACUUCAGACCCUAAUCCU	2409
AD-954299.1	uscsuau(Ghd)ccdCgdTguaaaguauaL96	3331	VPusdAsuadCudTuacadCgdGgdCauagasasa	3511	UUUCUAUGCCCGUGUAAAGUAUG	2410
AD-954221.1	ususuga(Ahd)ccdTcdTuguuauaaaaL96	3332	VPusdTsuudAudAacaadGadGgdTucaaascsa	3512	UGUUUGAACCUCUUGUUAUAAAA	928

Duplex ID	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-954229.1	ususaug(Ahd)acdGcdTaucauucaaaL96	3333	VPusdTsugdAadTgauadGcdGudTcauaasgsa	3513	UCUUAUGAACGCUAUCAUUCAAA	2411
AD-954237.1	ascsaug(Chd)uudTudAcggaguaugaL96	3334	VPusdCsaudAcdTccgudAadAadGcaugucscsu	3514	AGACAUGCUUUUACGGAGUAUGU	2412
AD-954245.1	ususguu(Chd)uudTcdTcguauucagaL96	3335	VPusdCsugdAadTacgadGadAadGaacaasusa	3515	UAUUGUUCUUUCUCGUAUUCAGG	916
AD-954253.1	asgscac(Ahd)aadGudTacuuaguccaL96	3336	VPusdGsgadCudAaguadAcdTudTgugcusgsg	3516	CCAGCACAAAGUUACUUAGUCCC	2413
AD-954261.1	csasggc(Ahd)audTcdAgucucguugaL96	3337	VPusdCsaadCgdAgacudGadAudTgccugsgsa	3517	UCCAGGCAAUUCAGUCUCGUUGU	2414
AD-954268.1	asusgca(Ahd)gadCudCacuuaguccaL96	3338	VPusdGsgadCudAagugdAgdTcdTugcausgsg	3518	CCAUGCAAGACUCACUUAGUCCC	2415
AD-954276.1	ascsugg(Ahd)gcdAadGuugaaugauaL96	3339	VPusdAsucdAudTcaacdTudGcdTccagusasg	3519	CUACUGGAGCAAGUUGAAUGAUC	2416
AD-954284.1	csasguc(Ghd)uadCudCaguuugaagaL96	3340	VPusdCsuudCadAacugdAgdTadCgacugsgsu	3520	ACCAGUCGUACUCAGUUUGAAGA	926
AD-954292.1	uscsaug(Ahd)acdAadAgucaucggaaL96	3341	VPusdTsccdGadTgacudTudGudTcaugasusg	3521	CAUCAUGAACAAAGUCAUCGGAG	2417
AD-954300.1	csusaug(Chd)ccdGudGuaaaguaugaL96	3342	VPusdCsaudAcdTuuacdAcdGgdGcauagsasa	3522	UUCUAUGCCCGUGUAAAGUAUGU	2418
AD-954222.1	asasgcu(Uhd)uadAadAcaguacacgaL96	3343	VPusdCsgudGudAcugudTudTadAagcuususu	3523	AAAAGCUUUAAAACAGUACACGA	2419
AD-954230.1	asascgc(Uhd)audCadTucaaaacagaL96	3344	VPusdCsugdTudTugaadTgdAudAgcguuscsa	3524	UGAACGCUAUCAUUCAAAACAGA	2420
AD-954238.1	csusuuu(Ahd)cgdGadGuauguucguaL96	3345	VPusdAscgdAadCauacdTcdCgdTaaaagscsa	3525	UGCUUUUACGGAGUAUGUUCGUC	2421
AD-954246.1	usgsuuc(Uhd)uudCudCguauucaggaL96	3346	VPusdCscudGadAuacgdAgdAadAgaacasasu	3526	AUUGUUCUUUCUCGUAUUCAGGA	931
AD-954254.1	asgsagg(Ahd)ggdAudTcugacuuggaL96	3347	VPusdCscadAgdTcagadAudCcdTccucususc	3527	GAAGAGGAGGAUUCUGACUUGGC	2422
AD-954262.1	asgsgca(Ahd)uudCadGucucguuguaL96	3348	VPusdAscadAcdGagacdTgdAadTugccusgsg	3528	CCAGGCAAUUCAGUCUCGUUGUG	2423
AD-954269.1	csascug(Ghd)aadAcdAgugaguccgaL96	3349	VPusdCsggdAcdTcacudGudTudCcagugsasc	3529	GUCACUGGAAACAGUGAGUCCGG	2424
AD-954277.1	usgsuca(Ahd)cadGcdTacacacgugaL96	3350	VPusdCsacdGudGuguadGcdTgdTugacasasg	3530	CUUGUCAACAGCUACACACGUGU	2425
AD-954285.1	asasgcu(Ghd)agdCadTuaucagaggaL96	3351	VPusdCscudCudGauaadTgdCudCagcuuscsc	3531	GGAAGCUGAGCAUUAUCAGAGGG	2426
AD-954293.1	csgsgcu(Ghd)cudGadCuuguuuacgaL96	3352	VPusdCsgudAadAcaagdTcdAgdCagccgsgsu	3532	ACCGGCUGCUGACUUGUUUACGA	2427

Duplex ID	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-954301.1	cscsgcu(Ghd)acdAudTuccguuguaaL96	3353	VPusdTsacdAadCggaadAudGudCagcggsgsu	3533	ACCCGCUGACAUUUCCGUUGUAC	2428
AD-954223.1	asgscug(Ghd)uudCadGuuacggguuaL96	3354	VPusdAsacdCcdGuaacdTgdAadCcagcusgsc	3534	GCAGCUGGUUCAGUUACGGGUUA	2429
AD-954231.1	gsusgga(Ahd)gcdGadCugucucgacaL96	3355	VPusdGsucdGadGacagdTcdGcdTuccacsusu	3535	AAGUGGAAGCGACUGUCUCGACA	2430
AD-954239.1	ususuua(Chd)ggdAgdTauguucgucaL96	3356	VPusdGsacdGadAcauadCudCcdGuaaaasgsc	3536	GCUUUUACGGAGUAUGUUCGUCA	2431
AD-954247.1	asususu(Chd)aadGgdTuucuauuacaL96	3357	VPusdGsuadAudAgaaadCcdTudGaaaausgsu	3537	ACAUUUUCAAGGUUUCUAUUACA	943
AD-954255.1	csasaua(Ghd)agdAadAuaguacgaaaL96	3358	VPusdTsucdGudAcuaudTudCudCuauugscsa	3538	UGCAAUAGAGAAAUAGUACGAAG	2432
AD-954263.1	gsgscaa(Uhd)ucdAgdTcucguugugaL96	3359	VPusdCsacdAadCgagadCudGadAuugccsusg	3539	CAGGCAAUUCAGUCUCGUUGUGA	2433
AD-954270.1	asgscug(Ghd)ugdAadTcggauuccuaL96	3360	VPusdAsggdAadTccgadTudCadCcagcuscsu	3540	AGAGCUGGUGAAUCGGAUUCCUG	2434
AD-954278.1	gsuscaa(Chd)agdCudAcacacguguaL96	3361	VPusdAscadCgdTgugudAgdCudGuugacsasa	3541	UUGUCAACAGCUACACACGUGUG	2435
AD-954286.1	ususgag(Chd)ugdAudGuaugugacgaL96	3362	VPusdCsgudCadCauacdAudCadGcucaasasc	3542	GUUUGAGCUGAUGUAUGUGACGC	2436
AD-954294.1	gsgscug(Chd)ugdAcdTuguuuacgaaL96	3363	VPusdTscgdTadAacaadGudCadGcagccsgsg	3543	CCGGCUGCUGACUUGUUUACGAA	2437
AD-954302.1	gsascug(Uhd)cadTgdTggcuugguuaL96	3364	VPusdAsacdCadAgccadCadTgdAcagucsgsc	3544	GCGACUGUCAUGUGGCUUGGUUU	3556
AD-954224.1	gsusuca(Ghd)uudAcdGgguuaauuaaL96	3365	VPusdTsaadTudAacccdGudAadCugaacscsa	3545	UGGUUCAGUUACGGGUUAAUUAC	957
AD-954232.1	gsascug(Uhd)cudCgdAcagauagcuaL96	3366	VPusdAsgcdTadTcugudCgdAgdAcagucsgsc	3546	GCGACUGUCUCGACAGAUAGCUG	2438
AD-954240.1	ususuac(Ghd)gadGudAuguucgucaaL96	3367	VPusdTsgadCgdAacaudAcdTcdCguaaasasg	3547	CUUUUACGGAGUAUGUUCGUCAC	2439
AD-954248.1	asasggu(Uhd)ucdTadTuacaacuggaL96	3368	VPusdCscadGudTguaadTadGadAaccuusgsa	3548	UCAAGGUUUCUAUUACAACUGGU	2440
AD-954256.1	gsascuc(Chd)gadGcdAcuuaacgugaL96	3369	VPusdCsacdGudTaagudGcdTcdGgagucsasu	3549	AUGACUCCGAGCACUUAACGUGG	2441
AD-954271.1	gscsugg(Uhd)gadAudCggauuccugaL96	3370	VPusdCsagdGadAuccgdAudTcdAccagcsusc	3550	GAGCUGGUGAAUCGGAUUCCUGC	2442
AD-954279.1	uscsaac(Ahd)gcdTadCacacgugugaL96	3371	VPusdCsacdAcdGugugdTadGcdTguugascsa	3551	UGUCAACAGCUACACACGUGUGC	2443
AD-954287.1	gsasgcu(Ghd)audGudAugugacgcuaL96	3372	VPusdAsgcdGudCacaudAcdAudCagcucsasa	3552	UUGAGCUGAUGUAUGUGACGCUG	2444

Duplex ID	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-954295.1	csusgcu(Ghd)acdTudGuuuacgaaaaL96	3373	VPusdTsuudCgdTaaacdAadGudCagcagscsc	3553	GGCUGCUGACUUGUUUACGAAAU	938

Table 17. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-1019439.1	cscsgcu(Chd)AfgGfUfUfcugcuuuusasa	3557	VPusUfsaaaAfgCfAfgaacCfuGfagcggscsc	3644	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1019442.1	csuscag(Ghd)UfuCfUfGfcuuuuaccsusa	3558	VPusAfsgguAfaAfAfgcagAfaCfcugagscsg	3645	CGCUCAGGUUCUGCUUUUACCUG	3732
AD-1019438.1	gscscgc(Uhd)CfaGfGfUfucugcuuususa	3559	VPusAfsaaaGfcAfGfaaccUfgAfgcggcscsg	3646	CGGCCGCUCAGGUUCUGCUUUUA	3733
AD-1019408.1	asasagc(Uhd)GfaUfGfAfaggccuucgaL96	3560	VPusCfsgaag(G2p)ccuucaUfcAfgcuuususc	3647	GAAAAGCUGAUGAAGGCCUUCGA	3734
AD-1019426.1	uscsccu(Chd)AfaGfUfCfcuuccagcaaL96	3561	VPusUfsgcug(G2p)aaggacUfuGfagggascsu	3648	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1019440.1	csgscuc(Ahd)GfgUfUfCfugcuuuuascsa	3562	VPusGfsuaaAfaGfCfagaaCfcUfgagcgsgsc	3649	GCCGCUCAGGUUCUGCUUUUACC	3736
AD-1019410.1	csusgau(Ghd)AfaGfGfCfcuucgagucaL96	3563	VPusGfsacuc(G2p)aaggccUfuCfaucagscsu	3650	AGCUGAUGAAGGCCUUCGAGUCC	3737
AD-1019405.1	ascsccu(Ghd)GfaAfAfAfgcugaugaaaL96	3564	VPusUfsucau(C2p)agcuuuUfcCfagggcscsg	3651	CGACCCUGGAAAAGCUGAUGAAG	3738
AD-1019422.1	csgsagu(Chd)CfcUfCfAfaguccuuccaL96	3565	VPusGfsgaag(G2p)acuugaGfgGfacucgsasa	3652	UUCGAGUCCCUCAAGUCCUUCCA	3739
AD-1019407.1	usgsgaa(Ahd)AfgCfUfGfaugaaggccaL96	3566	VPusGfsgccu(Tgn)caucagCfuUfuuccasgsg	3653	CCUGGAAAAGCUGAUGAAGGCCU	3740
AD-1019418.1	cscsuuc(Ghd)AfgUfCfCfcucaaguccaL96	3567	VPusGfsgacu(Tgn)gagggaCfuCfgaaggscsc	3654	GGCCUUCGAGUCCCUCAAGUCCU	3741
AD-1019436.1	ascsggc(Chd)GfcUfCfAfgguucugcsusa	3568	VPusAfsgcaGfaAfCfcugaGfcGfgccguscsc	3655	GGACGGCCGCUCAGGUUCUGCUU	3742
AD-1019406.1	csusgga(Ahd)AfaGfCfUfgaugaaggcaL96	3569	VPusGfsccuu(C2p)aucagcUfuUfuccagsgsg	3656	CCCUGGAAAAGCUGAUGAAGGCC	3743
AD-1019417.1	gscscuu(Chd)GfaGfUfCfccucaagucaL96	3570	VPusGfsacuu(G2p)agggacUfcGfaaggcscsu	3657	AGGCCUUCGAGUCCCUCAAGUCC	3744
AD-1019372.1	gscscgc(Uhd)CfaGfGfUfucugcuuuuaL96	3571	VPusAfsaaag(C2p)agaaccUfgAfgcggcscsg	3658	CGGCCGCUCAGGUUCUGCUUUUA	3733
AD-	gscsuca(Ghd)GfuUfCfUfgcuuuuaccaL96	3572	VPusGfsguaa(Agn)agcagaAfcCfugagcsgsg	3659	CCGCUCAGGUUCUGCUUUUACCU	3745

Duplex ID	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:
1019375.1						
AD-1019444.1	csasggu(Uhd)CfuGfCfUfuuuaccugscsa	3573	VPusGfscagGfuAfAfaagcAfgAfaccugsasg	3660	CUCAGGUUCUGCUUUUACCUGCG	3746
AD-1019448.1	cscsaga(Ghd)CfcCfCfAfuucauugcscsa	3574	VPusGfsgcaAfuGfAfauggGfgCfucuggsgsc	3661	GCCCAGAGCCCCAUUCAUUGCCC	3747
AD-1019365.1	uscscaa(Ghd)AfuGfGfAfcggccgcucaL96	3575	VPusGfsagcg(G2p)ccguccAfuCfuuggascsc	3662	GGUCCAAGAUGGACGGCCGCUCA	3748
AD-1019374.1	csgscuc(Ahd)GfgUfUfCfugcuuuuacaL96	3576	VPusGfsuaaa(Agn)gcagaaCfcUfgagcgsgsc	3663	GCCGCUCAGGUUCUGCUUUUACC	3736
AD-1019402.1	gscsgac(Chd)CfuGfGfAfaaagcugauaL96	3577	VPusAfsucag(C2p)uuuuccAfgGfgucgcscsa	3664	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1019441.1	gscsuca(Ghd)GfuUfCfUfgcuuuuacscsa	3578	VPusGfsguaAfaAfGfcagaAfcCfugagcsgsg	3665	CCGCUCAGGUUCUGCUUUUACCU	3745
AD-1019399.1	cscsaug(Ghd)CfgAfCfCfcuggaaaagaL96	3579	VPusCfsuuuu(C2p)caggguCfgCfcauggscsg	3666	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1019378.1	csasggu(Uhd)CfuGfCfUfuuuaccugcaL96	3580	VPusGfscagg(Tgn)aaaagcAfgAfaccugsasg	3667	CUCAGGUUCUGCUUUUACCUGCG	3746
AD-1019419.1	csusucg(Ahd)GfuCfCfCfucaaguccuaL96	3581	VPusAfsggac(Tgn)ugagggAfcUfcgaagsgsc	3668	GCCUUCGAGUCCCUCAAGUCCUU	3751
AD-1019423.1	gsasguc(Chd)CfuCfAfAfguccuuccaaL96	3582	VPusUfsggaa(G2p)gacuugAfgGfgacucsgsa	3669	UCGAGUCCCUCAAGUCCUUCCAG	3752
AD-1019437.1	csgsgcc(Ghd)CfuCfAfGfguucugcususa	3583	VPusAfsagcAfgAfAfccugAfgCfggccgsusc	3670	GACGGCCGCUCAGGUUCUGCUUU	3753
AD-1019376.1	csuscag(Ghd)UfuCfUfGfcuuuuaccuaL96	3584	VPusAfsggua(Agn)aagcagAfaCfcugagscsg	3671	CGCUCAGGUUCUGCUUUUACCUG	3732
AD-1019373.1	cscsgcu(Chd)AfgGfUfUfcugcuuuuaaL96	3585	VPusUfsaaaa(G2p)cagaacCfuGfagcggscsc	3672	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1019435.1	gsgsacg(Ghd)CfcGfCfUfcagguucusgsa	3586	VPusCfsagaAfcCfUfgagcGfgCfcguccsasu	3673	AUGGACGGCCGCUCAGGUUCUGC	3754
AD-1019411.1	usgsaug(Ahd)AfgGfCfCfuucgaguccaL96	3587	VPusGfsgacu(C2p)gaaggcCfuUfcaucasgsc	3674	GCUGAUGAAGGCCUUCGAGUCCC	3755
AD-1019434.1	usgsgac(Ghd)GfcCfGfCfucagguucsusa	3588	VPusAfsgaaCfcUfGfagcgGfcCfguccasusc	3675	GAUGGACGGCCGCUCAGGUUCUG	3756
AD-1019377.1	uscsagg(Uhd)UfcUfGfCfuuuuaccugaL96	3589	VPusCfsaggu(Agn)aaagcaGfaAfccugasgsc	3676	GCUCAGGUUCUGCUUUUACCUGC	3757
AD-1019412.1	gsasuga(Ahd)GfgCfCfUfucgagucccaL96	3590	VPusGfsggac(Tgn)cgaaggCfcUfucaucsasg	3677	CUGAUGAAGGCCUUCGAGUCCCU	3758
AD-1019403.1	csgsacc(Chd)UfgGfAfAfaagcugaugaL96	3591	VPusCfsauca(G2p)cuuuucCfaGfggucgscsc	3678	GGCGACCCUGGAAAAGCUGAUGA	3759

Duplex ID	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-1019368.1	usgsgac(Ghd)GfcCfGfCfucagguucuaL96	3592	VPusAfsgaac(C2p)ugagcgGfcCfguccasusc	3679	GAUGGACGGCCGCUCAGGUUCUG	3756
AD-1019404.1	gsasccc(Uhd)GfgAfAfAfagcugaugaaL96	3593	VPusUfscauc(Agn)gcuuuuCfcAfgggucsgsc	3680	GCGACCCUGGAAAAGCUGAUGAA	3760
AD-1019415.1	asasggc(Chd)UfuCfGfAfgucccucaaaL96	3594	VPusUfsugag(G2p)gacucgAfaGfgccuuscsa	3681	UGAAGGCCUUCGAGUCCCUCAAG	3761
AD-1019421.1	uscsgag(Uhd)CfcCfUfCfaaguccuucaL96	3595	VPusGfsaagg(Agn)cuugagGfgAfcucgasasg	3682	CUUCGAGUCCCUCAAGUCCUUCC	3762
AD-1019400.1	asusggc(Ghd)AfcCfCfUfggaaaagcuaL96	3596	VPusAfsgcuu(Tgn)uccaggGfuCfgccausgsg	3683	CCAUGGCGACCCUGGAAAAGCUG	3763
AD-1019450.1	cscsauu(Chd)AfuUfGfCfcccggugcsusa	3597	VPusAfsgcaCfcGfGfggcaAfuGfaauggsgsg	3684	CCCCAUUCAUUGCCCCGGUGCUG	3764
AD-1019420.1	ususcga(Ghd)UfcCfCfUfcaaguccuuaL96	3598	VPusAfsagga(C2p)uugaggGfaCfucgaasgsg	3685	CCUUCGAGUCCCUCAAGUCCUUC	3765
AD-1019429.1	gsascgg(Ghd)UfcCfAfAfgauggacgsgsa	3599	VPusCfscguCfcAfUfcuugGfaCfccgucscsc	3686	GGGACGGGUCCAAGAUGGACGGC	3766
AD-1019431.1	uscscaa(Ghd)AfuGfGfAfcggccgcuscsa	3600	VPusGfsagcGfgCfCfguccAfuCfuuggascsc	3687	GGUCCAAGAUGGACGGCCGCUCA	3748
AD-1019428.1	gsgsacg(Ghd)GfuCfCfAfagauggacsgsa	3601	VPusCfsgucCfaUfCfuuggAfcCfcguccscsg	3688	CGGGACGGGUCCAAGAUGGACGG	3767
AD-1019364.1	ascsggg(Uhd)CfcAfAfGfauggacggcaL96	3602	VPusGfsccgu(C2p)caucuuGfgAfcccguscsc	3689	GGACGGGUCCAAGAUGGACGGCC	3768
AD-1019413.1	asusgaa(Ghd)GfcCfUfUfcgagucccuaL96	3603	VPusAfsggga(C2p)ucgaagGfcCfuucauscsa	3690	UGAUGAAGGCCUUCGAGUCCCUC	3769
AD-1019394.1	cscsucc(Ghd)GfgGfAfCfugccgugccaL96	3604	VPusGfsgcac(G2p)gcagucCfcCfggaggscsc	3691	GGCCUCCGGGGACUGCCGUGCCG	3770
AD-1019398.1	gscscau(Ghd)GfcGfAfCfccuggaaaaaL96	3605	VPusUfsuuuc(C2p)agggucGfcCfauggcsgsg	3692	CCGCCAUGGCGACCCUGGAAAAG	3771
AD-1019366.1	asasgau(Ghd)GfaCfGfGfccgcucaggaL96	3606	VPusCfscuga(G2p)cggccgUfcCfaucuusgsg	3693	CCAAGAUGGACGGCCGCUCAGGU	3772
AD-1019432.1	asasgau(Ghd)GfaCfGfGfccgcucagsgsa	3607	VPusCfscugAfgCfGfgccgUfcCfaucuusgsg	3694	CCAAGAUGGACGGCCGCUCAGGU	3772
AD-1019380.1	ususcug(Chd)UfuUfUfAfccugcggccaL96	3608	VPusGfsgccg(C2p)agguaaAfaGfcagaascsc	3695	GGUUCUGCUUUUACCUGCGGCCC	3773
AD-1019382.1	cscsaga(Ghd)CfcCfCfAfuucauugccaL96	3609	VPusGfsgcaa(Tgn)gaauggGfgCfucuggsgsc	3696	GCCCAGAGCCCCAUUCAUUGCCC	3747
AD-1019433.1	asgsaug(Ghd)AfcGfGfCfcgcucaggsusa	3610	VPusAfsccuGfaGfCfggccGfuCfcaucususg	3697	CAAGAUGGACGGCCGCUCAGGUU	3774
AD-1019424.1	asgsucc(Chd)UfcAfAfGfuccuuccagaL96	3611	VPusCfsugga(Agn)ggacuuGfaGfggacuscsg	3698	CGAGUCCCUCAAGUCCUUCCAGC	3775

Duplex ID	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-1019445.1	gsgsuuc(Uhd)GfcUfUfUfuaccugcgsgsa	3612	VPusCfscgcAfgGfUfaaaaGfcAfgaaccsusg	3699	CAGGUUCUGCUUUUACCUGCGGC	3776
AD-1019369.1	gsgsacg(Ghd)CfcGfCfUfcagguucugaL96	3613	VPusCfsagaa(C2p)cugagcGfgCfcguccsasu	3700	AUGGACGGCCGCUCAGGUUCUGC	3754
AD-1019416.1	gsgsccu(Uhd)CfgAfGfUfcccucaaguaL96	3614	VPusAfscuug(Agn)gggacuCfgAfaggccsusu	3701	AAGGCCUUCGAGUCCCUCAAGUC	3777
AD-1019414.1	usgsaag(Ghd)CfcUfUfCfgagucccucaL96	3615	VPusGfsaggg(Agn)cucgaaGfgCfcuucasusc	3702	GAUGAAGGCCUUCGAGUCCCUCA	3778
AD-1019447.1	cscscag(Ahd)GfcCfCfCfauucauugscsa	3616	VPusGfscaaUfgAfAfugggGfcUfcugggscsc	3703	GGCCCAGAGCCCCAUUCAUUGCC	3779
AD-1019430.1	ascsggg(Uhd)CfcAfAfGfauggacggscsa	3617	VPusGfsccgUfcCfAfucuuGfgAfcccguscsc	3704	GGACGGGUCCAAGAUGGACGGCC	3768
AD-1019395.1	csusccg(Ghd)GfgAfCfUfgccgugccgaL96	3618	VPusCfsggca(C2p)ggcaguCfcCfcggagsgsc	3705	GCCUCCGGGGACUGCCGUGCCGG	3780
AD-1019396.1	cscsgug(Chd)CfgGfGfCfgggagaccgaL96	3619	VPusCfsgguc(Tgn)cccgccCfgGfcacggscsa	3706	UGCCGUGCCGGGCGGGAGACCGC	3781
AD-1019425.1	gsusccc(Uhd)CfaAfGfUfccuuccagcaL96	3620	VPusGfscugg(Agn)aggacuUfgAfgggacsusc	3707	GAGUCCCUCAAGUCCUUCCAGCA	3782
AD-1019363.1	gsascgg(Ghd)UfcCfAfAfgauggacggaL96	3621	VPusCfscguc(C2p)aucuugGfaCfccgucscsc	3708	GGGACGGGUCCAAGAUGGACGGC	3766
AD-1019367.1	asgsaug(Ghd)AfcGfGfCfcgcucagguaL96	3622	VPusAfsccug(Agn)gcggccGfuCfcaucususg	3709	CAAGAUGGACGGCCGCUCAGGUU	3774
AD-1019362.1	gsgsacg(Ghd)GfuCfCfAfagauggacgaL96	3623	VPusCfsgucc(Agn)ucuuggAfcCfcguccscsg	3710	CGGGACGGGUCCAAGAUGGACGG	3767
AD-1019379.1	gsgsuuc(Uhd)GfcUfUfUfuaccugcggaL96	3624	VPusCfscgca(G2p)guaaaaGfcAfgaaccsusg	3711	CAGGUUCUGCUUUUACCUGCGGC	3776
AD-1019397.1	ascscgc(Chd)AfuGfGfCfgacccuggaaL96	3625	VPusUfsccag(G2p)gucgccAfuGfgcgguscsu	3712	AGACCGCCAUGGCGACCCUGGAA	3783
AD-1019392.1	csgsagg(Chd)CfuCfCfGfgggacugccaL96	3626	VPusGfsgcag(Tgn)ccccggAfgGfccucgsgsg	3713	CCCGAGGCCUCCGGGGACUGCCG	3784
AD-1019409.1	asasgcu(Ghd)AfuGfAfAfggccuucgaaL96	3627	VPusUfscgaa(G2p)gccuucAfuCfagcuususu	3714	AAAAGCUGAUGAAGGCCUUCGAG	3785
AD-1019361.1	csgsgga(Chd)GfgGfUfCfcaagauggaaL96	3628	VPusUfsccau(C2p)uuggacCfcGfucccgsgsc	3715	GCCGGGACGGGUCCAAGAUGGAC	3786
AD-1019449.1	csasgag(Chd)CfcCfAfUfucauugccscsa	3629	VPusGfsggcAfaUfGfaaugGfgGfcucugsgsg	3716	CCCAGAGCCCCAUUCAUUGCCCC	3787
AD-1019385.1	usgscug(Ahd)GfcGfGfCfgccgcgaguaL96	3630	VPusAfscucg(C2p)ggcgccGfcUfcagcascsc	3717	GGUGCUGAGCGGCGCCGCGAGUC	3788
AD-1019427.1	csgsgga(Chd)GfgGfUfCfcaagauggsasa	3631	VPusUfsccaUfcUfUfggacCfcGfucccgsgsc	3718	GCCGGGACGGGUCCAAGAUGGAC	3786

Duplex ID	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-1019390.1	cscscga(Ghd)GfcCfUfCfcggggacugaL96	3632	VPusCfsaguc(C2p)ccggagGfcCfucgggscsc	3719	GGCCCGAGGCCUCCGGGGACUGC	3789
AD-1019383.1	csasgag(Chd)CfcCfAfUfucauugcccaL96	3633	VPusGfsggca(Agn)ugaaugGfgGfcucugsgsg	3720	CCCAGAGCCCCAUUCAUUGCCCC	3787
AD-1019401.1	usgsgcg(Ahd)CfcCfUfGfgaaaagcugaL96	3634	VPusCfsagcu(Tgn)uuccagGfgUfcgccasusg	3721	CAUGGCGACCCUGGAAAAGCUGA	3790
AD-1019393.1	gsasggc(Chd)UfcCfGfGfggacugccgaL96	3635	VPusCfsggca(G2p)uccccgGfaGfgccucsgsg	3722	CCGAGGCCUCCGGGGACUGCCGU	3791
AD-1019370.1	ascsggc(Chd)GfcUfCfAfgguucugcuaL96	3636	VPusAfsgcag(Agn)accugaGfcGfgccguscsc	3723	GGACGGCCGCUCAGGUUCUGCUU	3742
AD-1019391.1	cscsgag(Ghd)CfcUfCfCfgggacugcaL96	3637	VPusGfscagu(C2p)cccggaGfgCfcucggsgsc	3724	GCCCGAGGCCUCCGGGGACUGCC	3792
AD-1019446.1	ususcug(Chd)UfuUfUfAfccugcggcscsa	3638	VPusGfsgccGfcAfGfguaaAfaGfcagaascsc	3725	GGUUCUGCUUUUACCUGCGGCCC	3773
AD-1019371.1	csgsgcc(Ghd)CfuCfAfGfguucugcuuaL96	3639	VPusAfsagca(G2p)aaccugAfgCfggccgsusc	3726	GACGGCCGCUCAGGUUCUGCUUU	3753
AD-1019386.1	gscsuga(Ghd)CfgGfCfGfccgcgagucaL96	3640	VPusGfsacuc(G2p)cggcgcCfgCfucagcsasc	3727	GUGCUGAGCGGCGCCGCGAGUCG	3793
AD-1019389.1	gscsccg(Ahd)GfgCfCfUfccggggacuaL96	3641	VPusAfsgucc(C2p)cggaggCfcUfcgggcscsg	3728	CGGCCCGAGGCCUCCGGGGACUG	3794
AD-1019387.1	gsasguc(Ghd)GfcCfCfGfaggccuccgaL96	3642	VPusCfsggag(G2p)ccucggGfcCfgacucsgsc	3729	GCGAGUCGGCCCGAGGCCUCCGG	3795
AD-1019381.1	cscscag(Ahd)GfcCfCfCfauucauugcaL96	3643	VPusGfscaau(G2p)aaugggGfcUfcugggscsc	3730	GGCCCAGAGCCCCAUUCAUUGCC	3779

Table 18. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1019439.1	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UUAAAAGCAGAACCUGAGCGGCC	3861	27-49
AD-1019442.1	CUCAGGUUCUGCUUUUACCUA	3797	32-52	UAGGUAAAAGCAGAACCUGAGCG	3862	30-52
AD-1019438.1	GCCGCUCAGGUUCUGCUUUUA	3798	28-48	UAAAAGCAGAACCUGAGCGGCCG	3863	26-48
AD-1019408.1	AAAGCUGAUGAAGGCCUUCGA	3799	160-180	UCGAAGGCCUUCAUCAGCUUUUC	3864	158-180
AD-1019426.1	UCCCUCAAGUCCUUCCAGCAA	3800	182-202	UUGCUGGAAGGACUUGAGGGACU	3865	180-202
AD-1019440.1	CGCUCAGGUUCUGCUUUUACA	3801	30-50	UGUAAAAGCAGAACCUGAGCGGC	3866	28-50

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1019410.1	CUGAUGAAGGCCUUCGAGUCA	3802	164-184	UGACUCGAAGGCCUUCAUCAGCU	3867	162-184
AD-1019405.1	ACCCUGGAAAAGCUGAUGAAA	3803	152-172	UUUCAUCAGCUUUUCCAGGGUCG	3868	150-172
AD-1019422.1	CGAGUCCCUCAAGUCCUUCCA	3804	178-198	UGGAAGGACUUGAGGGACUCGAA	3869	176-198
AD-1019407.1	UGGAAAAGCUGAUGAAGGCCA	3805	156-176	UGGCCUTCAUCAGCUUUUCCAGG	3870	154-176
AD-1019418.1	CCUUCGAGUCCCUCAAGUCCA	3806	174-194	UGGACUTGAGGGACUCGAAGGCC	3871	172-194
AD-1019436.1	ACGGCCGCUCAGGUUCUGCUA	3807	25-45	UAGCAGAACCUGAGCGGCCGUCC	3872	23-45
AD-1019406.1	CUGGAAAAGCUGAUGAAGGCA	3808	155-175	UGCCUUCAUCAGCUUUUCCAGGG	3873	153-175
AD-1019417.1	GCCUUCGAGUCCCUCAAGUCA	3809	173-193	UGACUUGAGGGACUCGAAGGCCU	3874	171-193
AD-1019372.1	GCCGCUCAGGUUCUGCUUUUA	3798	28-48	UAAAAGCAGAACCUGAGCGGCCG	3863	26-48
AD-1019375.1	GCUCAGGUUCUGCUUUUACCA	3810	31-51	UGGUAAAAGCAGAACCUGAGCGG	3875	29-51
AD-1019444.1	CAGGUUCUGCUUUUACCUGCA	3811	34-54	UGCAGGUAAAAGCAGAACCUGAG	3876	32-54
AD-1019448.1	CCAGAGCCCCAUUCAUUGCCA	3812	57-77	UGGCAAUGAAUGGGGCUCUGGGC	3877	55-77
AD-1019365.1	UCCAAGAUGGACGGCCGCUCA	3813	15-35	UGAGCGGCCGUCCAUCUUGGACC	3878	13-35
AD-1019374.1	CGCUCAGGUUCUGCUUUUACA	3801	30-50	UGUAAAAGCAGAACCUGAGCGGC	3866	28-50
AD-1019402.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCA	3879	147-169
AD-1019441.1	GCUCAGGUUCUGCUUUUACCA	3810	31-51	UGGUAAAAGCAGAACCUGAGCGG	3875	29-51
AD-1019399.1	CCAUGGCGACCCUGGAAAAGA	3815	144-164	UCUUUUCCAGGGUCGCCAUGGCG	3880	142-164
AD-1019378.1	CAGGUUCUGCUUUUACCUGCA	3811	34-54	UGCAGGTAAAAGCAGAACCUGAG	3881	32-54
AD-1019419.1	CUUCGAGUCCCUCAAGUCCUA	3816	175-195	UAGGACTUGAGGGACUCGAAGGC	3882	173-195
AD-1019423.1	GAGUCCCUCAAGUCCUUCCAA	3817	179-199	UUGGAAGGACUUGAGGGACUCGA	3883	177-199
AD-1019437.1	CGGCCGCUCAGGUUCUGCUUA	3818	26-46	UAAGCAGAACCUGAGCGGCCGUC	3884	24-46
AD-1019376.1	CUCAGGUUCUGCUUUUACCUA	3797	32-52	UAGGUAAAAGCAGAACCUGAGCG	3862	30-52
AD-1019373.1	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UUAAAAGCAGAACCUGAGCGGCC	3861	27-49
AD-1019435.1	GGACGGCCGCUCAGGUUCUGA	3819	23-43	UCAGAACCUGAGCGGCCGUCCAU	3885	21-43
AD-1019411.1	UGAUGAAGGCCUUCGAGUCCA	3820	165-185	UGGACUCGAAGGCCUUCAUCAGC	3886	163-185
AD-1019434.1	UGGACGGCCGCUCAGGUUCUA	3821	22-42	UAGAACCUGAGCGGCCGUCCAUC	3887	20-42
AD-1019377.1	UCAGGUUCUGCUUUUACCUGA	3822	33-53	UCAGGUAAAAGCAGAACCUGAGC	3888	31-53

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1019412.1	GAUGAAGGCCUUCGAGUCCCA	3823	166-186	UGGGACTCGAAGGCCUUCAUCAG	3889	164-186
AD-1019403.1	CGACCCUGGAAAAGCUGAUGA	3824	150-170	UCAUCAGCUUUUCCAGGGUCGCC	3890	148-170
AD-1019368.1	UGGACGGCCGCUCAGGUUCUA	3821	22-42	UAGAACCUGAGCGGCCGUCCAUC	3887	20-42
AD-1019404.1	GACCCUGGAAAAGCUGAUGAA	3825	151-171	UUCAUCAGCUUUUCCAGGGUCGC	3891	149-171
AD-1019415.1	AAGGCCUUCGAGUCCCUCAAA	3826	170-190	UUUGAGGGACUCGAAGGCCUUCA	3892	168-190
AD-1019421.1	UCGAGUCCCUCAAGUCCUUCA	3827	177-197	UGAAGGACUUGAGGGACUCGAAG	3893	175-197
AD-1019400.1	AUGGCGACCCUGGAAAAGCUA	3828	146-166	UAGCUUTUCCAGGGUCGCCAUGG	3894	144-166
AD-1019450.1	CCAUUCAUUGCCCCGGUGCUA	3829	65-85	UAGCACCGGGGCAAUGAAUGGGG	3895	63-85
AD-1019420.1	UUCGAGUCCCUCAAGUCCUUA	3830	176-196	UAAGGACUUGAGGGACUCGAAGG	3896	174-196
AD-1019429.1	GACGGGUCCAAGAUGGACGGA	3831	9-29	UCCGUCCAUCUUGGACCCGUCCC	3897	7-29
AD-1019431.1	UCCAAGAUGGACGGCCGCUCA	3813	15-35	UGAGCGGCCGUCCAUCUUGGACC	3878	13-35
AD-1019428.1	GGACGGGUCCAAGAUGGACGA	3832	8-29	UCGUCCAUCUUGGACCCGUCCCG	3898	6-29
AD-1019364.1	ACGGGUCCAAGAUGGACGGCA	3833	10-30	UGCCGUCCAUCUUGGACCCGUCC	3899	10-30
AD-1019413.1	AUGAAGGCCUUCGAGUCCCUA	3834	167-187	UAGGGACUCGAAGGCCUUCAUCA	3900	165-187
AD-1019394.1	CCUCCGGGGACUGCCGUGCCA	3835	111-131	UGGCACGGCAGUCCCCGGAGGCC	3901	109-131
AD-1019398.1	GCCAUGGCGACCCUGGAAAAA	3836	143-163	UUUUUCCAGGGUCGCCAUGGCGG	3902	141-163
AD-1019366.1	AAGAUGGACGGCCGCUCAGGA	3837	18-38	UCCUGAGCGGCCGUCCAUCUUGG	3903	16-38
AD-1019432.1	AAGAUGGACGGCCGCUCAGGA	3837	18-38	UCCUGAGCGGCCGUCCAUCUUGG	3903	16-38
AD-1019380.1	UUCUGCUUUUACCUGCGGCCA	3838	38-58	UGGCCGCAGGUAAAAGCAGAACC	3904	36-58
AD-1019382.1	CCAGAGCCCCAUUCAUUGCCA	3812	57-77	UGGCAATGAAUGGGGCUCUGGGC	3905	55-77
AD-1019433.1	AGAUGGACGGCCGCUCAGGUA	3839	19-39	UACCUGAGCGGCCGUCCAUCUUG	3906	17-39
AD-1019424.1	AGUCCCUCAAGUCCUUCCAGA	3840	180-200	UCUGGAAGGACUUGAGGGACUCG	3907	178-200
AD-1019445.1	GGUUCUGCUUUUACCUGCGGA	3841	36-56	UCCGCAGGUAAAAGCAGAACCUG	3908	34-56
AD-1019369.1	GGACGGCCGCUCAGGUUCUGA	3819	23-43	UCAGAACCUGAGCGGCCGUCCAU	3885	21-43
AD-1019416.1	GGCCUUCGAGUCCCUCAAGUA	3842	172-192	UACUUGAGGGACUCGAAGGCCUU	3909	170-192
AD-1019414.1	UGAAGGCCUUCGAGUCCCUCA	3843	168-188	UGAGGGACUCGAAGGCCUUCAUC	3910	166-188
AD-1019447.1	CCCAGAGCCCCAUUCAUUGCA	3844	56-76	UGCAAUGAAUGGGGCUCUGGGCC	3911	54-76

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1019430.1	ACGGGUCCAAGAUGGACGGCA	3833	10-30	UGCCGUCCAUCUUGGACCCGUCC	3899	10-30
AD-1019395.1	CUCCGGGGACUGCCGUGCCGA	3845	112-132	UCGGCACGGCAGUCCCCGGAGGC	3912	110-132
AD-1019396.1	CCGUGCCGGGCGGGAGACCGA	3846	124-144	UCGGUCTCCCGCCCGGCACGGCA	3913	122-144
AD-1019425.1	GUCCCUCAAGUCCUUCCAGCA	3847	181-201	UGCUGGAAGGACUUGAGGGACUC	3914	179-201
AD-1019363.1	GACGGGUCCAAGAUGGACGGA	3831	9-29	UCCGUCCAUCUUGGACCCGUCCC	3897	7-29
AD-1019367.1	AGAUGGACGGCCGCUCAGGUA	3839	19-39	UACCUGAGCGGCCGUCCAUCUUG	3906	17-39
AD-1019362.1	GGACGGGUCCAAGAUGGACGA	3832	8-28	UCGUCCAUCUUGGACCCGUCCCG	3898	6-28
AD-1019379.1	GGUUCUGCUUUUACCUGCGGA	3841	36-56	UCCGCAGGUAAAAGCAGAACCUG	3908	34-56
AD-1019397.1	ACCGCCAUGGCGACCCUGGAA	3848	140-160	UUCCAGGGUCGCCAUGGCGGUCU	3915	138-160
AD-1019392.1	CGAGGCCUCCGGGGACUGCCA	3849	106-126	UGGCAGTCCCCGGAGGCCUCGGG	3916	104-126
AD-1019409.1	AAGCUGAUGAAGGCCUUCGAA	3850	161-181	UUCGAAGGCCUUCAUCAGCUUUU	3917	159-181
AD-1019361.1	CGGGACGGGUCCAAGAUGGAA	3851	6-26	UUCCAUCUUGGACCCGUCCCGGC	3918	4-26
AD-1019449.1	CAGAGCCCCAUUCAUUGCCCA	3852	58-78	UGGGCAAUGAAUGGGGCUCUGGG	3919	56-78
AD-1019385.1	UGCUGAGCGGCGCCGCGAGUA	3853	81-101	UACUCGCGGCGCCGCUCAGCACC	3920	79-101
AD-1019427.1	CGGGACGGGUCCAAGAUGGAA	3851	6-26	UUCCAUCUUGGACCCGUCCCGGC	3918	4-26
AD-1019390.1	CCCGAGGCCUCCGGGGACUGA	3854	104-124	UCAGUCCCCGGAGGCCUCGGGCC	3921	102-124
AD-1019383.1	CAGAGCCCCAUUCAUUGCCCA	3852	58-78	UGGGCAAUGAAUGGGGCUCUGGG	3919	56-78
AD-1019401.1	UGGCGACCCUGGAAAAGCUGA	3855	147-167	UCAGCUTUUCCAGGGUCGCCAUG	3922	145-167
AD-1019393.1	GAGGCCUCCGGGGACUGCCGA	3856	107-127	UCGGCAGUCCCCGGAGGCCUCGG	3923	105-127
AD-1019370.1	ACGGCCGCUCAGGUUCUGCUA	3807	25-45	UAGCAGAACCUGAGCGGCCGUCC	3872	23-45
AD-1019391.1	CCGAGGCCUCCGGGGACUGCA	3857	105-125	UGCAGUCCCCGGAGGCCUCGGGC	3924	103-125
AD-1019446.1	UUCUGCUUUUACCUGCGGCCA	3838	38-58	UGGCCGCAGGUAAAAGCAGAACC	3904	36-58
AD-1019371.1	CGGCCGCUCAGGUUCUGCUUA	3818	26-46	UAAGCAGAACCUGAGCGGCCGUC	3884	24-46
AD-1019386.1	GCUGAGCGGCGCCGCGAGUCA	3858	82-102	UGACUCGCGGCGCCGCUCAGCAC	3925	80-102
AD-1019389.1	GCCCGAGGCCUCCGGGGACUA	3859	103-123	UAGUCCCCGGAGGCCUCGGGCCG	3926	101-123
AD-1019387.1	GAGUCGGCCCGAGGCCUCCGA	3860	97-117	UCGGAGGCCUCGGGCCGACUCGC	3927	95-117
AD-1019381.1	CCCAGAGCCCCAUUCAUUGCA	3844	56-76	UGCAAUGAAUGGGGCUCUGGGCC	3911	54-76

Table 20. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-1019427	csgsgga(Chd)GfgGfUfCfcaagauggsasa	3631	VPusUfsccaUfcUfUfggacCfcGfucccgsgsc	3718	GCCGGGACGGGUCCAAGAUGGAC	3786
AD-1019428	gsgsacg(Ghd)GfuCfCfAfagauggacsgsa	3601	VPusCfsgucCfaUfCfuuggAfcCfcguccscsg	3688	CGGGACGGGUCCAAGAUGGACGG	3767
AD-1019429	gsascgg(Ghd)UfcCfAfAfgauggacgsgsa	3599	VPusCfscguCfcAfUfcuugGfaCfccgucscsc	3686	GGGACGGGUCCAAGAUGGACGGC	3766
AD-1019430	ascsggg(Uhd)CfcAfAfGfauggacggscsa	3617	VPusGfsccgUfcCfAfucuuGfgAfcccguscsc	3704	GGACGGGUCCAAGAUGGACGGCC	3768
AD-1019431	uscscaa(Ghd)AfuGfGfAfcggccgcuscsa	3600	VPusGfsagcGfgCfCfguccAfuCfuuggascsc	3687	GGUCCAAGAUGGACGGCCGCUCA	3748
AD-1019432	asasgau(Ghd)GfaCfGfGfccgcucagsgsa	3607	VPusCfscugAfgCfGfgccgUfcCfaucuusgsg	3694	CCAAGAUGGACGGCCGCUCAGGU	3772
AD-1019433	asgsaug(Ghd)AfcGfGfCfcgcucaggsusa	3610	VPusAfsccuGfaGfCfggccGfuCfcaucususg	3697	CAAGAUGGACGGCCGCUCAGGUU	3774
AD-1019434	usgsgac(Ghd)GfcCfGfCfucagguucsusa	3588	VPusAfsgaaCfcUfGfagcgGfcCfguccasusc	3675	GAUGGACGGCCGCUCAGGUUCUG	3756
AD-1019435	gsgsacg(Ghd)CfcGfCfUfcagguucusgsa	3586	VPusCfsagaAfcCfUfgagcGfgCfcguccsasu	3673	AUGGACGGCCGCUCAGGUUCUGC	3754
AD-1019436	ascsggc(Chd)GfcUfCfAfgguucugcsusa	3568	VPusAfsgcaGfaAfCfcugaGfcGfgccguscsc	3655	GGACGGCCGCUCAGGUUCUGCUU	3742
AD-1019437	csgsgcc(Ghd)CfuCfAfGfguucugcususa	3583	VPusAfsagcAfgAfAfccugAfgCfggccgsusc	3670	GACGGCCGCUCAGGUUCUGCUUU	3753
AD-1019438	gscscgc(Uhd)CfaGfGfUfucugcuuususa	3559	VPusAfsaaaGfcAfGfaaccUfgAfgcggcscsg	3646	CGGCCGCUCAGGUUCUGCUUUUA	3733
AD-1019439	cscsgcu(Chd)AfgGfUfUfcugcuuuusasa	3557	VPusUfsaaaAfgCfAfgaacCfuGfagcggscsc	3644	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1019440	csgscuc(Ahd)GfgUfUfCfugcuuuuascsa	3562	VPusGfsuaaAfaGfCfagaaCfcUfgagcgsgsc	3649	GCCGCUCAGGUUCUGCUUUUACC	3736
AD-1019441	gscsuca(Ghd)GfuUfCfUfgcuuuuacscsa	3578	VPusGfsguaAfaAfGfcagaAfcCfugagcsgsg	3665	CCGCUCAGGUUCUGCUUUUACCU	3745
AD-1019442	csuscag(Ghd)UfuCfUfGfcuuuuaccsusa	3558	VPusAfsgguAfaAfAfgcagAfaCfcugagscsg	3645	CGCUCAGGUUCUGCUUUUACCUG	3732
AD-1019444	csasggu(Uhd)CfuGfCfUfuuuaccugscsa	3573	VPusGfscagGfuAfAfaagcAfgAfaccugsasg	3660	CUCAGGUUCUGCUUUUACCUGCG	3746
AD-1019445	gsgsuuc(Uhd)GfcUfUfUfuaccugcgsgsa	3612	VPusCfscgcAfgGfUfaaaaGfcAfgaaccsusg	3699	CAGGUUCUGCUUUUACCUGCGGC	3776
AD-1019446	ususcug(Chd)UfuUfUfAfccugcggcscsa	3638	VPusGfsgccGfcAfGfguaaAfaGfcagaascsc	3725	GGUUCUGCUUUUACCUGCGGCCC	3773

Duplex ID	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-1019447	cscscag(Ahd)GfcCfCfCfauucauugscsa	3616	VPusGfscaaUfgAfAfugggGfcUfcugggscsc	3703	GGCCCAGAGCCCCAUUCAUUGCC	3779
AD-1019448	cscsaga(Ghd)CfcCfCfAfuucauugcscsa	3574	VPusGfsgcaAfuGfAfauggGfgCfucuggsgsc	3661	GCCCAGAGCCCCAUUCAUUGCCC	3747
AD-1019449	csasgag(Chd)CfcCfAfUfucauugccscsa	3629	VPusGfsggcAfaUfGfaaugGfgGfcucugsgsg	3716	CCCAGAGCCCCAUUCAUUGCCCC	3787
AD-1019450	cscsauu(Chd)AfuUfGfCfcccggugcsusa	3597	VPusAfsgcaCfcGfGfggcaAfuGfaauggsgsg	3684	CCCCAUUCAUUGCCCCGGUGCUG	3764

Table 21. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1019427	CGGGACGGGUCCAAGAUGGAA	3851	6-26	UUCCAUCUUGGACCCGUCCCGGC	3918	4-26
AD-1019428	GGACGGGUCCAAGAUGGACGA	3832	8-28	UCGUCCAUCUUGGACCCGUCCCG	3898	6-28
AD-1019429	GACGGGUCCAAGAUGGACGGA	3831	9-29	UCCGUCCAUCUUGGACCCGUCCC	3897	7-29
AD-1019430	ACGGGUCCAAGAUGGACGGCA	3833	10-30	UGCCGUCCAUCUUGGACCCGUCC	3899	8-30
AD-1019431	UCCAAGAUGGACGGCCGCUCA	3813	15-35	UGAGCGGCCGUCCAUCUUGGACC	3878	13-35
AD-1019432	AAGAUGGACGGCCGCUCAGGA	3837	18-38	UCCUGAGCGGCCGUCCAUCUUGG	3903	16-38
AD-1019433	AGAUGGACGGCCGCUCAGGUA	3839	19-39	UACCUGAGCGGCCGUCCAUCUUG	3906	17-39
AD-1019434	UGGACGGCCGCUCAGGUUCUA	3821	22-42	UAGAACCUGAGCGGCCGUCCAUC	3887	20-42
AD-1019435	GGACGGCCGCUCAGGUUCUGA	3819	23-43	UCAGAACCUGAGCGGCCGUCCAU	3885	21-43
AD-1019436	ACGGCCGCUCAGGUUCUGCUA	3807	25-45	UAGCAGAACCUGAGCGGCCGUCC	3872	23-45
AD-1019437	CGGCCGCUCAGGUUCUGCUUA	3818	26-46	UAAGCAGAACCUGAGCGGCCGUC	3884	24-46
AD-1019438	GCCGCUCAGGUUCUGCUUUUA	3798	28-48	UAAAAGCAGAACCUGAGCGGCCG	3863	26-48
AD-1019439	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UUAAAAGCAGAACCUGAGCGGCC	3861	27-49
AD-1019440	CGCUCAGGUUCUGCUUUUACA	3801	30-50	UGUAAAAGCAGAACCUGAGCGGC	3866	28-50
AD-1019441	GCUCAGGUUCUGCUUUUACCA	3810	31-51	UGGUAAAAGCAGAACCUGAGCGG	3875	29-51
AD-1019442	CUCAGGUUCUGCUUUUACCUA	3797	32-52	UAGGUAAAAGCAGAACCUGAGCG	3862	30-52
AD-1019444	CAGGUUCUGCUUUUACCUGCA	3811	34-54	UGCAGGUAAAAGCAGAACCUGAG	3876	32-54

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1019445	GGUUCUGCUUUUACCUGCGGA	3841	36-56	UCCGCAGGUAAAAGCAGAACCUG	3908	34-56
AD-1019446	UUCUGCUUUUACCUGCGGCCA	3838	38-58	UGGCCGCAGGUAAAAGCAGAACC	3904	36-58
AD-1019447	CCCAGAGCCCCAUUCAUUGCA	3844	56-76	UGCAAUGAAUGGGGCUCUGGGCC	3911	54-76
AD-1019448	CCAGAGCCCCAUUCAUUGCCA	3812	57-77	UGGCAAUGAAUGGGGCUCUGGGC	3877	55-77
AD-1019449	CAGAGCCCCAUUCAUUGCCCA	3852	58-78	UGGGCAAUGAAUGGGGCUCUGGG	3919	56-78
AD-1019450	CCAUUCAUUGCCCCGGUGCUA	3829	65-85	UAGCACCGGGGCAAUGAAUGGGG	3895	63-85

Table 24. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-1019451	usgscug(Ahd)GfcGfGfCfgccgcgagsusa	3928	VPusAfscucGfcGfGfcgccGfcUfcagcascsc	3968	GGUGCUGAGCGGCGCCGCGAGUC	3788
AD-1019452	gscsuga(Ghd)CfgGfCfGfccgcgaguscsa	3929	VPusGfsacuCfgCfGfgcgcCfgCfucagcsasc	3969	GUGCUGAGCGGCGCCGCGAGUCG	3793
AD-1019453	gsasguc(Ghd)GfcCfCfGfaggccuccsgsa	3930	VPusCfsggaGfgCfCfucggGfcCfgacucsgsc	3970	GCGAGUCGGCCCGAGGCCUCCGG	3795
AD-1019454	asgsucg(Ghd)CfcCfGfAfggccuccgsgsa	3931	VPusCfscggAfgGfCfcucgGfgCfcgacuscsg	3971	CGAGUCGGCCCGAGGCCUCCGGG	4008
AD-1019455	gscsccg(Ahd)GfgCfCfUfccggggacsusa	3932	VPusAfsgucCfcCfGfgaggCfcUfcgggcscsg	3972	CGGCCCGAGGCCUCCGGGGACUG	3794
AD-1019456	cscscga(Ghd)GfcCfUfCfcggggacusgsa	3933	VPusCfsaguCfcCfCfggagGfcCfucgggscsc	3973	GGCCCGAGGCCUCCGGGGACUGC	3789
AD-1019457	cscsgag(Ghd)CfcUfCfCfggggacugscsa	3934	VPusGfscagUfcCfCfcggaGfgCfcucggsgsc	3974	GCCCGAGGCCUCCGGGGACUGCC	3792
AD-1019458	csgsagg(Chd)CfuCfCfGfgggacugcscsa	3935	VPusGfsgcaGfuCfCfccggAfgGfccucgsgsg	3975	CCCGAGGCCUCCGGGGACUGCCG	3784
AD-1019459	gsasggc(Chd)UfcCfGfGfggacugccsgsa	3936	VPusCfsggcAfgUfCfcccgGfaGfgccucsgsg	3976	CCGAGGCCUCCGGGGACUGCCGU	3791
AD-1019460	cscsucc(Ghd)GfgGfAfCfugccgugcscsa	3937	VPusGfsgcaCfgGfCfagucCfcCfggaggscsc	3977	GGCCUCCGGGGACUGCCGUGCCG	3770
AD-1019461	csusccg(Ghd)GfgAfCfUfgccgugccsgsa	3938	VPusCfsggcAfcGfGfcaguCfcCfcggagsgsc	3978	GCCUCCGGGGACUGCCGUGCCGG	3780

Duplex ID	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-1019462	cscsgug(Chd)CfgGfGfCfgggagaccsgsa	3939	VPusCfsgguCfuCfCfcgccCfgGfcacggscsa	3979	UGCCGUGCCGGGCGGGAGACCGC	3781
AD-1019463	ascscgc(Chd)AfuGfGfCfgacccuggsasa	3940	VPusUfsccaGfgGfUfcgccAfuGfgcgguscsu	3980	AGACCGCCAUGGCGACCCUGGAA	3783
AD-1019464	gscscau(Ghd)GfcGfAfCfccuggaaasasa	3941	VPusUfsuuuCfcAfGfggucGfcCfauggcsgsg	3981	CCGCCAUGGCGACCCUGGAAAAG	3771
AD-1019465	cscsaug(Ghd)CfgAfCfCfcuggaaaasgsa	3942	VPusCfsuuuUfcCfAfggguCfgCfcauggscsg	3982	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1019466	asusggc(Ghd)AfcCfCfUfggaaaagcsusa	3943	VPusAfsgcuUfuUfCfcaggGfuCfgccausgsg	3983	CCAUGGCGACCCUGGAAAAGCUG	3763
AD-1019467	usgsgcg(Ahd)CfcCfUfGfgaaaagcusgsa	3944	VPusCfsagcUfuUfUfccagGfgUfcgccasusg	3984	CAUGGCGACCCUGGAAAAGCUGA	3790
AD-1019468	gscsgac(Chd)CfuGfGfAfaaagcugasusa	3945	VPusAfsucaGfcUfUfuuccAfgGfgucgcscsa	3985	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1019469	csgsacc(Chd)UfgGfAfAfaagcugausgsa	3946	VPusCfsaucAfgCfUfuuucCfaGfggucgscsc	3986	GGCGACCCUGGAAAAGCUGAUGA	3759
AD-1019470	gsasccc(Uhd)GfgAfAfAfagcugaugsasa	3947	VPusUfscauCfaGfCfuuuuCfcAfgggucsgsc	3987	GCGACCCUGGAAAAGCUGAUGAA	3760
AD-1019471	ascsccu(Ghd)GfaAfAfAfgcugaugasasa	3948	VPusUfsucaUfcAfGfcuuuUfcCfaggguscsg	3988	CGACCCUGGAAAAGCUGAUGAAG	3738
AD-1019472	csusgga(Ahd)AfaGfCfUfgaugaaggscsa	3949	VPusGfsccuUfcAfUfcagcUfuUfuccagsgsg	3989	CCCUGGAAAAGCUGAUGAAGGCC	3743
AD-1019473	usgsgaa(Ahd)AfgCfUfGfaugaaggcscsa	3950	VPusGfsgccUfuCfAfucagCfuUfuuccasgsg	3990	CCUGGAAAAGCUGAUGAAGGCCU	3740
AD-1019474	asasagc(Uhd)GfaUfGfAfaggccuucsgsa	3951	VPusCfsgaaGfgCfCfuucaUfcAfgcuuususc	3991	GAAAAGCUGAUGAAGGCCUUCGA	3734
AD-1019475	asasgcu(Ghd)AfuGfAfAfggccuucgsasa	3952	VPusUfscgaAfgGfCfcuucAfuCfagcuususu	3992	AAAAGCUGAUGAAGGCCUUCGAG	3785
AD-1019476	csusgau(Ghd)AfaGfGfCfcuucgaguscsa	3953	VPusGfsacuCfgAfAfggccUfuCfaucagscsu	3993	AGCUGAUGAAGGCCUUCGAGUCC	3737
AD-1019477	usgsaug(Ahd)AfgGfCfCfuucgagucscsa	3954	VPusGfsgacUfcGfAfaggcCfuUfcaucasgsc	3994	GCUGAUGAAGGCCUUCGAGUCCC	3755
AD-1019478	gsasuga(Ahd)GfgCfCfUfucgaguccscsa	3955	VPusGfsggaCfuCfGfaaggCfcUfucaucsasg	3995	CUGAUGAAGGCCUUCGAGUCCCU	3758
AD-1019479	asusgaa(Ghd)GfcCfUfUfcgagucccsusa	3956	VPusAfsgggAfcUfCfgaagGfcCfuucauscsa	3996	UGAUGAAGGCCUUCGAGUCCCUC	3769
AD-1019480	usgsaag(Ghd)CfcUfUfCfgagucccuscsa	3957	VPusGfsaggGfaCfUfcgaaGfgCfcuucasusc	3997	GAUGAAGGCCUUCGAGUCCCUCA	3778
AD-1019481	asasggc(Chd)UfuCfGfAfgucccucasasa	3958	VPusUfsugaGfgGfAfcucgAfaGfgccuuscsa	3998	UGAAGGCCUUCGAGUCCCUCAAG	3761

Duplex ID	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-1019482	gsgsccu(Uhd)CfgAfGfUfcccucaagsusa	3959	VPusAfscuuGfaGfGfgacuCfgAfaggccsusu	3999	AAGGCCUUCGAGUCCCUCAAGUC	3777
AD-1019483	gscscuu(Chd)GfaGfUfCfccucaaguscsa	3960	VPusGfsacuUfgAfGfggacUfcGfaaggcscsu	4000	AGGCCUUCGAGUCCCUCAAGUCC	3744
AD-1019484	cscsuuc(Ghd)AfgUfCfCfcucaagucscsa	3961	VPusGfsgacUfuGfAfgggaCfuCfgaaggscsc	4001	GGCCUUCGAGUCCCUCAAGUCCU	3741
AD-1019485	csusucg(Ahd)GfuCfCfCfucaaguccsusa	3962	VPusAfsggaCfuUfGfagggAfcUfcgaagsgsc	4002	GCCUUCGAGUCCCUCAAGUCCUU	3751
AD-1019486	ususcga(Ghd)UfcCfCfUfcaaguccususa	3963	VPusAfsaggAfcUfUfgaggGfaCfucgaasgsg	4003	CCUUCGAGUCCCUCAAGUCCUUC	3765
AD-1019487	uscsgag(Uhd)CfcCfUfCfaaguccuuscsa	3964	VPusGfsaagGfaCfUfugagGfgAfcucgasasg	4004	CUUCGAGUCCCUCAAGUCCUUCC	3762
AD-1019488	csgsagu(Chd)CfcUfCfAfaguccuucscsa	3965	VPusGfsgaaGfgAfCfuugaGfgGfacucgsasa	4005	UUCGAGUCCCUCAAGUCCUUCCA	3739
AD-1019489	gsasguc(Chd)CfuCfAfAfguccuuccsasa	3966	VPusUfsggaAfgGfAfcuugAfgGfgacucsgsa	4006	UCGAGUCCCUCAAGUCCUUCCAG	3752
AD-1019491	gsusccc(Uhd)CfaAfGfUfccuuccagscsa	3967	VPusGfscugGfaAfGfgacuUfgAfgggacsusc	4007	GAGUCCCUCAAGUCCUUCCAGCA	3782

Table 25. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1019451	UGCUGAGCGGCGCCGCGAGUA	3853	81-101	UACUCGCGGCGCCGCUCAGCACC	3920	79-101
AD-1019452	GCUGAGCGGCGCCGCGAGUCA	3858	82-102	UGACUCGCGGCGCCGCUCAGCAC	3925	80-102
AD-1019453	GAGUCGGCCCGAGGCCUCCGA	3860	97-117	UCGGAGGCCUCGGGCCGACUCGC	3927	95-117
AD-1019454	AGUCGGCCCGAGGCCUCCGGA	4009	98-118	UCCGGAGGCCUCGGGCCGACUCG	4010	96-118
AD-1019455	GCCCGAGGCCUCCGGGGACUA	3859	103-123	UAGUCCCCGGAGGCCUCGGGCCG	3926	101-123
AD-1019456	CCCGAGGCCUCCGGGGACUGA	3854	104-124	UCAGUCCCCGGAGGCCUCGGGCC	3921	102-124
AD-1019457	CCGAGGCCUCCGGGGACUGCA	3857	105-125	UGCAGUCCCCGGAGGCCUCGGGC	3924	103-125
AD-1019458	CGAGGCCUCCGGGGACUGCCA	3849	106-126	UGGCAGUCCCCGGAGGCCUCGGG	4011	104-126
AD-1019459	GAGGCCUCCGGGGACUGCCGA	3856	107-127	UCGGCAGUCCCCGGAGGCCUCGG	3923	105-127
AD-1019460	CCUCCGGGGACUGCCGUGCCA	3835	111-131	UGGCACGGCAGUCCCCGGAGGCC	3901	109-131

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1019461	CUCCGGGGACUGCCGUGCCGA	3845	112-132	UCGGCACGGCAGUCCCCGGAGGC	3912	110-132
AD-1019462	CCGUGCCGGGCGGGAGACCGA	3846	124-144	UCGGUCUCCCGCCCGGCACGGCA	4012	122-144
AD-1019463	ACCGCCAUGGCGACCCUGGAA	3848	140-160	UUCCAGGGUCGCCAUGGCGGUCU	3915	138-160
AD-1019464	GCCAUGGCGACCCUGGAAAAA	3836	143-163	UUUUUCCAGGGUCGCCAUGGCGG	3902	141-163
AD-1019465	CCAUGGCGACCCUGGAAAAGA	3815	144-164	UCUUUUCCAGGGUCGCCAUGGCG	3880	142-164
AD-1019466	AUGGCGACCCUGGAAAAGCUA	3828	146-166	UAGCUUUUCCAGGGUCGCCAUGG	4013	144-166
AD-1019467	UGGCGACCCUGGAAAAGCUGA	3855	147-167	UCAGCUUUUCCAGGGUCGCCAUG	4014	145-167
AD-1019468	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCA	3879	147-169
AD-1019469	CGACCCUGGAAAAGCUGAUGA	3824	150-170	UCAUCAGCUUUUCCAGGGUCGCC	3890	148-170
AD-1019470	GACCCUGGAAAAGCUGAUGAA	3825	151-171	UUCAUCAGCUUUUCCAGGGUCGC	3891	149-171
AD-1019471	ACCCUGGAAAAGCUGAUGAAA	3803	152-172	UUUCAUCAGCUUUUCCAGGGUCG	3868	150-172
AD-1019472	CUGGAAAAGCUGAUGAAGGCA	3808	155-175	UGCCUUCAUCAGCUUUUCCAGGG	3873	153-175
AD-1019473	UGGAAAAGCUGAUGAAGGCCA	3805	156-176	UGGCCUUCAUCAGCUUUUCCAGG	4015	154-176
AD-1019474	AAAGCUGAUGAAGGCCUUCGA	3799	160-180	UCGAAGGCCUUCAUCAGCUUUUC	3864	158-180
AD-1019475	AAGCUGAUGAAGGCCUUCGAA	3850	161-181	UUCGAAGGCCUUCAUCAGCUUUU	3917	159-181
AD-1019476	CUGAUGAAGGCCUUCGAGUCA	3802	164-184	UGACUCGAAGGCCUUCAUCAGCU	3867	162-184
AD-1019477	UGAUGAAGGCCUUCGAGUCCA	3820	165-185	UGGACUCGAAGGCCUUCAUCAGC	3886	163-185
AD-1019478	GAUGAAGGCCUUCGAGUCCCA	3823	166-186	UGGGACUCGAAGGCCUUCAUCAG	4016	164-186
AD-1019479	AUGAAGGCCUUCGAGUCCCUA	3834	167-187	UAGGGACUCGAAGGCCUUCAUCA	3900	165-187
AD-1019480	UGAAGGCCUUCGAGUCCCUCA	3843	168-188	UGAGGGACUCGAAGGCCUUCAUC	3910	166-188
AD-1019481	AAGGCCUUCGAGUCCCUCAAA	3826	170-190	UUUGAGGGACUCGAAGGCCUUCA	3892	168-190
AD-1019482	GGCCUUCGAGUCCCUCAAGUA	3842	172-192	UACUUGAGGGACUCGAAGGCCUU	3909	170-192
AD-1019483	GCCUUCGAGUCCCUCAAGUCA	3809	173-193	UGACUUGAGGGACUCGAAGGCCU	3874	171-193
AD-1019484	CCUUCGAGUCCCUCAAGUCCA	3806	174-194	UGGACUUGAGGGACUCGAAGGCC	4017	172-194
AD-1019485	CUUCGAGUCCCUCAAGUCCUA	3816	175-195	UAGGACUUGAGGGACUCGAAGGC	4018	173-195
AD-1019486	UUCGAGUCCCUCAAGUCCUUA	3830	176-196	UAAGGACUUGAGGGACUCGAAGG	3896	174-196
AD-1019487	UCGAGUCCCUCAAGUCCUUCA	3827	177-197	UGAAGGACUUGAGGGACUCGAAG	3893	175-197

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1019488	CGAGUCCCUCAAGUCCUUCCA	3804	178-198	UGGAAGGACUUGAGGGACUCGAA	3869	176-198
AD-1019489	GAGUCCCUCAAGUCCUUCCAA	3817	179-199	UUGGAAGGACUUGAGGGACUCGA	3883	177-199
AD-1019491	GUCCCUCAAGUCCUUCCAGCA	3847	181-201	UGCUGGAAGGACUUGAGGGACUC	3914	179-201

Table 27. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-1289928.1	ascscc(Uhd)ggaAfAfAfgcugaugaaaL96	4019	VPusUfsucdAu(C2p)agcuuuUfcCfagggususc	4070	CGACCCUGGAAAAGCUGAUGAAG	3738
AD-1289833.1	cscsaucg(Chd)gAfCfCfcuggaaaagaL96	4020	VPusCfsuudTu(C2p)caggguCfgCfgauggscsg	4071	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289929.1	cscsuggaAfAfAfgcuga(Uhd)gaaaL96	4021	VPusUfsucdAu(C2p)agcuuuUfcCfaggsgsu	4072	ACCCUGGAAAAGCUGAUGAAG	4134
AD-1289927.1	cscs(Uhd)ggaAfAfAfguugaugaaaL96	4022	VPusUfsucdAudCaacuuuUfcCfaggsgsu	4073	ACCCUGGAAAAGCUGAUGAAG	4134
AD-1289826.1	cscsaugg(Chd)gAfCfCfcuggaaaagaL96	4023	VPusCfsuudTudCaggguCfgCfcauggscsg	4074	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289831.1	asusgg(Chd)gAfCfCfcuggaaaagaL96	4024	VPusCfsuudTu(C2p)caggguCfgCfcausgsg	4075	CCAUGGCGACCCUGGAAAAGC	4135
AD-1289925.1	ascscc(Uhd)ggaAfAfAfgcugaugaaaL96	4019	VPusUfsucdAu(C2p)agcuuuUfcCfaggguscsg	4076	CGACCCUGGAAAAGCUGAUGAAG	3738
AD-1289824.1	cscsaugg(Chd)gAfCfCfcuggaaaagaL96	4023	VPusCfsuuuUfcCfAfggguCfgCfcauggscsg	3982	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289832.1	asusgg(Chd)gAfCfCfcuggaaaagaL96	4024	VPusCfsuudTu(C2p)caggguCfgCfcaususc	4077	CCAUGGCGACCCUGGAAAAGC	4135
AD-1289825.1	cscsauggcgAfCfCfcugg(Ahd)aaagaL96	4025	VPusCfsuuuUfcCfAfggguCfgCfcauggscsg	3982	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289852.1	cscsgcucAfgGfUfUfcugcu(Uhd)uuaaL96	4026	VPusUfsaadAadGcagaacCfudGagcggscsc	4078	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1289867.1	csusu(Chd)GfaGfUfCfccucaagucaL96	4027	VPusdGsacdTu(G2p)agggacUfcGfaagsgsc	4079	GCCUUCGAGUCCCUCAAGUCC	4136
AD-1289924.1	ascsccuggaAfAfAfgcuga(Uhd)gaaaL96	4028	VPusUfsucau(C2p)agcuuuUfcCfaggguscsg	3651	CGACCCUGGAAAAGCUGAUGAAG	3738
AD-1289853.1	cscsgcu(Chd)AfgGfUfUfcugauuuuaaL96	4029	VPusUfsaadAadTcagaacCfudGagcggscsc	4080	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1289860.1	cscsggu(Chd)AfgGfUfUfcugcuuuuaaL96	4030	VPusUfsaadAadGcagaacCfudGaccggscsc	4081	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1289931.1	cscs(Ahd)ggaAfAfAfgcugaugaaaL96	4031	VPusUfsucdAu(C2p)agcuuuUfcCfuggsgsu	4082	ACCCUGGAAAAGCUGAUGAAG	4134
AD-1289926.1	cscs(Uhd)ggaAfAfAfgcuuaugaaaL96	4032	VPusUfsucdAudAagcuuuUfcCfaggsgsu	4083	ACCCUGGAAAAGCUGAUGAAG	4134
AD-1289851.1	cscsgcu(Chd)AfgGfUfUfcugcuuuuaaL96	3585	VPusUfsaadAadGcagaacCfudGagcggscsc	4078	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1289930.1	cscsuggaAfAfAfgcuga(Uhd)gaaaL96	4021	VPusUfsucdAu(C2p)agcuuuUfcCfaggsusc	4084	ACCCUGGAAAAGCUGAUGAAG	4134
AD-1289859.1	cscsgca(Chd)AfgGfUfUfcugcuuuuaaL96	4033	VPusUfsaadAadGcagaacCfudGugcggscsc	4085	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1289932.1	csgs(Uhd)ggaAfAfAfgcugaugaaaL96	4034	VPusUfsucdAu(C2p)agcuuuUfcCfacgsgsu	4086	ACCCUGGAAAAGCUGAUGAAG	4134
AD-1019405.3	ascsccu(Ghd)GfaAfAfAfgcugaugaaaL96	3564	VPusUfsucau(C2p)agcuuuUfcCfaggguscsg	3651	CGACCCUGGAAAAGCUGAUGAAG	3738
AD-1289861.1	cscsccu(Chd)AfgGfUfUfcugcuuuuaaL96	4035	VPusUfsaadAadGcagaacCfudGaggggscsc	4087	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1107447.5	cscsaug(Ghd)CfgAfCfCfcuggaaaagaL96	3579	VPusCfsuuuUfcCfAfggguCfgCfcauggscsg	3982	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289948.1	uscsccu(Chd)AfagUfCfcuuccagcaaL96	4036	VPusUfsgcdTg(G2p)aaggacUfudGagggasusc	4088	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1289864.1	gscscuu(Chd)GfaGfUfCfccucaagucaL96	3570	VPusdGsacdTu(G2p)agggacUfcGfaaggcscsu	4089	AGGCCUUCGAGUCCCUCAAGUCC	3744
AD-1289913.1	gscsgac(Chd)CfudGgAfaaagcugauaL96	4037	VPusAfsucdAg(C2p)uuuuccAfgdGgucgcscsg	4090	UGGCGACCCUGGAAAAGCUGAUG	3749

AD-1289923.1	ascscc(Uhd)ggaAfAfAfgcugaugaaaL96	4019	VPusUfsucau(C2p)agcuuuUfcCfaggguscsg	3651	CGACCCUGGAAAAGCUGAUGAAG	3738
AD-1289921.1	gscsguc(Chd)CfudGgAfaaagcugauaL96	4038	VPusAfsucdAg(C2p)uuuuccAfgdGgacgcscsg	4091	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289865.1	gscscuu(Chd)GfaGfUfCfccuuaagucaL96	4039	VPusdGsacdTudAagggacUfcGfaaggcscsu	4092	AGGCCUUCGAGUCCCUCAAGUCC	3744
AD-1107442.5	cscsgcu(Chd)AfgGfUfUfcugcuuuuaaL96	3585	VPusUfsaaaAfgCfAfgaacCfuGfagcggscsc	3644	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1289830.1	cscsaugg(Uhd)gAfCfCfcuggaaaagaL96	4040	VPusCfsuudTudCcaggguCfaCfcauggsusc	4093	CCAUGGCGACCCUGGAAAAGC	4135
AD-1289866.1	gscscuu(Chd)GfaGfUfCfccucaagucaL96	3570	VPusdGsacdTu(G2p)agggacUfcGfaaggcsusc	4094	AGGCCUUCGAGUCCCUCAAGUCC	3744
AD-1289947.1	uscsccu(Chd)AfagUfCfcuuccagcaaL96	4036	VPusUfsgcdTg(G2p)aaggacUfudGagggascsu	4095	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1289933.1	gscs(Uhd)ggaAfAfAfgcugaugaaaL96	4041	VPusUfsucdAu(C2p)agcuuuUfcCfagcsgsu	4096	ACCCUGGAAAAGCUGAUGAAG	4134
AD-1289950.1	uscscca(Chd)AfagUfCfcuuccagcaaL96	4042	VPusUfsgcdTg(G2p)aaggacUfudGugggascsu	4097	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1289868.1	csusu(Chd)GfaGfUfCfccucaagucaL96	4027	VPusdGsacdTu(G2p)agggacUfcGfaagscsu	4098	GCCUUCGAGUCCCUCAAGUCC	4136
AD-1289946.1	uscsgcu(Chd)AfaGfUfCfcuuucagcaaL96	4043	VPusUfsgcdTgdAaaggacUfuGfagcgascsu	4099	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1289960.1	gscsguc(Chd)CfudGgAfaaagcugauaL96	4038	VPusAfsucdAg(C2p)uuuudCcAfgdGgacgcsusc	4100	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289956.1	gscsgac(Chd)CfudGgAfaaagcugauaL96	4037	VPusAfsucdAgdCuuuudCcAfgdGgucgcscsg	4101	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289827.1	cscsaugg(Chd)gAfCfCfcuggaaaagaL96	4023	VPusCfsuudTu(C2p)caggguCfgCfcauggscsg	4102	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289829.1	cscsaugg(Chd)gAfUfCfcuggaaaagaL96	4044	VPusCfsuudTudCcaggauCfgCfcauggsusc	4103	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289850.1	cscsgcu(Chd)aggUfUfcugcuuuuaaL96	4045	VPusUfsaaaAfgCfAfgaacCfuGfagcggscsc	3644	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1289945.1	uscsccu(Chd)AfaGfUfCfcuuucagcaaL96	4046	VPusUfsgcdTgdAaaggacUfuGfagggascsu	4104	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1289835.1	cscsuugg(Chd)gAfCfCfcuggaaaagaL96	4047	VPusCfsuudTu(C2p)caggguCfgCfcaaggscsg	4105	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289828.1	cscsaugg(Chd)gAfCfCfcuggaaaagaL96	4023	VPusCfsuudTu(C2p)caggguCfgCfcauggsusc	4106	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289949.1	cscsu(Chd)AfagUfCfcuuccagcaaL96	4048	VPusUfsgcdTg(G2p)aaggacUfudGaggscsg	4107	UCCCUCAAGUCCUUCCAGCAG	4137
AD-1289871.1	gscsguu(Chd)GfaGfUfCfccucaagucaL96	4049	VPusdGsacdTu(G2p)agggacUfcGfaacgcscsu	4108	AGGCCUUCGAGUCCCUCAAGUCC	3744
AD-1289914.1	gscsgac(Chd)CfudGgAfaaagcugauaL96	4037	VPusAfsucdAg(C2p)uuuudCcAfgdGgucgcscsg	4109	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289911.1	gscsgaccCfuGfGfAfaaagc(Uhd)gauaL96	4050	VPusAfsucag(C2p)uuuuccAfgGfgucgcscsa	3664	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289857.1	gscsu(Chd)AfgGfUfUfcugcuuuuaaL96	4051	VPusUfsaadAadGcagaacCfudGagcsusg	4110	CCGCUCAGGUUCUGCUUUUAC	4138
AD-1289944.1	uscsccucAfaGfUfCfcuucc(Ahd)gcaaL96	4052	VPusUfsgcug(G2p)aaggacUfuGfagggascsu	3648	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1289957.1	gscsgac(Chd)CfuGfGfAfaaagcugauaL96	3577	VPusAfsucdAg(C2p)uuuudCcAfgdGgucgcscsg	4109	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289955.1	gscsgac(Chd)CfudGgAfaaagcugauaL96	4037	VPusAfsucaGfcUfUfuuccAfgGfgucgcscsg	4111	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289834.1	cscsaagg(Chd)gAfCfCfcuggaaaagaL96	4053	VPusCfsuudTu(C2p)caggguCfgCfcuuggscsg	4112	CGCCAUGGCGACCCUGGAAAAGC	3750
AD-1289855.1	cscsgcu(Chd)agdGuUfcugcuuuuaaL96	4054	VPusUfsaadAadGcagadAcCfudGagcggscsc	4113	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1019402.3	gscsgac(Chd)CfuGfGfAfaaagcugauaL96	3577	VPusAfsucag(C2p)uuuuccAfgGfgucgcscsa	3664	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289954.1	gsasccCfuGfGfAfaaugc(Uhd)gauaL96	4055	VPusAfsucdAgdCauuudCcAfgdGgucsusc	4114	GCGACCCUGGAAAAGCUGAUG	4139
AD-1289920.1	gscsgag(Chd)CfudGgAfaaagcugauaL96	4056	VPusAfsucdAg(C2p)uuuuccAfgdGcucgcscsg	4115	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1019426.3	uscsccu(Chd)AfaGfUfCfcuuccagcaaL96	3561	VPusUfsgcug(G2p)aaggacUfuGfagggascsu	3648	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1289862.1	cscsgcu(Chd)agGfUfUfcugcuuuuaaL96	4057	VPusdTsaadAadGcagadAcCfudGagcggscsc	4116	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1289854.1	cscsgcu(Chd)aggUfUfcugcuuuuaaL96	4045	VPusUfsaadAadGcagaacCfudGagcggscsc	4078	GGCCGCUCAGGUUCUGCUUUUAC	3731
AD-1289914.2	gscsgac(Chd)CfudGgAfaaagcugauaL96	4037	VPusAfsucdAg(C2p)uuuudCcAfgdGgucgcscsg	4109	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289915.1	gscsgac(Chd)CfudGgAfaaagcugauaL96	4037	VPusAfsucdAg(C2p)uuuudCcAfgdGgucgcsusg	4117	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1107449.5	gscsgac(Chd)CfuGfGfAfaaagcugauaL96	3577	VPusAfsucaGfcUfUfuuccAfgGfgucgcscsa	3985	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289870.1	gscscau(Chd)GfaGfUfCfccucaagucaL96	4058	VPusdGsacdTu(G2p)agggacUfcGfauggcscsu	4118	AGGCCUUCGAGUCCCUCAAGUCC	3744
AD-1289953.1	gscsgaccCfuGfGfAfaaagc(Uhd)gauaL96	4050	VPusAfsucaGfcUfUfuuccAfgGfgucgcscsg	4111	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1107451.5	gscscuu(Chd)GfaGfUfCfccucaagucaL96	3570	VPusGfsacuUfgAfGfggacUfcGfaaggcscsu	4000	AGGCCUUCGAGUCCCUCAAGUCC	3744
AD-1289961.1	gscscac(Chd)CfudGgAfaaagcugauaL96	4059	VPusAfsucdAg(C2p)uuuudCcAfgdGguggcsusc	4119	CCAUGGCGACCCUGGAAAAGC	4135

AD-1289951.1	uscscgu(Chd)AfagUfCfcuuccagcaaL96	4060	VPusUfsgcdTg(G2p)aaggacUfudGacggascsu	4120	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1289915.2	gscsgac(Chd)CfudGgAfaaagcugauaL96	4037	VPusAfsucdAg(C2p)uuuudCcAfgdGgucgcsusg	4117	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289912.1	gscsgac(Chd)CfudGgAfaaagcugauaL96	4037	VPusAfsucag(C2p)uuuuccAfgGfgucgcscsg	4121	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289958.1	gsasc(Chd)CfudGgAfaaagcugauaL96	4061	VPusAfsucdAg(C2p)uuuudCcAfgdGgucsusg	4122	GCGACCCUGGAAAAGCUGAUG	4139
AD-1289869.1	gscscua(Chd)GfaGfUfCfccucaagucaL96	4062	VPusdGsacdTu(G2p)agggacUfcGfuaggcscsu	4123	AGGCCUUCGAGUCCCUCAAGUCC	3744
AD-1289916.2	gsasc(Chd)CfudGgAfaaagcugauaL96	4061	VPusAfsucdAg(C2p)uuuudCcAfgdGgucsgsc	4124	GCGACCCUGGAAAAGCUGAUG	4139
AD-1289858.1	gscsu(Chd)AfgGfUfUfcugcuuuuaaL96	4051	VPusUfsaadAa(G2p)cagaacCfudGagcsusg	4125	CCGCUCAGGUUCUGCUUUUAC	4138
AD-1289789.1	csasgcu(Uhd)CfcUfCfAfgccgccgccaL96	4063	VPusGfsgcgGfcGfGfcugaGfgAfagcugsasg	4126	CUCAGCUUCCUCAGCCGCCGCCG	4140
AD-1255821.1	uscsagc(Uhd)UfcCfUfCfagccgccgcaL96	4064	VPusGfscggCfgGfCfugagGfaAfgcugasgsg	4127	CCUCAGCUUCCUCAGCCGCCGCC	4141
AD-1289959.1	gscsgag(Chd)CfudGgAfaaagcugauaL96	4056	VPusAfsucdAg(C2p)uuuudCcAfgdGcucgcsusc	4128	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289790.1	asgscuu(Chd)CfuCfAfGfccgccgccgaL96	4065	VPusCfsggcGfgCfGfgcugAfgGfaagcusgsa	4129	UCAGCUUCCUCAGCCGCCGCCGC	4142
AD-1289952.1	uscsgcu(Chd)AfagUfCfcuuccagcaaL96	4066	VPusUfsgcdTg(G2p)aaggacUfudGagcgascsu	4130	AGUCCCUCAAGUCCUUCCAGCAG	3735
AD-1289791.1	gscsuuc(Chd)UfcAfGfCfcgccgccgcaL96	4067	VPusGfscggCfgGfCfggcuGfaGfgaagcsusg	4131	CAGCUUCCUCAGCCGCCGCCGCA	4143
AD-1289922.1	gscscac(Chd)CfudGgAfaaagcugauaL96	4059	VPusAfsucdAg(C2p)uuuuccAfgdGguggcscsg	4132	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289919.1	gscsgaccCfuGfGfAfaaugc(Uhd)gauaL96	4068	VPusAfsucdAgdCauuudCcAfgdGgucscsu	4133	UGGCGACCCUGGAAAAGCUGAUG	3749
AD-1289916.1	gsasc(Chd)CfudGgAfaaagcugauaL96	4061	VPusAfsucdAg(C2p)uuuudCcAfgdGgucsgsc	4124	GCGACCCUGGAAAAGCUGAUG	4139
AD-1289863.1	gscscuu(Chd)gagUfCfccucaagucaL96	4069	VPusGfsacuUfgAfGfggacUfcGfaaggcscsu	4000	AGGCCUUCGAGUCCCUCAAGUCC	3744

Table 28. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1289928.1	ACCCUGGAAAAGCUGAUGAAA	3803	152-172	UUUCAUCAGCUUUUCCAGGGUUC	4182	150-172
AD-1289833.1	CCAUCGCGACCCUGGAAAAGA	4144	144-164	UCUUTUCCAGGGUCGCGAUGGCG	4183	142-164
AD-1289929.1	CCUGGAAAAGCUGAUGAAA	4145	154-172	UUUCAUCAGCUUUUCCAGGGU	4184	152-172
AD-1289927.1	CCUGGAAAAGUUGAUGAAA	4146	154-172	UUUCAUCAACUUUUCCAGGGU	4185	152-172
AD-1289826.1	CCAUGGCGACCCUGGAAAAGA	3815	144-164	UCUUTUCCAGGGUCGCCAUGGCG	4186	142-164
AD-1289831.1	AUGGCGACCCUGGAAAAGA	4147	146-164	UCUUTUCCAGGGUCGCCAUGG	4187	144-164
AD-1289925.1	ACCCUGGAAAAGCUGAUGAAA	3803	152-172	UUUCAUCAGCUUUUCCAGGGUCG	3868	150-172
AD-1289824.1	CCAUGGCGACCCUGGAAAAGA	3815	144-164	UCUUUUCCAGGGUCGCCAUGGCG	3880	142-164
AD-1289832.1	AUGGCGACCCUGGAAAAGA	4147	146-164	UCUUTUCCAGGGUCGCCAUUC	4188	144-164
AD-1289825.1	CCAUGGCGACCCUGGAAAAGA	3815	144-164	UCUUUUCCAGGGUCGCCAUGGCG	3880	142-164
AD-1289852.1	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UUAAAAGCAGAACCUGAGCGGCC	3861	27-49
AD-1289867.1	CUUCGAGUCCCUCAAGUCA	4148	175-193	UGACTUGAGGGACUCGAAGGC	4189	173-193
AD-1289924.1	ACCCUGGAAAAGCUGAUGAAA	3803	152-172	UUUCAUCAGCUUUUCCAGGGUCG	3868	150-172

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1289853.1	CCGCUCAGGUUCUGAUUUUAA	4149	29-49	UUAAAATCAGAACCUGAGCGGCC	4190	27-49
AD-1289860.1	CCGGUCAGGUUCUGCUUUUAA	4150	29-49	UUAAAAGCAGAACCUGACCGGCC	4191	27-49
AD-1289931.1	CCAGGAAAAGCUGAUGAAA	4151	154-172	UUUCAUCAGCUUUUCCUGGGU	4192	152-172
AD-1289926.1	CCUGGAAAAGCUUAUGAAA	4152	154-172	UUUCAUAAGCUUUUCCAGGGU	4193	152-172
AD-1289851.1	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UUAAAAGCAGAACCUGAGCGGCC	3861	27-49
AD-1289930.1	CCUGGAAAAGCUGAUGAAA	4145	154-172	UUUCAUCAGCUUUUCCAGGUC	4194	152-172
AD-1289859.1	CCGCACAGGUUCUGCUUUUAA	4153	29-49	UUAAAAGCAGAACCUGUGCGGCC	4195	27-49
AD-1289932.1	CGUGGAAAAGCUGAUGAAA	4154	154-172	UUUCAUCAGCUUUUCCACGGU	4196	152-172
AD-1019405.3	ACCCUGGAAAAGCUGAUGAAA	3803	152-172	UUUCAUCAGCUUUUCCAGGGUCG	3868	150-172
AD-1289861.1	CCCCUCAGGUUCUGCUUUUAA	4155	29-49	UUAAAAGCAGAACCUGAGGGGCC	4197	27-49
AD-1107447.5	CCAUGGCGACCCUGGAAAAGA	3815	144-164	UCUUUUCCAGGGUCGCCAUGGCG	3880	142-164
AD-1289948.1	UCCCUCAAGUCCUUCCAGCAA	3800	182-202	UUGCTGGAAGGACUUGAGGGAUC	4198	180-202
AD-1289864.1	GCCUUCGAGUCCCUCAAGUCA	3809	173-193	UGACTUGAGGGACUCGAAGGCCU	4199	171-193
AD-1289913.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCG	4200	147-169
AD-1289923.1	ACCCUGGAAAAGCUGAUGAAA	3803	152-172	UUUCAUCAGCUUUUCCAGGGUCG	3868	150-172
AD-1289921.1	GCGUCCCUGGAAAAGCUGAUA	4156	149-169	UAUCAGCUUUUCCAGGGACGCCG	4201	147-169
AD-1289865.1	GCCUUCGAGUCCCUUAAGUCA	4157	173-193	UGACTUAAGGGACUCGAAGGCCU	4202	171-193
AD-1107442.5	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UUAAAAGCAGAACCUGAGCGGCC	3861	27-49
AD-1289830.1	CCAUGGUGACCCUGGAAAAGA	4158	144-164	UCUUTUCCAGGGUCACCAUGGUC	4203	142-164
AD-1289866.1	GCCUUCGAGUCCCUCAAGUCA	3809	173-193	UGACTUGAGGGACUCGAAGGCUC	4204	171-193
AD-1289947.1	UCCCUCAAGUCCUUCCAGCAA	3800	182-202	UUGCTGGAAGGACUUGAGGGACU	4205	180-202
AD-1289933.1	GCUGGAAAAGCUGAUGAAA	4159	154-172	UUUCAUCAGCUUUUCCAGCGU	4206	152-172
AD-1289950.1	UCCCACAAGUCCUUCCAGCAA	4160	182-202	UUGCTGGAAGGACUUGUGGGACU	4207	180-202
AD-1289868.1	CUUCGAGUCCCUCAAGUCA	4148	175-193	UGACTUGAGGGACUCGAAGCU	4208	173-193
AD-1289946.1	UCGCUCAAGUCCUUUCAGCAA	4161	182-202	UUGCTGAAAGGACUUGAGCGACU	4209	180-202
AD-1289960.1	GCGUCCCUGGAAAAGCUGAUA	4156	149-169	UAUCAGCUUUUCCAGGGACGCUC	4210	147-169
AD-1289956.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCG	4200	147-169

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1289827.1	CCAUGGCGACCCUGGAAAAGA	3815	144-164	UCUUTUCCAGGGUCGCCAUGGCG	4186	142-164
AD-1289829.1	CCAUGGCGAUCCUGGAAAAGA	4162	144-164	UCUUTUCCAGGAUCGCCAUGGUC	4211	142-164
AD-1289850.1	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UUAAAAGCAGAACCUGAGCGGCC	3861	27-49
AD-1289945.1	UCCCUCAAGUCCUUUCAGCAA	4163	182-202	UUGCTGAAAGGACUUGAGGGACU	4212	180-202
AD-1289835.1	CCUUGGCGACCCUGGAAAAGA	4164	144-164	UCUUTUCCAGGGUCGCCAAGGCG	4213	142-164
AD-1289828.1	CCAUGGCGACCCUGGAAAAGA	3815	144-164	UCUUTUCCAGGGUCGCCAUGGUC	4214	142-164
AD-1289949.1	CCUCAAGUCCUUCCAGCAA	4165	184-202	UUGCTGGAAGGACUUGAGGCG	4215	182-202
AD-1289871.1	GCGUUCGAGUCCCUCAAGUCA	4166	173-193	UGACTUGAGGGACUCGAACGCCU	4216	171-193
AD-1289914.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCG	4200	147-169
AD-1289911.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCA	3879	147-169
AD-1289857.1	GCUCAGGUUCUGCUUUUAA	4167	31-49	UUAAAAGCAGAACCUGAGCUG	4217	29-49
AD-1289944.1	UCCCUCAAGUCCUUCCAGCAA	3800	182-202	UUGCUGGAAGGACUUGAGGGACU	3865	180-202
AD-1289957.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCG	4200	147-169
AD-1289955.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCG	4200	147-169
AD-1289834.1	CCAAGGCGACCCUGGAAAAGA	4168	144-164	UCUUTUCCAGGGUCGCCUUGGCG	4218	142-164
AD-1289855.1	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UUAAAAGCAGAACCUGAGCGGCC	3861	27-49
AD-1019402.3	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCA	3879	147-169
AD-1289954.1	GACCCUGGAAAUGCUGAUA	4169	151-169	UAUCAGCAUUUCCAGGGUCUC	4219	149-169
AD-1289920.1	GCGAGCCUGGAAAAGCUGAUA	4170	149-169	UAUCAGCUUUUCCAGGCUCGCCG	4220	147-169
AD-1019426.3	UCCCUCAAGUCCUUCCAGCAA	3800	182-202	UUGCUGGAAGGACUUGAGGGACU	3865	180-202
AD-1289862.1	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UTAAAAGCAGAACCUGAGCGGCC	4221	27-49
AD-1289854.1	CCGCUCAGGUUCUGCUUUUAA	3796	29-49	UUAAAAGCAGAACCUGAGCGGCC	3861	27-49
AD-1289914.2	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCG	4200	147-169
AD-1289915.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCUG	4222	147-169
AD-1107449.5	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCA	3879	147-169
AD-1289870.1	GCCAUCGAGUCCCUCAAGUCA	4171	173-193	UGACTUGAGGGACUCGAUGGCCU	4223	171-193
AD-1289953.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCG	4200	147-169

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1107451.5	GCCUUCGAGUCCCUCAAGUCA	3809	173-193	UGACUUGAGGGACUCGAAGGCCU	3874	171-193
AD-1289961.1	GCCACCCUGGAAAAGCUGAUA	4172	149-169	UAUCAGCUUUUCCAGGGUGGCUC	4224	147-169
AD-1289951.1	UCCGUCAAGUCCUUCCAGCAA	4173	182-202	UUGCUGGAAGGACUUGACGGACU	4225	180-202
AD-1289915.2	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCUG	4222	147-169
AD-1289912.1	GCGACCCUGGAAAAGCUGAUA	3814	149-169	UAUCAGCUUUUCCAGGGUCGCCG	4200	147-169
AD-1289958.1	GACCCUGGAAAAGCUGAUA	4174	151-169	UAUCAGCUUUUCCAGGGUCUG	4226	149-169
AD-1289869.1	GCCUACGAGUCCCUCAAGUCA	4175	173-193	UGACTUGAGGGACUCGUAGGCCU	4227	171-193
AD-1289916.2	GACCCUGGAAAAGCUGAUA	4174	151-169	UAUCAGCUUUUCCAGGGUCGC	4228	149-169
AD-1289858.1	GCUCAGGUUCUGCUUUUAA	4167	31-49	UUAAAAGCAGAACCUGAGCUG	4217	29-49
AD-1289789.1	CAGCUUCCUCAGCCGCCGCCA	4176	299-319	UGGCGGCGGCUGAGGAAGCUGAG	4229	297-319
AD-1255821.1	UCAGCUUCCUCAGCCGCCGCA	4177	298-318	UGCGGCGGCUGAGGAAGCUGAGG	4230	296-318
AD-1289959.1	GCGAGCCUGGAAAAGCUGAUA	4170	149-169	UAUCAGCUUUUCCAGGCUCGCUC	4231	147-149
AD-1289790.1	AGCUUCCUCAGCCGCCGCCGA	4178	300-320	UCGGCGGCGGCUGAGGAAGCUGA	4232	298-320
AD-1289952.1	UCGCUCAAGUCCUUCCAGCAA	4179	182-202	UUGCTGGAAGGACUUGAGCGACU	4233	180-202
AD-1289791.1	GCUUCCUCAGCCGCCGCCGCA	4180	301-321	UGCGGCGGCGGCUGAGGAAGCUG	4234	299-321
AD-1289922.1	GCCACCCUGGAAAAGCUGAUA	4172	149-169	UAUCAGCUUUUCCAGGGUGGCCG	4235	147-169
AD-1289919.1	GCGACCCUGGAAAUGCUGAUA	4181	149-169	UAUCAGCAUUUCCAGGGUCCU	4236	147-169
AD-1289916.1	GACCCUGGAAAAGCUGAUA	4174	151-169	UAUCAGCUUUUCCAGGGUCGC	4228	149-169
AD-1289863.1	GCCUUCGAGUCCCUCAAGUCA	3809	173-193	UGACUUGAGGGACUCGAAGGCCU	3874	171-193

Table 29. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-1255829.1	ascsagc(Chd)GfcUfGfCfugccucagcaL96	4237	VPusGfscugAfgGfCfagcaGfcGfgcugusgsc	4282	GCACAGCCGCUGCUGCCUCAGCC	4327
AD-1289804.1	cscsgcc(Ghd)CfaGfGfCfacagccgcuaL96	4238	VPusAfsgcgGfcUfGfugccUfgCfggcggscsg	4283	CGCCGCCGCAGGCACAGCCGCUG	4328
AD-1255847.1	usgsagg(Ahd)GfcCfGfCfugcaccgacaL96	4239	VPusGfsucgGfuGfCfagcgGfcUfccucasgsc	4284	GCUGAGGAGCCGCUGCACCGACC	4329
AD-1255846.1	csusgag(Ghd)AfgCfCfGfcugcaccgaaL96	4240	VPusUfscggUfgCfAfgcggCfuCfcucagscsc	4285	GGCUGAGGAGCCGCUGCACCGAC	4330
AD-1255842.1	gsusggc(Uhd)GfaGfGfAfgccgcugcaaL96	4241	VPusUfsgcaGfcGfGfcuccUfcAfgccacsasg	4286	CUGUGGCUGAGGAGCCGCUGCAC	4331
AD-1255826.1	gsgscac(Ahd)GfcCfGfCfugcugccucaL96	4242	VPusGfsaggCfaGfCfagcgGfcUfgugccsusg	4287	CAGGCACAGCCGCUGCUGCCUCA	4332

Duplex ID	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-1255828.1	csascag(Chd)CfgCfUfGfcugccucagaL96	4243	VPusCfsugaGfgCfAfgcagCfgGfcugugcscsc	4288	GGCACAGCCGCUGCUGCCUCAGC	4333
AD-1255844.1	gsgscug(Ahd)GfgAfGfCfcgcugcaccaL96	4244	VPusGfsgugCfaGfCfggcuCfcUfcagccsasc	4289	GUGGCUGAGGAGCCGCUGCACCG	4334
AD-1289792.1	csusucc(Uhd)CfaGfCfCfgccgccgcaaL96	4245	VPusUfsgcgGfcGfGfcggcUfgAfggaagscsu	4290	AGCUUCCUCAGCCGCCGCCGCAG	4335
AD-1255825.1	asgsgca(Chd)AfgCfCfGfcugcugccuaL96	4246	VPusAfsggcAfgCfAfgcggCfuGfugccusgsc	4291	GCAGGCACAGCCGCUGCUGCCUC	4336
AD-1255822.1	cscsgca(Ghd)GfcAfCfAfgccgcugcuaL96	4247	VPusAfsgcaGfcGfGfcuguGfcCfugcggscsg	4292	CGCCGCAGGCACAGCCGCUGCUG	4337
AD-1255839.1	gscsugu(Ghd)GfcUfGfAfggagccgcuaL96	4248	VPusAfsgcgGfcUfCfcucaGfcCfacagcscsg	4293	CGGCUGUGGCUGAGGAGCCGCUG	4338
AD-1255827.1	gscsaca(Ghd)CfcGfCfUfgcugccucaaL96	4249	VPusUfsgagGfcAfGfcagcGfgCfugugcscsu	4294	AGGCACAGCCGCUGCUGCCUCAG	4339
AD-1255824.1	gscsagg(Chd)AfcAfGfCfcgcugcugcaL96	4250	VPusGfscagCfaGfCfggcuGfuGfccugcsgsg	4295	CCGCAGGCACAGCCGCUGCUGCC	4340
AD-1255845.1	gscsuga(Ghd)GfaGfCfCfgcugcaccgaL96	4251	VPusCfsgguGfcAfGfcggcUfcCfucagcscsa	4296	UGGCUGAGGAGCCGCUGCACCGA	4341
AD-1255830.1	cscsgcu(Ghd)CfuGfCfCfucagccgcaaL96	4252	VPusUfsgcgGfcUfGfaggcAfgCfagcggscsu	4297	AGCCGCUGCUGCCUCAGCCGCAG	4342
AD-1289806.1	gscscgc(Ahd)GfgCfAfCfagccgcugcaL96	4253	VPusGfscagCfgGfCfugugCfcUfgcggcsgsg	4298	CCGCCGCAGGCACAGCCGCUGCU	4343
AD-1255836.1	cscsggc(Uhd)GfuGfGfCfugaggagccaL96	4254	VPusGfsgcuCfcUfCfagccAfcAfgccggsgsc	4299	GCCCGGCUGUGGCUGAGGAGCCG	4344
AD-1289807.1	csasggc(Ahd)CfaGfCfCfgcugcugccaL96	4255	VPusGfsgcaGfcAfGfcggcUfgUfgccugscsg	4300	CGCAGGCACAGCCGCUGCUGCCU	4345
AD-1289805.1	csgsccg(Chd)AfgGfCfAfcagccgcugaL96	4256	VPusCfsagcGfgCfUfgugcCfuGfcggcgsgsc	4301	GCCGCCGCAGGCACAGCCGCUGC	4346
AD-1255840.1	csusgug(Ghd)CfuGfAfGfgagccgcugaL96	4257	VPusCfsagcGfgCfUfccucAfgCfcacagscsc	4302	GGCUGUGGCUGAGGAGCCGCUGC	4347
AD-1289808.1	csasgcc(Ghd)CfuGfCfUfgccucagccaL96	4258	VPusGfsgcuGfaGfGfcagcAfgCfggcugsusg	4303	CACAGCCGCUGCUGCCUCAGCCG	4348
AD-1289800.1	gscscgc(Chd)GfcCfGfCfaggcacagcaL96	4259	VPusGfscugUfgCfCfugcgGfcGfgcggcsusg	4304	CAGCCGCCGCCGCAGGCACAGCC	4349
AD-1255838.1	gsgscug(Uhd)GfgCfUfGfaggagccgcaL96	4260	VPusGfscggCfuCfCfucagCfcAfcagccsgsg	4305	CCGGCUGUGGCUGAGGAGCCGCU	4350
AD-1255843.1	usgsgcu(Ghd)AfgGfAfGfccgcugcacaL96	4261	VPusGfsugcAfgCfGfgcucCfuCfagccascsa	4306	UGUGGCUGAGGAGCCGCUGCACC	4351
AD-1255837.1	csgsgcu(Ghd)UfgGfCfUfgaggagccgaL96	4262	VPusCfsggcUfcCfUfcagcCfaCfagccgsgsg	4307	CCCGGCUGUGGCUGAGGAGCCGC	4352
AD-1255833.1	gsgsccc(Ghd)GfcUfGfUfggcugaggaaL96	4263	VPusUfsccuCfaGfCfcacaGfcCfgggccsgsg	4308	CCGGCCCGGCUGUGGCUGAGGAG	4353
AD-1289797.1	uscsagc(Chd)GfcCfGfCfcgcaggcacaL96	4264	VPusGfsugcCfuGfCfggcgGfcGfgcugasgsg	4309	CCUCAGCCGCCGCCGCAGGCACA	4354
AD-1255823.1	csgscag(Ghd)CfaCfAfGfccgcugcugaL96	4265	VPusCfsagcAfgCfGfgcugUfgCfcugcgsgsc	4310	GCCGCAGGCACAGCCGCUGCUGC	4355
AD-1289810.1	gscscgc(Uhd)GfcUfGfCfcucagccgcaL96	4266	VPusGfscggCfuGfAfggcaGfcAfgcggcsusg	4311	CAGCCGCUGCUGCCUCAGCCGCA	4356
AD-1289811.1	cscsggc(Chd)CfgGfCfUfguggcugagaL96	4267	VPusCfsucaGfcCfAfcagcCfgGfgccggsgsu	4312	ACCCGGCCCGGCUGUGGCUGAGG	4357
AD-1289812.1	csgsgcc(Chd)GfgCfUfGfuggcugaggaL96	4268	VPusCfscucAfgCfCfacagCfcGfggccgsgsg	4313	CCCGGCCCGGCUGUGGCUGAGGA	4358
AD-1255841.1	usgsugg(Chd)UfgAfGfGfagccgcugcaL96	4269	VPusGfscagCfgGfCfuccuCfaGfccacasgsc	4314	GCUGUGGCUGAGGAGCCGCUGCA	4359
AD-1289799.1	asgsccg(Chd)CfgCfCfGfcaggcacagaL96	4270	VPusCfsuguGfcCfUfgcggCfgGfcggcusgsa	4315	UCAGCCGCCGCCGCAGGCACAGC	4360
AD-1255834.1	gscsccg(Ghd)CfuGfUfGfgcugaggagaL96	4271	VPusCfsuccUfcAfGfccacAfgCfcgggcscsg	4316	CGGCCCGGCUGUGGCUGAGGAGC	4361
AD-1289809.1	asgsccg(Chd)UfgCfUfGfccucagccgaL96	4272	VPusCfsggcUfgAfGfgcagCfaGfcggcusgsu	4317	ACAGCCGCUGCUGCCUCAGCCGC	4362
AD-1289801.1	cscsgcc(Ghd)CfcGfCfAfggcacagccaL96	4273	VPusGfsgcuGfuGfCfcugcGfgCfggcggscsu	4318	AGCCGCCGCCGCAGGCACAGCCG	4363
AD-1289793.1	ususccu(Chd)AfgCfCfGfccgccgcagaL96	4274	VPusCfsugcGfgCfGfgcggCfuGfaggaasgsc	4319	GCUUCCUCAGCCGCCGCCGCAGG	4364
AD-1289798.1	csasgcc(Ghd)CfcGfCfCfgcaggcacaaL96	4275	VPusUfsgugCfcUfGfcggcGfgCfggcugsasg	4320	CUCAGCCGCCGCCGCAGGCACAG	4365
AD-1289796.1	csuscag(Chd)CfgCfCfGfccgcaggcaaL96	4276	VPusUfsgccUfgCfGfgcggCfgGfcugagsgsa	4321	UCCUCAGCCGCCGCCGCAGGCAC	4366
AD-1289803.1	gscscgc(Chd)GfcAfGfGfcacagccgcaL96	4277	VPusGfscggCfuGfUfgccuGfcGfgcggcsgsg	4322	CCGCCGCCGCAGGCACAGCCGCU	4367
AD-1255835.1	cscscgg(Chd)UfgUfGfGfcugaggagcaL96	4278	VPusGfscucCfuCfAfgccaCfaGfccgggscsc	4323	GGCCCGGCUGUGGCUGAGGAGCC	4368
AD-1289802.1	csgsccg(Chd)CfgCfAfGfgcacagccgaL96	4279	VPusCfsggcUfgUfGfccugCfgGfcggcgsgsc	4324	GCCGCCGCCGCAGGCACAGCCGC	4369
AD-1289794.1	uscscuc(Ahd)GfcCfGfCfcgccgcaggaL96	4280	VPusCfscugCfgGfCfggcgGfcUfgaggasasg	4325	CUUCCUCAGCCGCCGCCGCAGGC	4370
AD-1289795.1	cscsuca(Ghd)CfcGfCfCfgccgcaggcaL96	4281	VPusGfsccuGfcGfGfcggcGfgCfugaggsasa	4326	UUCCUCAGCCGCCGCCGCAGGCA	4371

Table 30. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1255829.1	ACAGCCGCUGCUGCCUCAGCA	4372	325-345	UGCUGAGGCAGCAGCGGCUGUGC	4417	323-345
AD-1289804.1	CCGCCGCAGGCACAGCCGCUA	4373	314-334	UAGCGGCUGUGCCUGCGGCGGCG	4418	312-334
AD-1255847.1	UGAGGAGCCGCUGCACCGACA	4374	394-414	UGUCGGUGCAGCGGCUCCUCAGC	4419	392-414
AD-1255846.1	CUGAGGAGCCGCUGCACCGAA	4375	393-413	UUCGGUGCAGCGGCUCCUCAGCC	4420	391-413
AD-1255842.1	GUGGCUGAGGAGCCGCUGCAA	4376	389-409	UUGCAGCGGCUCCUCAGCCACAG	4421	387-409
AD-1255826.1	GGCACAGCCGCUGCUGCCUCA	4377	322-342	UGAGGCAGCAGCGGCUGUGCCUG	4422	320-342
AD-1255828.1	CACAGCCGCUGCUGCCUCAGA	4378	324-344	UCUGAGGCAGCAGCGGCUGUGCC	4423	322-344
AD-1255844.1	GGCUGAGGAGCCGCUGCACCA	4379	391-411	UGGUGCAGCGGCUCCUCAGCCAC	4424	389-411
AD-1289792.1	CUUCCUCAGCCGCCGCCGCAA	4380	302-322	UUGCGGCGGCGGCUGAGGAAGCU	4425	300-322
AD-1255825.1	AGGCACAGCCGCUGCUGCCUA	4381	321-341	UAGGCAGCAGCGGCUGUGCCUGC	4426	319-341
AD-1255822.1	CCGCAGGCACAGCCGCUGCUA	4382	317-337	UAGCAGCGGCUGUGCCUGCGGCG	4427	315-337
AD-1255839.1	GCUGUGGCUGAGGAGCCGCUA	4383	386-406	UAGCGGCUCCUCAGCCACAGCCG	4428	384-406
AD-1255827.1	GCACAGCCGCUGCUGCCUCAA	4384	323-343	UUGAGGCAGCAGCGGCUGUGCCU	4429	321-343
AD-1255824.1	GCAGGCACAGCCGCUGCUGCA	4385	319-339	UGCAGCAGCGGCUGUGCCUGCGG	4430	317-339
AD-1255845.1	GCUGAGGAGCCGCUGCACCGA	4386	392-412	UCGGUGCAGCGGCUCCUCAGCCA	4431	390-412
AD-1255830.1	CCGCUGCUGCCUCAGCCGCAA	4387	329-349	UUGCGGCUGAGGCAGCAGCGGCU	4432	327-349
AD-1289806.1	GCCGCAGGCACAGCCGCUGCA	4388	316-336	UGCAGCGGCUGUGCCUGCGGCGG	4433	314-336
AD-1255836.1	CCGGCUGUGGCUGAGGAGCCA	4389	383-403	UGGCUCCUCAGCCACAGCCGGGC	4434	381-403
AD-1289807.1	CAGGCACAGCCGCUGCUGCCA	4390	320-340	UGGCAGCAGCGGCUGUGCCUGCG	4435	318-340
AD-1289805.1	CGCCGCAGGCACAGCCGCUGA	4391	315-335	UCAGCGGCUGUGCCUGCGGCGGC	4436	313-335
AD-1255840.1	CUGUGGCUGAGGAGCCGCUGA	4392	387-407	UCAGCGGCUCCUCAGCCACAGCC	4437	385-407
AD-1289808.1	CAGCCGCUGCUGCCUCAGCCA	4393	326-346	UGGCUGAGGCAGCAGCGGCUGUG	4438	324-346
AD-1289800.1	GCCGCCGCCGCAGGCACAGCA	4394	310-330	UGCUGUGCCUGCGGCGGCGGCUG	4439	308-330
AD-1255838.1	GGCUGUGGCUGAGGAGCCGCA	4395	385-405	UGCGGCUCCUCAGCCACAGCCGG	4440	383-405
AD-1255843.1	UGGCUGAGGAGCCGCUGCACA	4396	390-410	UGUGCAGCGGCUCCUCAGCCACA	4441	388-410
AD-1255837.1	CGGCUGUGGCUGAGGAGCCGA	4397	384-404	UCGGCUCCUCAGCCACAGCCGGG	4442	382-404

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1255833.1	GGCCCGGCUGUGGCUGAGGAA	4398	380-400	UUCCUCAGCCACAGCCGGGCCGG	4443	378-400
AD-1289797.1	UCAGCCGCCGCCGCAGGCACA	4399	307-327	UGUGCCUGCGGCGGCGGCUGAGG	4444	305-327
AD-1255823.1	CGCAGGCACAGCCGCUGCUGA	4400	318-338	UCAGCAGCGGCUGUGCCUGCGGC	4445	316-338
AD-1289810.1	GCCGCUGCUGCCUCAGCCGCA	4401	328-348	UGCGGCUGAGGCAGCAGCGGCUG	4446	326-348
AD-1289811.1	CCGGCCCGGCUGUGGCUGAGA	4402	378-398	UCUCAGCCACAGCCGGGCCGGGU	4447	376-398
AD-1289812.1	CGGCCCGGCUGUGGCUGAGGA	4403	379-399	UCCUCAGCCACAGCCGGGCCGGG	4448	377-399
AD-1255841.1	UGUGGCUGAGGAGCCGCUGCA	4404	388-408	UGCAGCGGCUCCUCAGCCACAGC	4449	386-408
AD-1289799.1	AGCCGCCGCCGCAGGCACAGA	4405	309-329	UCUGUGCCUGCGGCGGCGGCUGA	4450	307-329
AD-1255834.1	GCCCGGCUGUGGCUGAGGAGA	4406	381-401	UCUCCUCAGCCACAGCCGGGCCG	4451	379-401
AD-1289809.1	AGCCGCUGCUGCCUCAGCCGA	4407	327-347	UCGGCUGAGGCAGCAGCGGCUGU	4452	325-347
AD-1289801.1	CCGCCGCCGCAGGCACAGCCA	4408	311-331	UGGCUGUGCCUGCGGCGGCGGCU	4453	309-331
AD-1289793.1	UUCCUCAGCCGCCGCCGCAGA	4409	303-323	UCUGCGGCGGCGGCUGAGGAAGC	4454	301-323
AD-1289798.1	CAGCCGCCGCCGCAGGCACAA	4410	308-328	UUGUGCCUGCGGCGGCGGCUGAG	4455	306-328
AD-1289796.1	CUCAGCCGCCGCCGCAGGCAA	4411	306-326	UUGCCUGCGGCGGCGGCUGAGGA	4456	304-326
AD-1289803.1	GCCGCCGCAGGCACAGCCGCA	4412	313-333	UGCGGCUGUGCCUGCGGCGGCGG	4457	311-333
AD-1255835.1	CCCGGCUGUGGCUGAGGAGCA	4413	382-402	UGCUCCUCAGCCACAGCCGGGCC	4458	380-402
AD-1289802.1	CGCCGCCGCAGGCACAGCCGA	4414	312-332	UCGGCUGUGCCUGCGGCGGCGGC	4459	310-332
AD-1289794.1	UCCUCAGCCGCCGCCGCAGGA	4415	304-324	UCCUGCGGCGGCGGCUGAGGAAG	4460	302-324
AD-1289795.1	CCUCAGCCGCCGCCGCAGGCA	4416	305-325	UGCCUGCGGCGGCGGCUGAGGAA	4461	303-325

Table 32. Modified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex ID	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-1107441	ascsggc(Chd)GfcUfCfAfgguucugcuaL96	3636	VPusAfsgcaGfaAfCfcugaGfcGfgccguscsc	3655	GGACGGCCGCUCAGGUUCUGCUU	3742
AD-1107446	cscsaga(Ghd)CfcCfCfAfuucauugccaL96	3609	VPusGfsgcaAfuGfAfauggGfgCfucuggsgsc	3661	GCCCAGAGCCCCAUUCAUUGCCC	3747
AD-1107445	csuscag(Ghd)UfuCfUfGfcuuuuaccuaL96	3584	VPusAfsgguAfaAfAfgcagAfaCfcugagscsg	3645	CGCUCAGGUUCUGCUUUUACCUG	3732
AD-1107440	gsgsacg(Ghd)CfcGfCfUfcagguucugaL96	3613	VPusCfsagaAfcCfUfgagcGfgCfcguccsasu	3673	AUGGACGGCCGCUCAGGUUCUGC	3754
AD-1107444	gscsuca(Ghd)GfuUfCfUfgcuuuuaccaL96	3572	VPusGfsguaAfaAfGfcagaAfcCfugagcsgsg	3665	CCGCUCAGGUUCUGCUUUUACCU	3745
AD-1107443	csgscuc(Ahd)GfgUfUfCfugcuuuuacaL96	3576	VPusGfsuaaAfaGfCfagaaCfcUfgagcgsgsc	3649	GCCGCUCAGGUUCUGCUUUUACC	3736

Duplex ID	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-1107450	csusgau(Ghd)AfaGfGfCfcuucgagucaL96	3563	VPusGfsacuCfgAfAfggccUfuCfaucagscsu	3993	AGCUGAUGAAGGCCUUCGAGUCC	3737
AD-1107452	cscsuuc(Ghd)AfgUfCfCfcucaaguccaL96	3567	VPusGfsgacUfuGfAfgggaCfuCfgaaggscsc	4001	GGCCUUCGAGUCCCUCAAGUCCU	3741
AD-1107454	gsusccc(Uhd)CfaAfGfUfccuuccagcaL96	3620	VPusGfscugGfaAfGfgacuUfgAfgggacsusc	4007	GAGUCCCUCAAGUCCUUCCAGCA	3782
AD-1107453	ususcga(Ghd)UfcCfCfUfcaaguccuuaL96	3598	VPusAfsaggAfcUfUfgaggGfaCfucgaasgsg	4003	CCUUCGAGUCCCUCAAGUCCUUC	3765
AD-1107439	usgsgac(Ghd)GfcCfGfCfucagguucuaL96	3592	VPusAfsgaaCfcUfGfagcgGfcCfguccasusc	3675	GAUGGACGGCCGCUCAGGUUCUG	3756
AD-1107448	asusggc(Ghd)AfcCfCfUfggaaaagcuaL96	3596	VPusAfsgcuUfuUfCfcaggGfuCfgccausgsg	3983	CCAUGGCGACCCUGGAAAAGCUG	3763
AD-1289840	csusga(Uhd)gAfaGfGfCfcuucgagucaL96	4462	VPusdGsacdTc(G2p)aaggccUfuCfaucagscsu	4470	AGCUGAUGAAGGCCUUCGAGUCC	3737
AD-1289848	csusga(Ahd)gAfaGfGfCfcuucgagucaL96	4463	VPusdGsacdTc(G2p)aaggccUfuCfuucagscsu	4471	AGCUGAUGAAGGCCUUCGAGUCC	3737
AD-1210232	gsasccc(Uhd)GfgAfAfAfagcugaugaaL96	3593	VPusUfscauCfaGfCfuuuuCfcAfgggucsgsc	3987	GCGACCCUGGAAAAGCUGAUGAA	3760
AD-1210237	usgsgaa(Ahd)AfgCfUfGfaugaaggccaL96	3566	VPusGfsgccUfuCfAfucagCfuUfuuccasgsg	3990	CCUGGAAAAGCUGAUGAAGGCCU	3740
AD-1210241	asasagc(Uhd)GfaUfGfAfaggccuucgaL96	3560	VPusCfsgaaGfgCfCfuucaUfcAfgcuuususc	3991	GAAAAGCUGAUGAAGGCCUUCGA	3734
AD-1210242	usgsaug(Ahd)AfgGfCfCfuucgaguccaL96	3587	VPusGfsgacUfcGfAfaggcCfuUfcaucasgsc	3994	GCUGAUGAAGGCCUUCGAGUCCC	3755
AD-1210244	gsgsccu(Uhd)CfgAfGfUfcccucaaguaL96	3614	VPusAfscuuGfaGfGfgacuCfgAfaggccsusu	3999	AAGGCCUUCGAGUCCCUCAAGUC	3777
AD-1210245	csusucg(Ahd)GfuCfCfCfucaaguccuaL96	3581	VPusAfsggaCfuUfGfagggAfcUfcgaagsgsc	4002	GCCUUCGAGUCCCUCAAGUCCUU	3751
AD-1210247	gsasguc(Chd)CfuCfAfAfguccuuccaaL96	3582	VPusUfsggaAfgGfAfcuugAfgGfgacucsgsa	4006	UCGAGUCCCUCAAGUCCUUCCAG	3752
AD-1289816	gscsucagguUfCfUfgcuu(Uhd)uaccaL96	4464	VPusdGsgudAa(Agn)agcagaAfcCfugagcsgsg	4472	CCGCUCAGGUUCUGCUUUUACCU	3745
AD-1289819	uscsagguUfCfUfgcuu(Uhd)uaccaL96	4465	VPusdGsgudAa(A2p)agcagaAfcCfugasgsc	4473	GCUCAGGUUCUGCUUUUACCU	4479
AD-1289886	csuscaggUfuCfUfGfcuuu(Uhd)accuaL96	4466	VPusAfsggdTa(Agn)aagcagAfaCfcugagscsg	4474	CGCUCAGGUUCUGCUUUUACCUG	3732
AD-1289906	uscsg(Ahd)guCfCfCfucaaguccuaL96	4467	VPusAfsggdAc(Tgn)ugagggAfcUfcgasgsg	4475	CUUCGAGUCCCUCAAGUCCUU	4480
AD-1289907	uscsg(Ahd)guCfCfCfucaaguccuaL96	4467	VPusAfsggdAc(U2p)ugagggAfcUfcgasusc	4476	CUUCGAGUCCCUCAAGUCCUU	4480
AD-1289909	csusugg(Ahd)guCfCfCfucaaguccuaL96	4468	VPusAfsggdAc(U2p)ugagggAfcUfccaagsgsc	4477	GCCUUCGAGUCCCUCAAGUCCUU	3751
AD-1289964	gscscgc(Uhd)CfadGgUfucugcuuuuaL96	4469	VPusAfsaadAg(C2p)agaadCcUfgAfgcggcscsg	4478	CGGCCGCUCAGGUUCUGCUUUUA	3733

Table 33. Unmodified Sense and Antisense Strand Sequences of Huntingtin (HTT) dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002111.8
AD-1107441	ACGGCCGCUCAGGUUCUGCUA	3807	25-45	UAGCAGAACCUGAGCGGCCGUCC	3872	23-45
AD-1107446	CCAGAGCCCCAUUCAUUGCCA	3812	57-77	UGGCAAUGAAUGGGGCUCUGGGC	3877	55-77
AD-1107445	CUCAGGUUCUGCUUUUACCUA	3797	32-52	UAGGUAAAAGCAGAACCUGAGCG	3862	30-52
AD-1107440	GGACGGCCGCUCAGGUUCUGA	3819	23-43	UCAGAACCUGAGCGGCCGUCCAU	3885	21-43
AD-1107444	GCUCAGGUUCUGCUUUUACCA	3810	31-51	UGGUAAAAGCAGAACCUGAGCGG	3875	29-51
AD-1107443	CGCUCAGGUUCUGCUUUUACA	3801	30-50	UGUAAAAGCAGAACCUGAGCGGC	3866	28-50

AD-1107450	CUGAUGAAGGCCUUCGAGUCA	3802	164-184	UGACUCGAAGGCCUUCAUCAGCU	3867	162-184
AD-1107452	CCUUCGAGUCCCUCAAGUCCA	3806	174-194	UGGACUUGAGGGACUCGAAGGCC	4017	172-194
AD-1107454	GUCCCUCAAGUCCUUCCAGCA	3847	181-201	UGCUGGAAGGACUUGAGGGACUC	3914	179-201
AD-1107453	UUCGAGUCCCUCAAGUCCUUA	3830	176-196	UAAGGACUUGAGGGACUCGAAGG	3896	174-196
AD-1107439	UGGACGGCCGCUCAGGUUCUA	3821	22-42	UAGAACCUGAGCGGCCGUCCAUC	3887	20-42
AD-1107448	AUGGCGACCCUGGAAAAGCUA	3828	146-166	UAGCUUUUCCAGGGUCGCCAUGG	4013	144-166
AD-1289840	CUGAUGAAGGCCUUCGAGUCA	3802	164-184	UGACTCGAAGGCCUUCAUCAGCU	4485	162-184
AD-1289848	CUGAAGAAGGCCUUCGAGUCA	4481	164-184	UGACTCGAAGGCCUUCUUCAGCU	4486	162-184
AD-1210232	GACCCUGGAAAAGCUGAUGAA	3825	151-171	UUCAUCAGCUUUUCCAGGGUCGC	3891	149-171
AD-1210237	UGGAAAAGCUGAUGAAGGCCA	3805	156-176	UGGCCUUCAUCAGCUUUUCCAGG	4015	154-176
AD-1210241	AAAGCUGAUGAAGGCCUUCGA	3799	160-180	UCGAAGGCCUUCAUCAGCUUUUC	3864	158-180
AD-1210242	UGAUGAAGGCCUUCGAGUCCA	3820	165-185	UGGACUCGAAGGCCUUCAUCAGC	3886	163-185
AD-1210244	GGCCUUCGAGUCCCUCAAGUA	3842	172-192	UACUUGAGGGACUCGAAGGCCUU	3909	170-192
AD-1210245	CUUCGAGUCCCUCAAGUCCUA	3816	175-195	UAGGACUUGAGGGACUCGAAGGC	4018	173-195
AD-1210247	GAGUCCCUCAAGUCCUUCCAA	3817	179-199	UUGGAAGGACUUGAGGGACUCGA	3883	177-199
AD-1289816	GCUCAGGUUCUGCUUUUACCA	3810	31-51	UGGUAAAAGCAGAACCUGAGCGG	3875	29-51
AD-1289819	UCAGGUUCUGCUUUUACCA	4482	33-51	UGGUAAAAGCAGAACCUGAGC	4487	31-51
AD-1289886	CUCAGGUUCUGCUUUUACCUA	3797	32-52	UAGGTAAAAGCAGAACCUGAGCG	4488	30-52
AD-1289906	UCGAGUCCCUCAAGUCCUA	4483	177-195	UAGGACTUGAGGGACUCGAGG	4489	175-195
AD-1289907	UCGAGUCCCUCAAGUCCUA	4483	177-195	UAGGACUUGAGGGACUCGAUC	4490	175-195
AD-1289909	CUUGGAGUCCCUCAAGUCCUA	4484	175-195	UAGGACUUGAGGGACUCCAAGGC	4491	173-195
AD-1289964	GCCGCUCAGGUUCUGCUUUUA	3798	28-48	UAAAAGCAGAACCUGAGCGGCCG	3863	26-48

Table 4. HTT Single Dose Screens in BE(2)C Cells

	10 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-384118.1	51.69	25.40	46.89	7.33
AD-380543.1	95.92	27.12	71.60	24.68
AD-380533.1	105.39	28.38	91.67	26.80
AD-384038.1	154.15	20.25	125.43	25.19
AD-380805.1	101.15	19.55	114.28	15.36
AD-380117.1	130.05	21.16	122.25	14.15
AD-381341.1	138.31	25.62	146.74	39.17
AD-379426.1	145.46	25.51	151.86	38.36
AD-380888.1	130.28	16.92	134.28	21.73
AD-384841.1	125.51	34.07	115.98	15.20
AD-380853.1	107.44	23.39	98.68	4.67
AD-379602.1	84.02	18.25	172.53	35.05
AD-382484.1	75.19	25.05	57.22	13.43
AD-380741.1	118.53	24.70	73.00	3.77
AD-380534.1	143.75	30.13	103.24	23.54
AD-384053.1	87.87	16.27	130.20	13.77
AD-380916.1	95.50	29.09	144.05	13.23
AD-380402.1	139.27	15.07	126.43	16.30
AD-381464.1	135.36	39.85	134.37	31.20
AD-379729.1	84.36	24.54	137.33	26.49
AD-381065.1	141.96	30.56	136.29	12.84
AD-379466.1	115.44	40.22	120.93	21.48
AD-380885.1	95.86	10.93	139.28	22.72
AD-379897.1	95.59	22.26	172.12	33.52
AD-381124.1	59.94	26.80	51.93	10.57
AD-380807.1	99.61	30.47	77.87	21.23
AD-380806.1	132.18	39.93	102.86	19.45
AD-384843.1	117.21	24.86	123.71	11.78
AD-381257.1	99.30	30.21	124.74	10.99
AD-380408.1	157.70	44.86	129.06	19.38
AD-381570.1	193.38	37.37	125.32	13.13
AD-380093.1	192.68	42.81	135.16	26.86
AD-381148.1	187.13	28.75	137.42	11.82
AD-379475.1	149.83	36.22	124.88	9.89
AD-381142.1	131.62	40.12	121.85	12.50
AD-380852.1	76.23	5.88	198.90	40.31
AD-379935.1	64.90	29.25	53.70	13.77
AD-381117.1	95.64	33.48	68.03	15.97
AD-380808.1	124.46	39.75	95.85	8.44
AD-379471.1	93.97	29.87	104.28	18.99

	10 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-381342.1	107.50	20.99	126.66	32.01
AD-380411.1	148.77	15.63	134.25	21.15
AD-382487.1	155.26	47.54	136.80	13.12
AD-380116.1	156.98	36.49	156.00	25.80
AD-381150.1	149.99	39.15	135.76	22.27
AD-379476.1	132.34	43.09	131.15	14.36
AD-382444.1	122.07	26.37	118.65	22.02
AD-380883.1	52.18	15.97	257.45	13.08
AD-379941.1	59.35	31.34	58.84	13.25
AD-381578.1	75.64	37.02	60.08	4.32
AD-381460.1	101.15	24.87	96.09	11.60
AD-379939.1	156.24	25.09	99.44	17.05
AD-384039.1	127.13	42.92	108.45	32.25
AD-380735.1	137.74	42.47	128.37	15.25
AD-382525.1	154.67	44.65	124.68	26.66
AD-380713.1	163.12	43.55	130.38	21.77
AD-382149.1	135.62	22.90	139.99	28.87
AD-379855.1	145.22	39.96	122.14	13.22
AD-383508.1	135.52	24.12	118.15	5.12
AD-381273.1	74.96	3.61	192.17	24.11
AD-382483.1	51.15	24.35	67.84	17.97
AD-382481.1	82.28	22.45	74.06	8.54
AD-382485.1	100.70	33.99	90.08	11.68
AD-380092.1	101.09	37.56	93.42	10.74
AD-379420.1	102.06	37.49	99.35	10.17
AD-380800.1	84.91	25.98	116.09	25.96
AD-384030.1	143.57	39.66	115.50	24.98
AD-380737.1	149.04	34.89	137.50	24.60
AD-382780.1	155.32	21.47	145.73	18.80
AD-379944.1	146.65	40.50	148.17	14.59
AD-379461.1	134.09	14.71	129.84	8.09
AD-381856.1	51.32	13.29	125.92	43.49
AD-379418.1	23.32	9.32	37.51	6.01
AD-382924.1	76.58	31.10	51.58	11.97
AD-383759.1	88.53	29.71	73.95	12.45
AD-380409.1	121.08	24.07	83.54	6.71
AD-379380.1	33.65	6.37	100.25	16.79
AD-381145.1	113.55	24.69	100.19	22.11
AD-384054.1	113.24	20.54	116.75	20.01
AD-380796.1	145.88	42.84	140.74	14.73
AD-382960.1	145.68	37.86	138.28	27.41

	10 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-380555.1	106.36	26.58	139.27	18.75
AD-379462.1	158.82	47.01	119.08	13.60
AD-382118.1	88.57	19.33	110.03	27.29
AD-380414.1	37.65	8.76	33.69	1.29
AD-380091.1	52.46	27.92	47.36	13.94
AD-383761.1	51.55	19.45	61.12	13.37
AD-380740.1	32.40	12.55	65.91	18.47
AD-379945.1	47.84	25.04	94.57	15.24
AD-379425.1	52.33	16.94	89.98	12.20
AD-380886.1	111.81	24.52	137.52	37.78
AD-384366.1	103.34	14.61	105.10	18.86
AD-380798.1	109.34	31.61	103.41	21.42
AD-379463.1	112.46	30.89	92.69	9.78
AD-382148.1	40.89	7.63	59.31	20.48
AD-357754.1	25.92	3.91	59.47	11.65
AD-356938.1	19.38	3.74	66.11	22.41
AD-355054.1	73.88	18.14	121.65	15.38
AD-357748.1	58.16	15.88	122.16	5.44
AD-355704.1	37.44	4.59	165.32	50.68
AD-356946.1	48.39	8.85	162.43	42.24
AD-353499.1	32.30	7.21	139.76	50.75
AD-354076.1	88.26	13.12	133.42	42.69
AD-356630.1	37.53	3.16	92.04	25.79
AD-353351.1	41.71	6.98	96.78	14.30
AD-359803.1	54.29	19.36	177.30	41.38
AD-382526.1	38.58	7.17	54.67	10.40
AD-356975.1	33.90	7.35	80.03	9.50
AD-356974.1	32.22	5.95	120.19	17.90
AD-355117.1	37.63	2.69	117.21	11.97
AD-357755.1	104.49	8.71	136.50	16.63
AD-356382.1	94.77	7.03	150.60	13.96
AD-356973.1	85.49	7.63	148.93	18.16
AD-358488.1	46.44	2.36	139.29	25.52
AD-354078.1	46.34	5.84	129.77	43.58
AD-356638.1	77.64	14.67	138.53	22.89
AD-357096.1	48.16	2.44	135.84	19.68
AD-361492.1	56.56	15.98	124.38	30.67
AD-382775.1	42.95	11.66	76.60	16.23
AD-357239.1	24.39	3.37	60.14	11.30
AD-357756.1	78.94	10.48	109.26	30.70
AD-356384.1	36.95	9.36	105.38	12.36

	10 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-357879.1	42.50	4.51	117.99	20.11
AD-356386.1	68.71	7.28	147.92	36.10
AD-356995.1	60.22	5.01	168.66	25.76
AD-353516.1	33.15	9.36	133.30	18.51
AD-354079.1	49.35	5.31	130.79	14.08
AD-356639.1	36.33	3.49	117.25	22.43
AD-357649.1	85.70	2.07	91.78	58.01
AD-361496.1	41.93	12.04	140.37	30.87
AD-382777.1	56.23	13.88	58.04	19.93
AD-353525.1	21.75	2.08	58.46	7.82
AD-358480.1	26.74	5.28	64.94	13.24
AD-356388.1	45.10	10.22	109.51	34.60
AD-353500.1	40.43	3.34	102.99	14.32
AD-356407.1	61.59	6.59	157.31	42.34
AD-357068.1	45.70	7.82	160.84	46.87
AD-359802.1	33.72	4.31	149.89	20.91
AD-354638.1	65.21	2.80	170.34	27.30
AD-356663.1	58.99	6.53	128.37	38.64
AD-357651.1	88.23	17.45	107.54	38.79
AD-362085.1	86.17	27.21	170.36	24.85
AD-384329.1	61.30	6.83	52.87	3.24
AD-354067.1	23.37	4.21	62.78	10.75
AD-353526.1	50.82	2.45	106.49	16.48
AD-356422.1	51.12	12.80	99.93	3.64
AD-353519.1	43.78	4.69	109.71	25.51
AD-356443.1	80.02	8.39	151.50	30.84
AD-357115.1	64.98	6.65	178.41	43.34
AD-361493.1	29.23	6.24	136.35	20.49
AD-354639.1	48.20	4.60	155.53	33.91
AD-356955.1	62.09	6.19	164.98	46.88
AD-358471.1	31.12	3.36	108.67	37.20
AD-354066.1	77.57	12.13	205.05	15.39
AD-384665.1	62.62	11.80	51.01	1.70
AD-355045.1	13.21	1.82	32.78	5.49
AD-353715.1	19.44	1.85	51.85	13.55
AD-356429.1	35.74	7.82	76.89	14.02
AD-359761.1	53.86	7.22	92.90	36.39
AD-356669.1	67.14	12.99	122.69	54.26
AD-357684.1	38.66	2.19	171.32	21.29
AD-361981.1	89.01	10.03	136.10	45.50
AD-355423.1	50.85	3.22	126.34	24.37

	10 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-356956.1	45.99	3.04	152.10	57.21
AD-353522.1	60.07	5.92	119.82	39.14
AD-354075.1	30.04	2.60	154.25	28.87
AD-355059.1	32.62	6.80	43.67	9.90
AD-356951.1	19.64	3.03	41.52	5.36
AD-353871.1	57.71	3.61	59.99	14.88
AD-356996.1	36.58	9.28	77.80	17.06
AD-354068.1	27.76	6.17	47.95	10.59
AD-356678.1	32.90	4.26	87.03	18.12
AD-357963.1	45.86	6.23	132.93	44.34
AD-362090.1	94.25	8.99	125.66	40.95
AD-355745.1	41.18	3.07	103.13	19.96
AD-357066.1	90.93	13.20	112.28	36.69
AD-353527.1	57.92	8.02	112.27	9.38
AD-354236.1	56.76	5.34	193.83	27.51
AD-357750.1	7.74	2.65	18.65	3.02
AD-356389.1	13.11	2.30	35.47	3.73
AD-354939.1	18.83	5.26	49.46	4.06
AD-357218.1	16.19	4.22	32.72	6.57
AD-354640.1	18.37	2.59	41.06	5.66
AD-358018.1	25.29	8.01	63.68	15.77
AD-362093.1	95.57	21.34	100.80	19.61
AD-356385.1	28.71	2.03	63.42	13.57
AD-357069.1	31.85	2.96	90.71	14.52
AD-358764.1	17.72	5.20	54.27	8.41
AD-354316.1	83.70	20.63	199.24	10.55
AD-355775.1	61.70	17.03	158.42	20.42
AD-354320.1	61.59	15.49	160.96	7.90
AD-355783.1	55.33	15.69	133.29	18.94
AD-354322.1	191.64	54.47	179.71	36.74
AD-356408.1	159.84	36.30	213.32	24.70
AD-354805.1	172.07	29.14	199.39	27.62
AD-356409.1	83.23	12.52	173.24	19.82
AD-355118.1	102.46	24.74	170.98	23.64
AD-358958.1	187.06	30.88	199.91	32.39
AD-355422.1	72.78	24.21	226.00	37.15
AD-358959.1	100.77	30.11	199.23	10.37
AD-355424.1	54.88	14.67	156.21	37.30
AD-379420.2	162.26	36.61	179.07	34.36
AD-355524.1	85.94	17.37	175.30	31.43
AD-379380.2	90.64	12.90	153.32	39.65

Table 7. HTT Single Dose Screens in BE(2)C Cells

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953583.1	65.73	3.69	68.52	3.59	81.29	4.52	81.77	7.38
AD-953591.1	58.10	7.40	62.11	6.03	78.16	9.19	87.18	7.93
AD-953599.1	57.26	5.59	58.05	5.65	67.00	6.55	75.18	7.92
AD-953607.1	76.53	11.31	78.85	9.00	89.54	4.07	93.39	7.95
AD-953615.1	76.53	6.30	80.78	4.38	92.95	6.29	106.03	9.52
AD-953623.1	66.90	7.69	67.88	6.90	82.93	8.14	92.69	11.53
AD-953630.1	94.68	3.29	101.89	11.32	104.63	8.08	105.94	3.82
AD-953638.1	42.99	6.32	41.59	3.46	64.62	4.89	73.39	3.32
AD-953646.1	70.95	4.23	66.70	4.72	97.86	8.88	95.46	13.41
AD-953654.1	100.02	6.41	98.76	5.28	101.05	3.32	94.44	9.22
AD-953662.1	58.24	3.55	59.42	4.65	70.38	3.35	81.97	6.26
AD-953670.1	94.50	6.27	104.75	19.49	101.22	16.84	98.02	9.61
AD-953584.1	75.92	8.67	64.59	3.37	83.74	4.97	83.52	8.34
AD-953592.1	74.32	6.15	83.15	3.03	91.25	3.66	87.69	2.83
AD-953600.1	66.63	5.56	72.19	4.32	82.18	7.79	88.40	8.30
AD-953608.1	39.95	1.44	37.97	2.56	50.35	1.45	59.10	4.86
AD-953616.1	55.54	6.07	58.76	3.89	66.92	2.95	82.14	3.85
AD-953624.1	59.50	6.03	65.30	8.40	84.89	4.79	99.56	8.34
AD-953631.1	58.38	5.72	65.35	6.45	51.38	25.23	91.21	10.80
AD-953639.1	61.64	3.35	66.52	8.42	79.18	19.97	93.20	7.44
AD-953647.1	85.61	6.31	88.65	3.05	106.42	7.45	99.83	6.89
AD-953655.1	104.92	13.38	100.12	4.72	115.45	11.59	102.49	2.83
AD-953663.1	82.13	6.07	81.32	3.82	91.83	1.33	92.32	8.82

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953671.1	100.07	15.43	99.10	7.82	107.01	9.34	105.01	12.00
AD-953585.1	68.95	9.55	61.23	3.65	74.87	7.80	81.74	7.20
AD-953593.1	85.35	3.46	97.48	1.55	100.73	13.93	93.10	10.76
AD-953601.1	77.13	7.42	84.97	5.15	89.10	4.71	91.41	9.31
AD-953609.1	46.34	3.08	47.10	5.91	51.32	1.83	64.58	5.59
AD-953617.1	77.35	6.64	86.08	6.66	94.95	9.83	93.88	7.96
AD-953625.1	74.64	7.17	81.66	5.25	78.02	9.39	95.15	7.25
AD-953632.1	77.51	7.12	89.57	9.14	90.60	3.10	98.16	23.71
AD-953640.1	83.31	3.82	89.18	7.83	102.72	9.30	96.01	7.82
AD-953648.1	57.67	1.63	65.09	6.24	76.89	8.29	87.91	7.83
AD-953656.1	99.23	7.82	93.97	6.04	105.33	7.69	114.77	15.98
AD-953664.1	98.54	7.70	99.52	1.09	104.78	10.71	92.95	5.76
AD-953672.1	100.25	12.34	88.22	6.82	96.10	5.13	113.16	16.49
AD-953586.1	55.47	7.17	51.83	2.45	70.27	6.04	85.64	11.03
AD-953594.1	85.85	15.81	87.47	4.38	98.58	6.57	101.50	8.72
AD-953602.1	41.93	3.04	47.45	5.33	58.52	8.83	74.66	7.74
AD-953610.1	38.40	3.08	43.49	5.30	53.06	6.83	69.18	8.59
AD-953618.1	53.81	1.55	55.94	4.80	76.25	4.38	84.62	4.50
AD-953626.1	132.27	15.59	123.27	12.89	120.22	12.84	107.76	14.81
AD-953633.1	98.35	3.09	111.46	12.11	109.58	14.76	107.71	14.87
AD-953641.1	75.61	6.32	86.93	8.49	86.57	8.36	89.55	3.27
AD-953649.1	92.18	8.31	97.93	5.62	97.81	4.37	94.25	5.70
AD-953657.1	69.99	10.60	85.39	4.71	101.53	6.78	112.01	13.76
AD-953665.1	97.57	5.24	87.23	8.45	107.27	13.55	95.34	7.96
AD-953673.1	92.01	9.92	94.45	18.78	111.78	7.01	100.86	12.99

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953587.1	68.70	6.66	61.13	3.55	74.72	0.99	75.52	5.19
AD-953595.1	55.25	2.40	59.95	10.47	73.01	14.85	83.12	6.44
AD-953603.1	41.36	4.30	45.84	6.02	50.82	4.36	72.34	5.27
AD-953611.1	30.59	6.97	42.23	5.89	49.55	3.33	58.05	4.27
AD-953619.1	85.04	6.60	84.15	2.66	92.49	6.64	105.62	13.92
AD-953627.1	122.45	6.77	121.67	8.15	115.37	10.37	101.98	3.81
AD-953634.1	94.74	5.02	98.17	2.46	94.99	4.68	103.34	14.41
AD-953642.1	97.38	4.57	101.48	3.54	102.35	5.46	108.12	7.59
AD-953650.1	87.24	8.42	92.14	4.81	86.84	5.30	109.74	5.84
AD-953658.1	84.73	6.08	89.05	8.27	97.51	11.09	98.79	13.15
AD-953666.1	85.26	5.11	89.22	12.04	102.53	5.36	100.98	5.34
AD-953674.1	77.69	11.54	89.93	11.06	111.28	16.28	121.78	24.22
AD-953588.1	61.12	3.42	52.22	3.21	74.78	6.36	81.13	3.04
AD-953596.1	62.94	11.35	68.95	5.19	67.32	6.16	99.40	12.55
AD-953604.1	55.03	9.69	61.31	6.72	73.83	5.30	98.96	6.64
AD-953612.1	43.94	3.27	48.39	4.57	52.67	1.79	58.41	6.63
AD-953620.1	91.36	14.02	94.64	8.89	105.50	7.50	99.73	10.63
AD-953628.1	109.80	6.56	130.58	21.51	110.07	9.27	102.73	8.48
AD-953635.1	65.33	12.81	71.01	5.41	78.77	14.06	102.21	16.98
AD-953643.1	113.32	10.85	114.70	7.78	113.65	1.32	119.32	13.91
AD-953651.1	92.51	8.51	102.42	11.22	96.93	2.88	101.02	13.41
AD-953659.1	110.37	6.31	110.02	7.07	114.25	8.01	102.65	2.34
AD-953667.1	80.72	6.03	82.89	4.05	98.54	5.69	102.25	17.23
AD-953675.1	92.90	16.65	83.78	11.99	105.12	8.40	117.15	13.27
AD-953589.1	36.03	3.99	37.09	3.93	47.90	8.18	65.62	8.58

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953597.1	84.76	6.85	83.08	5.17	70.66	15.70	90.06	9.84
AD-953605.1	31.15	1.73	36.82	5.10	41.77	3.33	62.59	7.87
AD-953613.1	40.91	2.79	50.41	8.12	57.95	6.23	82.40	11.89
AD-953621.1	95.71	7.99	107.50	8.86	105.83	6.97	103.24	10.64
AD-953629.1	94.99	2.17	99.81	5.71	104.87	13.34	106.22	15.58
AD-953636.1	34.50	2.03	44.33	6.24	53.82	3.03	69.97	4.61
AD-953644.1	75.18	2.13	84.50	4.58	93.01	4.04	102.93	8.86
AD-953652.1	102.12	6.62	108.95	3.92	102.50	14.43	102.09	6.83
AD-953660.1	100.98	4.32	105.70	9.85	103.96	9.02	105.07	15.10
AD-953676.1	97.29	12.62	90.38	6.80	104.26	13.38	113.36	14.80
AD-953590.1	40.56	6.67	37.30	8.25	60.77	5.55	64.45	11.54
AD-953598.1	47.12	5.20	48.93	3.87	66.94	9.54	75.49	4.38
AD-953606.1	38.33	3.00	43.30	2.46	53.37	4.82	71.51	5.85
AD-953614.1	45.05	3.95	52.34	5.39	65.63	4.84	86.96	7.13
AD-953622.1	84.86	8.26	87.00	6.92	93.95	6.81	91.20	5.59
AD-953637.1	32.84	1.10	42.70	7.04	56.90	8.71	95.38	19.98
AD-953645.1	47.64	4.52	53.70	5.27	69.42	3.59	92.71	7.28
AD-953653.1	105.41	8.04	111.93	16.66	102.13	12.99	106.61	10.07
AD-953661.1	49.36	2.09	53.43	5.21	67.92	12.66	101.20	13.79
AD-953677.1	45.65	3.56	42.77	4.59	57.33	10.35	77.95	5.43
AD-953685.1	48.42	10.41	46.82	4.11	63.78	7.35	86.60	11.82
AD-953693.1	93.50	6.26	89.55	14.61	95.96	25.61	98.07	8.42
AD-953701.1	100.99	25.01	90.05	6.66	106.35	9.81	99.41	4.05
AD-953709.1	111.06	20.00	99.36	11.71	107.61	8.85	111.13	31.48
AD-953717.1	87.09	9.97	72.85	12.95	90.34	12.98	102.74	8.46

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953724.1	61.62	2.67	59.42	7.22	72.38	6.31	97.59	8.53
AD-953732.1	36.91	3.27	36.45	2.72	49.11	4.45	75.61	9.88
AD-953740.1	57.47	6.77	55.67	9.18	78.54	4.76	94.03	7.16
AD-953748.1	41.94	4.36	34.60	5.45	53.28	4.89	75.42	7.20
AD-953756.1	26.38	1.58	25.66	2.26	31.90	4.42	52.80	4.10
AD-953678.1	39.42	4.37	42.44	2.89	54.37	4.54	70.49	8.50
AD-953686.1	47.73	4.51	49.18	7.58	63.76	10.38	78.32	18.31
AD-953694.1	78.72	6.97	85.82	12.25	97.80	10.27	111.29	11.78
AD-953702.1	101.14	10.57	101.53	10.33	117.42	7.40	105.83	11.09
AD-953710.1	107.38	6.85	107.87	8.46	112.98	6.08	115.03	19.01
AD-953718.1	105.19	12.03	102.57	14.87	108.64	7.61	104.65	7.29
AD-953733.1	54.90	6.22	63.24	10.51	70.74	5.85	103.23	2.58
AD-953741.1	53.57	4.65	56.02	4.29	81.67	10.58	101.25	13.78
AD-953749.1	82.34	4.62	81.11	7.23	94.63	7.27	100.71	11.80
AD-953757.1	31.43	1.99	38.04	2.38	42.02	8.56	63.01	7.88
AD-953679.1	68.32	7.90	73.96	3.66	75.85	6.87	82.08	5.08
AD-953687.1	54.92	7.52	54.63	7.06	65.52	8.91	83.85	14.01
AD-953695.1	101.51	14.48	95.01	6.55	104.09	7.93	105.23	12.85
AD-953703.1	85.19	6.51	80.28	4.95	92.69	3.83	103.61	10.67
AD-953711.1	112.96	8.24	109.11	7.12	120.35	12.16	106.85	15.15
AD-953719.1	114.81	12.49	119.99	7.03	113.69	8.85	119.23	9.37
AD-953726.1	35.11	2.22	31.46	15.34	57.67	6.30	69.34	8.95
AD-953734.1	65.77	6.38	69.99	3.84	81.13	3.99	106.57	11.42
AD-953742.1	58.72	7.50	61.53	6.18	80.00	3.55	119.74	27.68
AD-953750.1	49.32	3.17	51.48	4.12	68.72	6.03	100.69	9.29

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953758.1	44.88	3.61	44.90	4.85	63.24	5.71	84.39	11.25
AD-953680.1	74.90	10.00	75.77	8.06	83.61	5.45	86.00	5.23
AD-953688.1	81.42	6.03	82.20	12.97	92.96	14.02	95.86	15.69
AD-953696.1	72.19	7.93	67.92	6.92	94.23	6.09	104.55	13.60
AD-953704.1	61.45	5.62	57.14	12.13	83.24	6.56	95.70	13.67
AD-953712.1	91.32	22.75	93.92	23.35	103.07	5.72	115.58	24.96
AD-953720.1	49.31	2.84	54.74	6.31	73.48	3.04	104.52	14.03
AD-953727.1	45.24	3.13	49.26	0.69	71.27	8.02	99.78	13.10
AD-953735.1	31.95	3.33	40.15	0.28	57.09	5.22	67.75	11.15
AD-953743.1	78.37	2.03	85.25	4.14	108.96	9.61	117.13	18.52
AD-953751.1	69.59	6.18	79.91	15.30	91.65	8.73	111.31	15.81
AD-953759.1	32.77	2.20	36.29	3.15	46.58	3.68	63.10	0.91
AD-953681.1	63.72	8.96	62.53	10.90	69.20	7.75	73.85	14.26
AD-953689.1	84.37	9.37	89.59	8.90	87.64	6.11	94.10	8.40
AD-953697.1	68.67	6.28	70.47	3.84	93.16	11.56	87.50	27.30
AD-953705.1	76.26	9.26	82.71	9.78	101.83	5.76	113.88	25.71
AD-953713.1	72.81	6.33	122.98	18.47	121.70	6.11	126.85	17.30
AD-953721.1	60.09	9.07	61.94	6.28	83.99	7.06	113.53	27.30
AD-953728.1	95.99	7.09	108.81	4.05	105.69	2.61	114.43	15.15
AD-953736.1	43.65	2.02	52.40	3.01	64.42	5.17	107.14	11.36
AD-953744.1	34.38	1.85	38.20	1.43	52.26	2.92	87.44	11.10
AD-953752.1	39.11	3.78	42.14	3.86	55.97	4.34	65.34	13.30
AD-953760.1	39.56	5.60	48.26	1.06	57.17	2.95	69.88	14.70
AD-953682.1	72.92	6.13	77.05	5.65	64.24	10.41	68.65	12.16
AD-953690.1	56.69	5.84	63.32	3.95	69.67	3.82	87.15	7.13

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953698.1	84.41	5.61	93.42	7.30	100.01	7.77	108.17	23.60
AD-953706.1	79.57	29.33	101.33	7.52	109.13	5.67	95.20	13.29
AD-953714.1	111.33	25.98	125.62	15.31	121.04	5.09	121.24	16.17
AD-953722.1	93.22	15.35	99.91	7.15	108.30	8.00	119.11	13.70
AD-953729.1	42.66	6.10	48.25	6.35	69.79	3.86	81.80	40.67
AD-953737.1	86.74	4.91	92.04	8.22	106.08	8.22	112.46	14.11
AD-953745.1	45.37	6.06	51.60	3.18	72.29	6.94	101.78	13.92
AD-953753.1	43.19	1.55	48.00	4.80	52.93	1.12	68.38	8.85
AD-953761.1	39.17	3.62	48.79	4.14	67.01	4.98	107.76	31.81
AD-953683.1	54.19	11.40	55.49	9.00	47.23	9.63	50.48	20.26
AD-953691.1	51.35	3.73	52.28	5.39	56.24	0.80	75.71	12.94
AD-953699.1	64.00	6.71	70.30	2.19	77.97	8.78	76.70	4.51
AD-953707.1	82.64	4.93	99.12	4.80	93.51	14.02	103.34	13.49
AD-953715.1	67.17	5.00	74.93	8.83	89.71	4.29	107.26	12.67
AD-953723.1	53.25	5.37	57.01	4.45	60.65	5.16	72.75	16.34
AD-953730.1	41.03	3.52	48.59	3.57	57.66	2.68	85.34	8.56
AD-953738.1	88.72	13.13	100.11	3.39	112.47	11.06	111.34	12.58
AD-953746.1	40.09	4.99	42.65	2.74	56.37	4.56	80.77	15.66
AD-953754.1	56.31	8.93	60.39	6.69	74.84	4.85	88.46	30.20
AD-953762.1	32.45	1.33	39.24	2.29	45.27	4.18	63.80	2.81
AD-953684.1	33.34	3.17	33.75	3.02	36.55	4.48	65.44	4.73
AD-953692.1	36.65	6.50	37.31	4.94	43.81	6.87	49.97	13.15
AD-953700.1	58.41	8.15	79.31	15.47	81.12	8.60	75.62	22.12
AD-953708.1	88.19	10.97	104.34	10.02	89.15	12.84	95.41	18.93
AD-953716.1	65.20	4.34	69.54	15.10	84.30	10.53	98.17	23.29

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953731.1	41.68	2.39	46.72	5.76	55.67	1.61	78.17	10.58
AD-953739.1	67.29	5.08	75.80	4.41	84.19	5.33	85.46	21.86
AD-953747.1	39.12	1.33	48.43	3.51	71.76	8.07	84.11	5.65
AD-953755.1	34.37	1.72	43.66	1.92	40.70	4.34	56.45	12.42

Table 10. HTT Single Dose Screens in BE(2)C Cells

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953857.1	16.05	2.43	18.37	6.33	37.83	3.99	61.37	32.24
AD-953865.1	21.46	1.84	21.52	2.08	41.90	6.47	66.45	9.60
AD-953873.1	47.68	1.44	41.42	6.98	66.65	7.70	107.00	4.95
AD-953881.1	57.77	5.42	61.52	12.28	71.46	8.69	93.49	10.37
AD-953889.1	21.18	1.43	21.45	3.67	36.96	5.59	49.35	5.80
AD-953897.1	26.52	2.95	25.80	4.38	44.35	0.36	62.96	9.00
AD-953904.1	15.29	2.08	14.33	1.46	27.94	3.94	38.13	10.23
AD-953912.1	20.77	1.06	17.31	1.44	32.90	3.56	42.66	3.78
AD-953920.1	29.21	5.44	23.86	2.65	41.37	5.53	60.07	6.41
AD-953928.1	26.06	5.15	23.19	2.25	45.61	1.04	59.95	10.49
AD-953936.1	20.24	1.03	18.53	1.67	38.84	3.09	49.16	2.52
AD-953858.1	15.45	1.79	15.12	3.49	29.10	5.63	44.55	6.67
AD-953866.1	22.40	0.79	19.07	1.56	33.29	1.60	61.67	5.23
AD-953874.1	22.91	3.18	21.92	2.47	32.57	1.93	55.52	7.14

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953882.1	23.56	2.92	25.69	4.05	42.19	5.80	73.33	9.11
AD-953890.1	22.71	1.67	24.89	2.42	37.31	6.20	49.23	5.16
AD-953898.1	24.80	0.30	22.21	2.80	35.18	2.80	43.93	4.68
AD-953905.1	26.85	2.44	24.82	2.69	42.91	5.14	72.01	10.43
AD-953913.1	25.90	1.86	25.28	1.84	43.55	7.23	69.03	11.98
AD-953921.1	22.21	1.76	19.64	1.53	34.67	3.91	54.24	8.28
AD-953929.1	36.47	5.87	36.02	2.85	61.06	2.86	83.91	22.13
AD-953937.1	16.73	0.96	19.44	3.72	31.00	4.55	34.78	4.00
AD-953859.1	16.27	1.03	16.96	0.82	30.38	3.42	53.51	10.75
AD-953867.1	22.01	3.84	21.97	2.10	35.05	3.59	57.11	1.53
AD-953875.1	24.36	1.23	26.15	2.97	38.19	2.22	74.02	8.43
AD-953883.1	24.73	1.85	21.07	1.38	30.54	4.74	46.61	7.10
AD-953891.1	24.26	0.86	24.22	4.04	38.49	5.50	47.81	7.76
AD-953899.1	24.59	2.33	20.26	2.51	31.05	4.32	41.14	13.31
AD-953906.1	22.78	1.44	20.10	7.25	46.92	2.16	75.40	9.82
AD-953914.1	28.46	1.16	29.74	4.80	64.66	8.34	96.65	11.03
AD-953922.1	19.19	1.32	19.92	3.18	29.66	1.82	34.86	3.55
AD-953930.1	21.85	5.90	21.01	0.82	43.94	3.67	62.33	7.01
AD-953938.1	63.20	5.78	66.64	7.02	79.51	8.87	80.39	3.46
AD-953860.1	19.05	4.26	18.65	0.79	33.32	5.75	48.63	5.08
AD-953868.1	19.63	3.05	18.41	0.48	32.04	2.63	45.92	4.72
AD-953876.1	33.16	2.94	31.85	1.36	66.49	7.48	102.46	4.40
AD-953884.1	14.13	2.63	16.42	2.11	29.70	2.63	38.29	1.64
AD-953892.1	27.64	2.38	25.56	1.96	47.71	9.73	73.34	17.01
AD-953900.1	17.05	0.96	18.87	1.40	32.04	4.65	42.31	8.16

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953907.1	26.95	3.88	22.93	2.59	39.97	8.06	71.61	4.01
AD-953915.1	30.95	4.60	28.16	5.40	46.16	10.23	71.46	7.54
AD-953923.1	21.89	2.66	17.20	1.12	27.43	1.64	40.87	3.85
AD-953931.1	27.06	2.01	27.01	2.05	42.09	4.90	63.01	3.94
AD-953939.1	77.68	4.69	76.66	10.80	88.25	6.19	94.95	4.51
AD-953861.1	20.65	1.55	18.60	2.50	29.63	3.05	40.90	5.14
AD-953869.1	21.08	2.86	21.03	2.28	33.09	2.30	55.70	4.88
AD-953877.1	31.47	1.50	32.22	0.31	60.90	5.92	88.72	15.86
AD-953885.1	22.81	2.02	22.11	1.91	33.11	1.36	54.46	6.06
AD-953893.1	25.43	3.20	26.90	1.72	35.40	3.43	58.81	5.74
AD-953901.1	23.55	2.39	22.74	2.14	30.83	2.19	46.56	6.45
AD-953908.1	28.14	3.66	24.79	4.32	49.98	6.67	74.89	11.28
AD-953916.1	20.50	1.45	20.84	3.59	32.80	3.07	55.53	5.20
AD-953924.1	20.30	2.89	19.94	2.37	31.99	1.48	53.87	2.32
AD-953932.1	22.26	4.04	22.14	1.06	37.97	1.68	64.51	5.33
AD-953940.1	78.14	8.15	84.67	10.84	91.71	2.98	95.60	7.68
AD-953862.1	22.74	1.44	21.07	0.21	32.76	4.07	51.54	3.32
AD-953870.1	20.18	2.42	19.12	1.30	30.42	3.19	40.34	7.91
AD-953878.1	33.07	2.38	31.34	3.70	53.01	3.47	88.88	9.26
AD-953886.1	17.86	1.46	19.86	1.08	31.56	1.68	55.48	5.88
AD-953894.1	27.61	2.51	28.83	1.74	56.14	0.45	82.15	15.86
AD-953902.1	18.50	2.11	19.26	1.83	28.69	1.66	37.61	5.71
AD-953909.1	26.17	1.74	28.69	2.80	48.35	4.44	68.14	4.57
AD-953917.1	26.83	2.16	27.61	2.62	36.73	1.02	70.07	10.65
AD-953925.1	46.16	7.34	44.27	1.82	71.56	4.90	107.36	4.41

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953933.1	18.24	2.49	20.81	2.28	31.13	1.91	52.83	9.20
AD-953941.1	59.99	7.78	52.78	7.30	82.81	6.48	110.20	9.13
AD-953863.1	32.05	2.19	28.11	1.01	34.98	0.73	50.43	7.83
AD-953871.1	28.02	2.21	28.90	2.25	34.68	3.48	46.87	5.69
AD-953879.1	23.07	2.42	25.80	2.96	36.76	3.23	59.20	7.03
AD-953887.1	18.24	1.05	20.75	1.99	28.07	2.87	41.77	7.81
AD-953895.1	20.39	2.35	22.41	3.55	26.86	3.42	43.97	4.42
AD-953903.1	15.66	2.01	19.65	2.14	29.56	1.93	39.81	7.11
AD-953910.1	23.32	4.24	23.75	2.89	37.97	3.81	62.99	3.58
AD-953918.1	31.96	4.06	32.74	2.53	45.30	1.60	79.21	8.97
AD-953926.1	21.45	0.48	24.19	2.05	40.34	5.85	72.83	12.05
AD-953934.1	23.64	1.04	25.29	0.71	38.99	2.17	67.06	7.90
AD-953864.1	26.24	3.28	22.71	2.58	38.72	3.45	52.72	12.31
AD-953872.1	25.36	5.20	25.00	2.09	37.92	4.88	45.09	6.85
AD-953880.1	21.96	1.35	23.44	2.50	37.41	4.29	49.37	9.72
AD-953888.1	26.33	2.91	24.11	1.45	40.29	3.43	55.22	10.38
AD-953896.1	21.04	0.64	22.26	2.38	36.44	4.77	56.58	9.76
AD-953911.1	22.96	1.06	24.03	2.14	37.86	2.21	66.71	11.29
AD-953919.1	62.76	5.76	56.02	5.60	76.99	2.81	99.08	13.73
AD-953927.1	25.86	2.58	23.39	2.44	31.73	2.85	46.22	9.20
AD-953935.1	16.38	1.42	17.59	1.08	29.00	3.19	53.23	4.33
AD-953763.1	33.44	10.21	31.06	6.57	43.69	4.70	48.31	5.99
AD-953771.1	42.75	6.50	41.28	9.16	75.61	9.00	92.60	10.47
AD-953779.1	27.92	5.35	31.67	9.74	37.29	4.50	57.23	5.65
AD-953787.1	32.95	4.58	35.35	8.17	41.84	4.58	59.06	4.46

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953795.1	34.28	2.28	41.91	3.73	53.55	5.26	85.25	1.65
AD-953803.1	61.61	10.04	46.74	4.05	83.38	4.24	110.46	5.45
AD-953810.1	32.03	4.20	30.31	3.53	46.84	8.35	52.79	9.88
AD-953818.1	35.62	7.77	39.33	3.83	64.80	4.51	83.71	8.90
AD-953834.1	38.17	10.19	39.24	9.05	69.47	5.13	84.84	12.05
AD-953842.1	48.14	5.74	42.18	11.18	64.07	8.26	83.21	9.99
AD-953764.1	35.95	3.92	32.36	4.78	52.82	1.31	84.76	7.49
AD-953772.1	34.22	7.68	38.93	10.45	43.52	4.44	68.49	4.03
AD-953780.1	30.99	9.57	31.93	10.20	39.08	2.92	60.57	5.48
AD-953788.1	38.27	4.23	37.18	5.59	47.91	5.42	76.84	1.80
AD-953796.1	42.51	6.58	44.21	4.90	67.01	5.42	102.06	6.64
AD-953804.1	37.65	5.98	34.34	7.25	41.18	3.27	67.16	2.81
AD-953811.1	35.49	4.59	33.88	3.83	69.90	4.22	92.57	4.77
AD-953819.1	72.71	8.61	64.21	4.15	84.79	6.50	115.08	3.54
AD-953827.1	54.49	6.72	47.64	2.73	68.71	6.19	102.52	4.97
AD-953835.1	50.86	9.70	45.75	3.45	70.68	2.02	109.76	6.91
AD-953843.1	40.24	13.59	34.25	4.72	42.61	4.27	72.86	11.78
AD-953851.1	28.35	1.65	29.66	1.70	38.15	2.59	52.40	6.40
AD-953765.1	28.75	5.69	26.86	10.34	41.08	2.80	59.02	5.49
AD-953773.1	47.21	11.49	44.85	8.81	49.28	4.61	75.12	5.20
AD-953781.1	36.10	8.50	36.11	10.46	52.43	3.14	88.89	6.54
AD-953789.1	33.84	5.38	30.41	2.64	41.12	5.33	61.12	4.22
AD-953797.1	50.45	9.38	48.61	3.65	74.12	3.88	107.92	12.56
AD-953805.1	38.52	4.74	35.18	3.86	48.85	6.72	74.95	4.48
AD-953812.1	50.94	4.43	47.30	4.06	44.30	3.90	65.73	4.56

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953828.1	41.55	3.96	36.91	1.60	48.35	3.41	84.09	2.25
AD-953836.1	77.62	9.75	74.18	18.66	102.18	6.41	126.56	2.57
AD-953852.1	36.55	1.38	38.33	2.34	49.12	9.28	76.84	7.57
AD-953766.1	26.95	4.97	26.63	9.68	34.64	4.42	55.02	6.92
AD-953774.1	31.82	8.79	29.89	6.65	47.56	6.79	76.30	11.63
AD-953782.1	33.99	4.66	33.27	1.66	58.33	2.52	88.13	2.99
AD-953790.1	35.99	9.97	36.56	5.57	52.53	6.12	76.07	5.88
AD-953798.1	31.59	5.99	30.43	2.92	48.48	9.26	58.30	7.98
AD-953806.1	29.95	2.89	29.95	3.45	47.19	0.64	72.89	3.91
AD-953813.1	35.04	6.15	31.69	2.55	37.67	2.51	55.37	5.38
AD-953821.1	30.63	2.16	27.43	2.03	35.15	2.54	51.11	4.67
AD-953829.1	68.42	15.84	60.97	8.15	84.94	2.74	110.99	4.30
AD-953837.1	36.88	3.79	32.34	0.88	41.99	3.69	79.41	5.74
AD-953845.1	49.96	25.03	37.73	5.40	51.07	4.49	71.53	4.38
AD-953853.1	17.30	1.56	22.03	4.16	37.46	4.85	62.29	9.25
AD-953767.1	24.93	5.50	28.42	10.66	40.33	3.22	69.76	2.61
AD-953775.1	45.40	10.62	36.34	9.82	73.68	7.21	102.63	7.31
AD-953783.1	29.99	12.53	29.51	4.63	49.16	6.13	80.74	6.86
AD-953791.1	30.97	8.17	29.31	7.02	46.06	7.18	74.93	6.54
AD-953799.1	32.72	4.42	31.33	1.95	54.01	3.60	86.02	6.50
AD-953807.1	37.52	7.06	37.17	3.09	55.11	2.71	82.01	4.66
AD-953822.1	33.78	5.99	30.78	3.36	46.16	8.11	69.15	2.45
AD-953830.1	34.73	3.76	31.58	2.53	41.37	0.94	66.10	6.80
AD-953838.1	33.55	9.39	34.52	2.10	49.15	2.33	86.79	3.75
AD-953846.1	33.45	7.53	33.66	5.78	50.46	4.49	78.12	13.11

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953854.1	23.08	2.75	19.69	3.46	27.90	1.19	48.41	6.99
AD-953768.1	26.98	4.47	27.38	10.87	33.82	3.92	45.54	4.57
AD-953776.1	39.69	16.74	31.10	7.28	54.45	2.97	90.09	8.42
AD-953784.1	29.34	10.82	24.02	5.30	40.23	2.64	61.39	5.18
AD-953792.1	31.76	9.30	29.07	4.26	37.11	3.03	56.21	8.23
AD-953800.1	29.00	3.03	28.36	1.20	35.08	3.37	55.13	4.63
AD-953808.1	31.85	5.96	28.41	1.27	40.18	3.14	60.87	3.28
AD-953815.1	35.68	6.34	33.39	1.73	56.62	1.49	89.20	2.68
AD-953823.1	47.61	8.60	43.41	7.31	76.73	6.34	105.86	12.49
AD-953831.1	33.88	4.75	29.70	2.85	51.07	2.83	87.65	1.33
AD-953839.1	36.98	6.09	30.68	4.56	43.56	4.04	73.41	4.37
AD-953847.1	36.41	2.21	28.52	3.20	37.39	4.16	50.12	2.49
AD-953855.1	17.03	0.92	20.33	2.28	31.95	1.93	50.61	5.00
AD-953769.1	20.41	6.91	19.71	9.17	31.58	2.32	36.59	3.40
AD-953777.1	27.72	11.77	25.22	7.75	41.72	3.97	70.38	3.27
AD-953785.1	30.05	8.76	25.46	3.08	47.74	2.90	81.22	2.03
AD-953793.1	32.70	14.69	26.09	4.10	45.08	5.84	70.67	4.24
AD-953801.1	38.99	5.29	35.13	6.56	41.40	2.07	60.29	1.63
AD-953809.1	28.15	2.21	26.23	3.63	40.42	2.30	54.00	6.94
AD-953816.1	28.53	4.61	25.41	3.81	36.82	2.32	54.76	2.99
AD-953824.1	30.25	1.84	30.25	1.56	58.47	3.40	80.60	4.45
AD-953832.1	43.14	6.36	40.76	5.26	72.55	2.64	92.56	7.75
AD-953840.1	30.53	5.72	28.62	1.53	40.53	1.46	67.24	4.83
AD-953848.1	24.84	5.73	25.53	2.19	28.59	3.67	43.01	1.45
AD-953856.1	24.53	4.30	32.92	13.93	40.47	4.05	64.17	6.57

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953770.1	24.22	4.79	24.71	11.20	33.60	2.40	49.01	2.65
AD-953778.1	25.28	9.47	20.21	6.37	33.84	2.50	48.13	5.65
AD-953786.1	26.47	9.22	22.25	7.17	40.55	4.25	62.15	3.45
AD-953794.1	36.49	20.58	28.21	9.14	45.54	5.69	67.37	2.13
AD-953802.1	35.57	5.56	25.34	4.52	42.55	3.28	64.50	4.55
AD-953817.1	32.24	3.60	26.88	7.17	39.15	4.10	62.75	8.52
AD-953825.1	38.84	3.96	35.19	5.34	42.76	5.17	52.16	11.63
AD-953833.1	25.14	4.13	26.42	6.33	38.39	5.09	50.29	8.28
AD-953841.1	29.86	1.31	31.23	3.65	53.57	9.16	66.57	2.48
AD-953849.1	22.59	4.11	22.30	7.94	27.51	5.06	37.40	3.16

Table 13. HTT Single Dose Screens in BE(2)C Cells

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953943.1	25.28	8.03	29.30	6.44	32.57	12.47	46.70	13.54
AD-953944.1	41.24	7.70	40.89	7.91	59.91	20.20	85.25	18.83
AD-953945.1	33.55	5.45	42.11	3.45	70.29	23.77	73.31	19.65
AD-953946.1	52.10	8.38	60.45	8.41	81.46	14.40	91.79	18.06
AD-953947.1	71.37	9.54	78.72	8.60	106.79	23.62	87.11	18.93
AD-953948.1	28.84	2.55	32.11	3.84	51.95	11.17	66.84	15.72
AD-953949.1	27.80	2.41	28.29	0.53	48.44	9.11	57.01	13.39
AD-953950.1	19.18	1.56	22.28	2.23	41.90	4.85	50.60	10.20

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953951.1	35.52	3.47	40.06	2.38	59.55	8.65	63.30	13.81
AD-953952.1	40.78	3.62	47.38	6.25	73.82	14.74	83.70	15.18
AD-953953.1	35.33	4.75	40.88	5.35	54.48	11.58	76.41	16.22
AD-953954.1	80.48	13.33	94.11	5.00	114.77	17.14	112.09	13.16
AD-953955.1	61.44	7.57	67.95	5.96	100.83	16.48	112.12	11.33
AD-953956.1	52.28	1.18	53.04	4.66	84.55	6.04	103.05	13.02
AD-953957.1	27.47	4.33	32.42	1.80	60.62	14.19	82.35	11.15
AD-953958.1	42.36	8.94	52.33	5.08	101.09	14.02	74.85	14.06
AD-953959.1	75.40	11.80	89.04	9.94	94.52	26.23	91.62	23.89
AD-953960.1	49.59	6.40	47.82	6.33	75.30	5.89	101.99	14.34
AD-953961.1	43.00	5.18	47.78	8.88	70.77	3.43	80.17	9.16
AD-953962.1	41.41	6.11	46.17	2.48	70.52	9.03	87.06	47.29
AD-953963.1	61.88	13.44	69.79	8.45	126.67	29.69	119.20	18.58
AD-953964.1	49.04	4.98	43.29	2.06	73.17	16.11	95.22	10.94
AD-953965.1	79.15	12.41	79.79	6.49	112.95	26.48	106.87	9.13
AD-953966.1	39.29	4.71	46.51	3.06	93.79	10.89	78.31	9.71
AD-953967.1	102.74	15.60	102.27	8.94	113.11	28.49	123.76	9.66
AD-953968.1	56.27	5.92	58.12	6.20	88.92	11.11	104.25	16.19
AD-953969.1	49.05	7.61	48.14	4.34	78.67	13.96	100.12	9.43
AD-953970.1	73.15	6.87	77.89	3.81	114.55	15.98	122.14	27.56
AD-953971.1	92.44	12.13	108.14	6.62	141.31	17.87	125.68	17.13
AD-953972.1	43.95	9.17	46.62	3.59	75.63	8.78	79.19	9.91
AD-953973.1	58.39	7.73	62.98	3.93	110.01	14.70	117.11	19.26
AD-953974.1	47.46	5.57	52.59	3.19	110.79	8.08	89.64	14.12
AD-953975.1	53.14	11.39	51.38	5.50	87.70	16.68	99.11	21.62

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-953976.1	49.95	4.47	52.61	3.52	83.42	12.10	98.52	19.53
AD-953977.1	87.78	13.24	89.20	5.02	135.24	13.49	127.28	19.87
AD-953978.1	126.71	11.93	145.34	6.50	166.62	14.28	114.56	18.35
AD-953979.1	48.28	4.97	51.36	1.50	68.12	7.23	102.36	19.14
AD-953980.1	57.96	6.20	74.25	4.62	110.83	20.10	131.34	20.04
AD-953981.1	49.45	8.32	53.06	3.50	78.64	6.37	101.33	17.60
AD-953982.1	33.37	2.16	42.62	3.56	64.77	7.97	73.11	11.94
AD-953983.1	39.40	10.93	35.92	2.28	57.13	6.68	78.16	14.03
AD-953984.1	57.27	7.41	54.74	3.56	77.90	18.18	99.74	14.21
AD-953985.1	130.23	15.12	137.00	5.31	137.26	18.25	128.33	32.12
AD-953986.1	50.95	10.45	54.33	4.64	105.85	9.70	103.85	21.90
AD-953987.1	69.56	6.28	77.39	4.68	81.55	10.03	126.82	37.96
AD-953988.1	66.19	16.21	91.07	11.88	112.42	22.54	142.20	17.51
AD-953989.1	65.71	14.37	80.99	7.71	122.89	11.49	136.06	13.06
AD-953990.1	83.61	12.96	64.84	5.57	88.44	12.20	104.08	14.59
AD-953991.1	94.27	13.29	80.81	9.00	101.66	8.48	113.51	9.05
AD-953992.1	44.46	5.75	39.33	3.94	58.24	10.81	87.29	5.55
AD-953993.1	114.46	11.88	119.55	18.54	138.88	4.29	139.56	15.56
AD-953994.1	109.68	16.66	113.20	13.74	85.48	22.04	132.49	25.95
AD-953995.1	44.47	8.00	43.63	3.03	60.41	1.70	85.58	8.98
AD-953996.1	55.33	4.94	65.39	5.34	90.87	10.20	128.94	17.18
AD-953997.1	54.33	4.23	54.39	5.44	91.96	7.82	107.48	13.93
AD-953998.1	89.94	12.50	77.20	9.55	83.97	14.41	99.62	24.71
AD-953999.1	85.41	13.43	77.50	8.43	77.70	8.48	110.99	13.64
AD-954000.1	120.60	19.15	112.70	6.22	85.64	27.09	120.51	15.78

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-954001.1	94.88	10.89	96.63	6.17	118.17	11.83	127.17	24.97
AD-954002.1	51.53	4.49	49.17	3.34	66.31	8.86	112.46	28.45
AD-954003.1	123.28	14.54	118.10	13.16	157.56	23.31	135.59	15.72
AD-954004.1	75.28	8.21	98.59	21.80	125.64	7.09	140.25	21.72
AD-954005.1	102.97	31.98	113.10	12.44	159.34	23.27	129.47	16.72
AD-954006.1	97.35	19.09	94.31	15.52	71.85	14.67	92.08	15.42
AD-954007.1	49.86	4.43	47.55	2.82	70.97	11.19	94.69	14.77
AD-954008.1	51.41	7.18	41.24	1.97	57.95	4.19	89.30	14.74
AD-954009.1	89.01	12.41	84.78	3.63	107.09	5.23	97.41	9.85
AD-954010.1	49.84	6.28	41.44	1.50	54.91	3.86	103.82	11.64
AD-954011.1	105.29	12.79	90.10	11.94	153.30	16.20	120.57	21.63
AD-954012.1	90.03	8.01	87.39	8.23	140.07	15.18	132.56	20.06
AD-954013.1	34.92	5.03	36.29	5.46	62.17	6.83	77.52	8.18
AD-954014.1	81.22	23.88	86.33	11.49	67.65	13.37	90.11	8.95
AD-954015.1	70.36	13.12	60.63	5.52	66.58	5.12	90.80	13.51
AD-954016.1	44.53	7.30	38.81	1.70	56.12	6.21	98.73	12.81
AD-954017.1	97.19	12.84	81.90	6.70	106.75	9.38	88.14	13.94
AD-954018.1	72.64	8.33	65.38	3.02	84.16	6.84	72.28	35.23
AD-954019.1	67.29	8.93	61.61	1.61	97.42	23.69	110.48	16.04
AD-954020.1	63.68	8.73	63.56	6.39	110.81	15.91	125.91	24.47
AD-954021.1	100.05	21.36	92.98	5.12	127.14	10.83	116.82	15.90
AD-954022.1	28.29	9.46	29.23	2.71	34.21	9.00	68.48	7.86
AD-954023.1	30.29	6.42	35.88	4.22	40.46	3.69	68.43	11.76
AD-954024.1	50.98	9.28	46.06	4.64	52.39	4.98	87.55	10.91
AD-954025.1	75.43	8.49	64.94	11.65	64.26	3.84	100.45	17.56

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-954026.1	46.65	11.78	44.30	2.74	43.02	4.24	74.87	12.89
AD-954027.1	57.79	8.79	54.28	8.40	67.25	12.15	100.97	18.05
AD-954028.1	45.79	6.10	44.14	3.91	55.59	5.40	97.37	12.76
AD-954029.1	40.81	3.90	58.93	15.43	73.62	7.62	94.19	5.76
AD-954030.1	43.55	12.13	52.94	11.13	73.85	21.70	99.17	16.74
AD-954031.1	49.31	6.60	52.96	11.91	83.10	14.06	102.31	16.01
AD-954032.1	127.12	23.82	128.56	12.32	133.30	14.88	128.31	14.51
AD-954033.1	73.92	10.70	80.98	18.52	113.54	30.70	130.72	14.26
AD-954034.1	49.31	6.67	52.15	10.90	84.31	20.73	110.44	23.97
AD-954035.1	114.40	15.11	119.60	14.69	134.36	19.21	129.08	17.91
AD-954036.1	43.48	8.39	47.72	10.68	67.08	8.75	106.73	21.10
AD-954037.1	39.27	4.77	44.74	6.11	72.17	11.91	69.59	13.73
AD-954038.1	30.64	4.65	28.78	2.96	43.66	8.99	56.53	12.31
AD-954039.1	36.40	11.20	30.20	5.20	39.81	8.41	53.83	9.89
AD-954040.1	50.62	10.89	40.11	7.49	55.41	10.77	81.88	12.15
AD-954041.1	35.66	3.12	24.01	4.69	32.00	3.54	44.11	6.53
AD-954042.1	41.12	8.18	24.88	4.04	44.89	6.14	61.21	11.11
AD-954043.1	24.89	5.72	15.90	2.81	22.25	4.24	32.58	5.77
AD-954044.1	65.02	12.76	24.80	3.20	36.34	3.58	43.61	4.19
AD-954045.1	29.56	5.27	33.04	8.55	45.38	9.97	61.31	9.41
AD-954046.1	50.62	13.97	43.21	5.02	53.53	2.70	82.32	9.29
AD-954047.1	112.14	11.02	85.80	11.37	84.42	14.84	92.74	14.20
AD-954048.1	45.07	4.29	39.26	5.31	61.14	4.62	76.48	11.06
AD-954049.1	74.41	7.46	54.16	4.25	73.62	7.71	86.63	15.31
AD-954050.1	43.19	7.71	34.41	3.69	54.34	6.87	64.75	6.48

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-954051.1	40.81	4.58	27.32	4.69	35.97	4.35	48.62	5.79
AD-954052.1	57.53	7.53	34.95	2.91	45.72	15.91	55.47	8.35
AD-954053.1	91.59	24.57	86.71	28.24	112.72	17.38	95.41	11.00
AD-954054.1	97.79	27.39	72.68	9.74	92.74	9.94	97.46	7.00
AD-954055.1	97.83	2.74	87.42	9.52	101.94	20.54	98.18	20.94
AD-954056.1	37.01	8.47	36.02	5.25	59.20	5.18	67.31	5.75
AD-954057.1	72.64	27.91	60.87	7.90	92.38	4.23	97.42	11.31
AD-954058.1	40.42	5.48	31.51	4.21	50.10	5.34	64.00	5.40
AD-954059.1	110.34	24.77	79.75	10.33	90.93	11.33	93.25	8.24
AD-954060.1	105.41	10.82	68.12	9.92	67.92	19.45	77.29	9.57
AD-954061.1	48.19	12.83	45.41	7.18	82.81	16.32	89.79	11.76
AD-954062.1	112.79	28.14	117.81	19.59	130.07	14.97	114.35	9.21
AD-954063.1	69.36	6.09	65.94	8.67	103.63	13.94	103.38	7.59
AD-954065.1	55.37	13.42	43.03	5.34	73.02	12.77	86.97	3.99
AD-954066.1	49.73	13.11	39.91	5.94	75.64	13.85	91.95	7.81
AD-954067.1	87.82	13.15	64.69	7.46	98.59	18.86	93.71	14.09
AD-954068.1	40.19	6.13	33.47	4.27	53.53	6.72	63.74	6.42
AD-954069.1	48.15	13.31	52.79	11.46	73.81	8.41	91.06	10.26
AD-954070.1	65.48	11.48	75.23	15.82	115.87	3.64	102.39	5.57
AD-954071.1	123.38	32.06	81.03	11.89	110.37	8.08	103.39	10.42
AD-954072.1	35.49	5.00	36.19	5.15	61.74	7.13	61.94	5.11
AD-954073.1	85.49	23.02	67.03	5.33	111.70	10.83	105.50	19.88
AD-954074.1	124.78	23.26	90.09	14.54	129.47	9.93	111.03	8.56
AD-954075.1	52.62	12.43	39.80	11.15	71.55	4.83	81.99	12.05
AD-954076.1	73.79	11.02	45.41	7.32	74.27	6.14	89.39	6.76

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-954077.1	36.90	4.73	49.38	9.45	61.64	8.52	80.49	15.53
AD-954078.1	42.82	8.28	56.34	12.92	81.78	2.08	82.10	6.11
AD-954079.1	146.69	40.61	152.79	32.89	150.99	10.06	109.19	12.69
AD-954080.1	80.97	14.87	77.63	13.06	116.41	7.28	93.41	25.93
AD-954081.1	132.71	24.87	111.25	18.32	144.22	6.86	106.52	13.53
AD-954082.1	53.58	11.30	49.94	8.38	90.95	15.32	102.40	14.73
AD-954083.1	52.38	9.89	49.44	7.90	84.24	2.72	84.39	13.42
AD-954084.1	61.73	14.66	79.26	14.19	93.30	14.70	93.82	9.65
AD-954085.1	36.35	5.49	44.12	5.16	54.76	3.22	55.64	7.08
AD-954086.1	45.60	11.57	50.65	6.54	64.43	12.90	68.12	7.00
AD-954087.1	137.98	20.04	124.29	18.80	118.93	16.69	92.84	19.91
AD-954088.1	41.87	8.36	52.21	6.46	78.64	3.87	62.24	2.62
AD-954089.1	70.86	15.32	62.56	15.26	107.73	3.13	100.55	22.65
AD-954090.1	70.40	19.51	61.35	6.11	87.91	8.25	105.18	2.75
AD-954091.1	37.74	5.94	45.78	7.62	63.97	11.22	98.88	15.71
AD-954092.1	49.19	12.83	59.59	17.25	71.13	7.86	80.52	7.44
AD-954093.1	79.76	26.13	125.17	23.01	113.91	8.99	101.46	8.08
AD-954094.1	61.37	8.05	78.73	5.77	91.71	19.60	84.72	14.75
AD-954095.1	90.36	16.00	96.13	13.68	101.60	4.03	76.09	16.53
AD-954096.1	69.55	22.01	80.82	24.89	83.29	14.39	77.15	10.78
AD-954097.1	50.60	5.74	60.89	7.04	81.66	15.06	93.85	17.16
AD-954098.1	50.89	7.69	54.42	6.61	79.36	4.81	91.22	8.67
AD-954099.1	44.06	10.32	40.54	3.88	51.58	11.04	66.69	8.02
AD-954100.1	68.73	15.47	80.94	24.34	85.21	11.36	82.63	10.62
AD-954101.1	96.29	18.69	82.73	18.38	102.29	7.72	77.19	23.29

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD
AD-954102.1	97.04	16.96	107.63	40.67	106.07	24.77	94.95	9.34
AD-954103.1	53.12	19.06	61.48	8.80	96.56	9.11	81.60	4.45
AD-954104.1	39.24	14.17	43.90	6.64	63.80	21.66	74.13	17.46
AD-954105.1	92.22	40.50	92.14	6.14	121.87	12.99	117.35	4.61
AD-954106.1	94.69	22.86	81.66	34.22	109.92	14.27	120.28	6.00
AD-954107.1	52.54	5.70	54.68	6.50	58.71	8.77	86.39	7.37
AD-954108.1	32.60	9.35	36.30	8.08	52.25	9.42	65.38	12.97
AD-954109.1	49.22	14.42	49.54	15.31	65.91	5.75	80.95	9.56
AD-954110.1	68.41	9.31	76.51	10.13	76.09	19.11	99.23	8.36
AD-954111.1	92.65	22.73	101.91	26.67	98.02	8.77	94.90	10.57
AD-954112.1	64.00	17.39	59.14	9.11	83.34	9.57	83.36	12.35
AD-954113.1	58.25	12.41	57.75	13.56	81.37	7.99	93.07	7.70
AD-954114.1	71.05	16.06	77.64	9.56	87.97	8.84	109.33	15.36
AD-954115.1	60.65	15.19	56.61	8.62	76.60	6.08	101.81	10.73
AD-954116.1	26.64	11.15	26.49	3.81	36.33	5.62	45.17	7.32
AD-954117.1	52.54	12.72	40.89	8.82	55.89	4.54	67.65	7.51
AD-954118.1	40.93	7.86	43.47	15.03	62.96	4.72	53.36	8.79
AD-954119.1	89.09	13.93	93.53	23.25	85.36	8.16	79.38	9.09
AD-954120.1	108.81	24.28	103.12	24.39	96.43	3.32	95.36	8.32
AD-954121.1	109.72	19.61	106.73	17.99	113.83	23.58	105.34	7.28
AD-954122.1	124.06	25.59	104.70	14.12	98.12	9.91	91.42	2.87

Table 16. HTT Single Dose Screens in BE(2)C Cells

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining
AD-954123.1	52.02	12.80	46.66	11.06	51.72	10.80	70.22	6.18
AD-954131.1	37.98	5.90	34.57	5.77	56.27	5.95	74.72	6.16
AD-954139.1	31.28	1.26	30.33	5.65	43.37	8.28	61.47	3.88
AD-954147.1	33.48	1.73	36.49	5.47	49.67	12.95	74.93	16.31
AD-954155.1	55.01	1.15	66.47	0.62	91.29	8.22	78.41	9.98
AD-954163.1	62.90	5.16	50.49	7.01	66.53	6.52	90.24	7.19
AD-954170.1	29.27	2.86	34.63	5.08	46.01	6.99	66.85	2.30
AD-954178.1	43.47	4.36	41.39	2.26	79.85	16.32	87.04	14.48
AD-954186.1	54.17	5.38	61.30	6.21	83.63	16.19	89.18	4.75
AD-954194.1	47.87	5.42	39.24	2.46	50.47	7.85	77.94	7.02
AD-954202.1	70.30	6.02	59.62	8.57	62.98	11.40	81.62	14.21
AD-954210.1	32.28	5.26	36.94	6.00	64.76	9.98	93.72	4.84
AD-954124.1	46.70	4.05	41.03	1.99	66.79	12.84	57.90	2.15
AD-954132.1	81.87	6.77	63.41	9.43	84.80	13.63	84.67	7.53
AD-954140.1	30.47	2.31	30.26	3.39	48.06	11.20	55.00	9.66
AD-954148.1	34.16	3.45	39.06	6.94	54.16	2.59	75.41	4.55
AD-954156.1	42.59	5.18	43.79	9.06	70.61	10.32	74.37	10.49
AD-954164.1	29.49	1.14	34.96	6.24	50.44	2.05	64.40	5.75
AD-954171.1	39.79	1.38	42.98	6.89	61.44	18.83	78.26	2.31
AD-954179.1	78.67	4.09	90.13	10.14	116.94	15.14	96.51	6.99
AD-954187.1	92.74	4.59	100.39	6.46	109.57	10.84	95.69	9.79
AD-954195.1	62.30	7.07	68.94	6.67	87.94	2.35	93.65	11.99
AD-954203.1	40.27	2.78	39.36	4.99	59.62	12.43	69.24	3.49

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining
AD-954211.1	27.50	2.70	35.44	1.43	57.60	7.45	84.16	6.91
AD-954125.1	44.62	3.51	37.71	2.42	53.96	5.73	72.84	9.76
AD-954133.1	44.69	1.50	45.67	5.60	72.15	4.87	91.31	13.88
AD-954141.1	30.90	4.83	39.50	3.44	58.12	15.89	80.61	3.02
AD-954149.1	26.66	1.89	37.09	5.81	47.06	6.03	54.88	8.32
AD-954157.1	76.68	6.90	86.87	14.20	123.87	14.44	96.35	2.83
AD-954165.1	46.70	2.49	57.71	7.06	94.90	6.91	81.55	14.03
AD-954172.1	36.92	2.44	41.21	4.86	53.31	11.00	75.26	6.57
AD-954180.1	58.96	1.62	61.78	3.73	83.87	13.62	95.17	6.80
AD-954188.1	73.92	6.24	65.52	8.60	75.12	7.69	77.77	4.08
AD-954196.1	99.61	6.03	106.63	13.54	117.44	16.32	93.30	8.20
AD-954204.1	26.94	2.60	27.10	1.95	33.35	1.88	44.67	2.25
AD-954212.1	42.77	2.77	53.14	1.61	76.16	7.15	101.27	15.46
AD-954126.1	31.15	4.59	28.37	7.55	41.47	8.71	64.69	6.72
AD-954134.1	34.95	4.43	37.04	3.07	64.75	10.62	81.41	5.61
AD-954142.1	85.11	5.64	76.57	8.62	103.15	15.39	104.54	3.92
AD-954150.1	34.95	5.56	43.60	5.54	61.62	3.99	76.87	4.98
AD-954158.1	36.70	7.95	44.96	9.26	62.06	18.09	98.72	23.25
AD-954166.1	51.85	3.54	71.74	8.49	99.76	6.78	101.54	8.54
AD-954173.1	30.73	2.97	37.17	3.06	41.53	3.10	61.63	2.52
AD-954181.1	65.36	3.45	70.56	8.63	72.93	2.04	96.04	3.73
AD-954189.1	38.01	3.43	47.12	5.07	62.93	1.22	76.77	7.56
AD-954197.1	52.15	4.15	61.12	5.20	82.73	7.76	95.55	7.69
AD-954205.1	31.38	2.29	33.79	2.85	52.38	10.33	81.33	3.38
AD-954213.1	24.59	2.15	30.30	2.83	40.86	3.44	66.86	6.00

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining
AD-954127.1	51.38	5.89	39.04	7.84	55.31	11.49	64.90	4.83
AD-954135.1	95.14	9.88	102.58	8.08	104.48	5.54	94.95	12.83
AD-954143.1	41.30	4.61	43.90	3.89	71.08	2.83	93.56	2.98
AD-954151.1	49.96	2.57	58.67	3.77	87.43	9.85	94.12	8.27
AD-954159.1	37.64	2.71	42.68	7.34	86.42	13.02	92.18	15.52
AD-954167.1	64.60	10.08	62.25	24.93	104.37	19.93	79.75	5.74
AD-954174.1	26.34	2.62	33.31	8.11	53.96	9.59	67.80	7.33
AD-954182.1	39.88	1.79	44.29	2.43	74.11	10.67	87.71	8.66
AD-954190.1	31.54	2.31	34.55	2.79	52.19	6.47	71.74	4.87
AD-954198.1	80.34	4.43	87.33	9.35	101.06	10.72	99.18	6.53
AD-954206.1	33.58	1.34	33.90	3.58	50.24	4.96	82.01	8.04
AD-954214.1	23.40	2.25	31.57	2.68	38.95	2.46	63.16	9.52
AD-954128.1	27.26	1.75	25.22	3.34	29.83	4.96	47.17	0.54
AD-954136.1	87.99	6.49	91.17	9.71	83.92	2.27	82.07	8.82
AD-954144.1	29.88	2.85	33.73	4.85	43.14	7.17	69.14	6.09
AD-954152.1	35.17	2.44	36.61	4.59	53.44	4.84	77.50	3.94
AD-954160.1	33.26	1.92	28.97	5.90	50.16	5.97	74.36	8.41
AD-954168.1	42.69	3.89	49.18	4.95	68.36	12.19	71.75	5.10
AD-954175.1	43.24	1.41	51.66	2.51	84.47	5.48	97.60	14.78
AD-954183.1	75.62	6.73	84.16	18.23	99.04	8.72	98.12	5.76
AD-954191.1	38.92	1.79	46.32	7.58	71.86	10.90	103.08	3.01
AD-954199.1	42.26	2.80	45.98	3.56	73.52	6.66	81.46	8.27
AD-954207.1	28.21	1.56	30.80	3.11	45.83	7.89	73.61	10.14
AD-954215.1	21.72	1.42	27.71	2.94	43.81	4.05	75.95	9.32
AD-954129.1	24.27	1.44	21.17	3.24	19.07	6.69	60.49	6.62

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining
AD-954137.1	43.53	3.12	48.64	7.04	59.95	19.21	88.81	6.41
AD-954145.1	32.85	2.77	33.76	10.34	56.45	10.32	88.01	10.24
AD-954153.1	48.99	6.02	49.20	3.77	78.83	10.81	64.73	7.14
AD-954161.1	32.14	3.02	34.48	2.60	46.36	4.16	54.76	8.47
AD-954169.1	34.74	2.18	35.81	3.43	61.71	5.68	75.21	5.66
AD-954176.1	38.53	2.13	44.69	5.07	61.75	4.66	77.80	6.95
AD-954184.1	55.56	3.60	56.59	1.49	93.42	1.56	99.69	6.36
AD-954192.1	100.12	11.38	98.85	0.79	101.06	14.32	110.37	16.13
AD-954200.1	35.93	1.36	34.58	2.13	56.52	5.39	76.79	2.50
AD-954208.1	32.18	2.82	31.64	2.62	41.68	1.38	60.48	6.31
AD-954216.1	23.72	2.06	30.51	2.01	49.35	4.19	81.27	3.16
AD-954130.1	19.85	7.94	23.85	3.60	24.29	7.01	61.79	3.84
AD-954138.1	34.61	3.77	29.28	2.86	37.50	6.25	73.17	3.15
AD-954146.1	30.29	4.48	28.72	4.62	46.06	8.29	71.77	2.25
AD-954154.1	47.57	5.76	45.17	4.28	72.44	11.48	95.85	11.77
AD-954162.1	33.21	2.19	32.86	2.61	40.48	1.74	71.90	2.58
AD-954177.1	44.09	4.74	41.57	7.32	64.87	6.95	84.18	6.50
AD-954185.1	40.16	6.27	39.88	6.12	70.92	9.62	91.41	5.71
AD-954193.1	40.67	3.75	47.36	1.96	83.44	7.54	90.57	7.54
AD-954201.1	88.90	6.15	86.29	11.24	93.95	13.19	75.31	5.30
AD-954209.1	26.15	1.78	26.42	3.92	37.25	8.70	57.03	2.95
AD-954217.1	22.08	3.65	26.35	0.46	40.24	8.85	69.89	18.22
AD-954225.1	32.81	0.74	45.33	7.32	67.38	4.84	104.66	12.11
AD-954233.1	85.46	11.15	91.24	8.51	88.64	9.42	114.91	10.27
AD-954241.1	106.86	9.14	133.05	11.27	124.00	18.20	134.56	31.54

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining
AD-954249.1	33.83	3.03	45.04	2.16	54.32	8.90	81.13	9.45
AD-954257.1	49.77	2.63	61.84	7.61	88.87	28.12	120.76	4.78
AD-954264.1	30.81	1.88	45.45	4.97	58.79	10.96	101.10	11.20
AD-954272.1	32.73	1.95	45.08	6.85	62.03	12.19	93.98	8.23
AD-954280.1	106.62	3.67	133.82	8.30	110.97	16.89	132.84	13.83
AD-954288.1	73.24	7.83	76.91	15.22	90.96	13.48	129.55	12.49
AD-954296.1	30.93	3.59	35.55	5.19	51.27	11.72	78.93	5.41
AD-954218.1	26.56	3.53	28.97	3.37	38.53	8.13	64.10	5.89
AD-954226.1	50.34	3.59	44.04	3.70	51.26	4.10	91.30	6.11
AD-954234.1	90.21	10.40	88.98	6.99	76.60	10.14	100.15	8.01
AD-954242.1	82.30	7.82	103.00	6.33	101.96	16.94	130.97	9.81
AD-954250.1	44.08	4.85	54.36	3.62	66.86	18.27	105.59	6.63
AD-954258.1	64.12	7.04	69.51	4.38	71.00	14.41	107.71	8.55
AD-954265.1	44.56	2.69	69.05	0.84	77.32	15.12	119.63	11.20
AD-954273.1	39.40	2.40	59.31	2.24	71.10	15.25	115.15	7.40
AD-954281.1	43.61	1.85	62.18	5.17	77.33	10.83	119.66	11.64
AD-954289.1	120.87	10.51	152.02	7.08	119.60	23.43	135.41	10.87
AD-954297.1	30.95	3.35	35.55	3.32	49.47	8.36	85.22	10.09
AD-954219.1	47.42	7.81	43.53	4.97	46.70	4.05	84.71	15.02
AD-954227.1	31.72	1.76	36.01	1.47	50.93	2.68	97.43	10.60
AD-954235.1	61.17	5.15	68.18	6.27	77.19	8.53	108.81	3.40
AD-954243.1	30.31	5.06	40.81	5.97	36.38	3.93	56.86	6.40
AD-954251.1	50.50	4.90	60.15	2.62	65.56	11.90	110.36	11.58
AD-954259.1	29.29	1.64	42.87	2.90	48.94	2.60	86.86	2.56
AD-954266.1	58.75	2.34	79.79	6.51	85.54	17.99	119.76	12.98

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining
AD-954274.1	103.48	10.00	136.04	14.71	107.73	18.89	119.37	6.52
AD-954282.1	63.93	4.55	72.13	2.20	82.83	16.10	115.03	9.20
AD-954290.1	73.27	4.25	76.95	3.77	73.76	8.96	116.13	15.67
AD-954298.1	95.40	16.15	116.77	3.72	95.35	16.29	116.44	4.43
AD-954220.1	30.05	3.04	32.41	2.71	47.25	3.70	92.34	7.65
AD-954228.1	28.75	1.80	39.35	4.39	48.16	4.85	95.79	8.46
AD-954236.1	51.97	2.64	61.61	12.31	74.92	7.84	112.83	3.27
AD-954244.1	25.23	3.09	32.22	0.67	36.54	4.41	59.50	5.69
AD-954252.1	41.80	4.89	52.60	11.56	58.19	12.54	104.28	27.43
AD-954260.1	32.19	0.53	47.42	3.44	50.72	6.34	93.22	6.32
AD-954267.1	74.62	8.93	77.43	1.94	65.23	6.95	105.17	5.36
AD-954275.1	54.18	2.72	65.06	5.80	66.73	11.88	102.06	3.54
AD-954283.1	38.12	2.23	49.23	2.88	49.95	10.25	94.58	3.70
AD-954291.1	101.23	7.90	123.82	1.81	92.72	16.12	123.82	14.21
AD-954299.1	100.34	14.27	115.52	7.80	94.48	11.11	117.27	9.31
AD-954221.1	29.81	2.74	28.20	3.92	35.63	5.34	61.00	7.73
AD-954229.1	61.95	4.21	61.45	3.69	57.20	5.13	97.46	5.45
AD-954237.1	51.14	5.39	66.14	6.61	68.62	6.00	105.63	7.44
AD-954245.1	54.15	6.59	59.92	7.17	73.80	4.02	108.37	7.01
AD-954253.1	39.91	4.15	45.61	5.11	46.87	2.60	80.73	7.62
AD-954261.1	37.65	3.22	46.65	2.61	47.75	2.08	79.75	7.69
AD-954268.1	73.28	4.56	76.13	6.04	69.79	10.57	103.51	12.89
AD-954276.1	34.99	2.68	42.88	4.07	47.04	6.06	72.15	5.12
AD-954284.1	23.70	2.57	35.98	4.80	41.75	2.69	58.05	6.27
AD-954292.1	36.70	2.32	49.24	3.20	70.75	7.06	109.52	10.64

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining
AD-954300.1	95.58	13.44	116.85	15.24	98.47	15.60	109.57	8.11
AD-954222.1	34.43	4.82	31.52	4.46	46.36	3.69	83.27	9.62
AD-954230.1	24.15	0.70	28.87	2.68	35.78	9.17	61.15	3.50
AD-954238.1	52.45	3.33	52.94	7.85	52.93	8.19	96.17	6.44
AD-954246.1	37.41	4.41	48.17	3.67	61.41	5.39	113.20	7.83
AD-954254.1	54.05	4.03	59.72	10.49	58.06	5.78	93.76	3.73
AD-954262.1	45.38	4.69	46.22	3.64	50.32	4.42	76.36	8.74
AD-954269.1	47.10	2.89	66.30	3.54	81.45	12.33	114.12	6.38
AD-954277.1	48.62	4.99	66.89	3.79	79.00	10.51	104.56	14.40
AD-954285.1	66.27	6.04	98.18	9.60	90.64	17.39	111.14	9.29
AD-954293.1	40.39	6.73	53.53	1.35	66.11	4.95	87.61	6.50
AD-954301.1	104.24	15.65	129.65	11.46	95.00	13.31	115.12	10.56
AD-954223.1	48.53	3.41	47.89	9.69	63.25	5.62	97.14	11.15
AD-954231.1	60.66	5.40	71.72	4.73	77.55	2.90	103.25	6.93
AD-954239.1	34.51	1.10	39.17	2.39	52.21	8.96	91.15	6.20
AD-954247.1	22.02	2.03	28.16	1.36	36.99	6.62	59.18	8.13
AD-954255.1	25.12	2.48	30.60	1.38	42.70	4.95	57.04	5.98
AD-954263.1	41.04	6.36	50.36	4.59	61.31	3.42	100.72	5.62
AD-954270.1	79.14	6.00	74.55	10.12	80.65	13.01	100.52	4.78
AD-954278.1	55.56	5.50	57.02	2.83	62.72	9.15	93.46	7.86
AD-954286.1	73.12	6.19	92.01	5.10	87.34	10.06	105.80	7.29
AD-954294.1	72.37	6.17	78.67	6.17	78.62	18.09	97.60	4.71
AD-954302.1	96.95	14.38	109.14	8.35	98.40	19.02	109.36	7.78
AD-954224.1	46.96	10.54	45.56	7.22	64.07	6.38	88.53	29.17
AD-954232.1	58.45	18.51	60.74	11.61	72.28	3.88	103.49	3.84

	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining	SD	Duplex	Avg % HTT mRNA Remaining	SD	Avg % HTT mRNA Remaining
AD-954240.1	33.07	1.88	37.40	6.08	57.76	20.62	94.18	5.99
AD-954248.1	30.79	4.54	32.41	4.32	47.75	9.88	84.11	7.18
AD-954256.1	46.98	6.73	51.72	6.39	82.38	5.87	107.79	6.63
AD-954271.1	57.61	6.76	69.95	3.43	83.90	4.71	115.57	17.75
AD-954279.1	107.65	17.29	104.96	9.00	86.16	9.88	112.41	7.65
AD-954287.1	68.75	4.71	66.42	11.11	77.12	10.56	106.01	2.85
AD-954295.1	39.45	1.79	40.12	3.52	61.80	8.89	102.42	7.93

Table 19. HTT Single Dose Screens in BE(2)C Cells

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD
AD-1019439.1	26.33	2.98	33.43	1.95	44.24	3.94	69.16	16.03
AD-1019442.1	26.68	3.71	38.86	6.48	42.42	6.68	55.50	5.70
AD-1019438.1	26.88	5.41	33.28	10.09	38.25	3.40	64.16	11.54
AD-1019408.1	27.81	2.88	38.50	5.30	63.17	11.67	89.78	38.20
AD-1019426.1	28.13	3.88	39.70	14.47	53.66	23.30	64.65	30.16
AD-1019440.1	30.30	4.22	33.05	6.61	37.88	7.04	60.38	10.12
AD-1019410.1	31.80	4.96	32.53	10.80	50.70	8.85	89.25	55.87
AD-1019405.1	32.12	5.75	40.14	8.14	54.55	11.42	82.13	14.98
AD-1019422.1	32.13	2.02	42.46	5.75	51.78	2.68	67.56	3.76
AD-1019407.1	33.66	6.11	58.75	11.88	80.18	12.89	125.80	26.45

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD
AD-1019418.1	36.00	10.12	51.87	18.91	97.46	22.32	72.77	13.55
AD-1019436.1	36.32	3.03	43.89	2.64	60.54	5.29	72.72	8.47
AD-1019406.1	36.67	7.79	40.03	5.18	54.98	16.17	72.36	12.32
AD-1019417.1	37.43	9.80	34.14	9.23	47.79	12.90	60.93	25.48
AD-1019372.1	37.50	8.16	34.12	3.72	60.81	10.31	103.20	13.72
AD-1019375.1	37.69	9.79	34.46	6.10	49.56	5.83	66.26	5.42
AD-1019444.1	38.95	4.50	43.40	1.91	37.44	18.40	52.46	14.08
AD-1019448.1	39.20	2.03	42.53	9.51	54.64	8.72	66.41	8.54
AD-1019365.1	40.07	3.04	45.42	6.80	59.29	8.64	68.99	4.11
AD-1019374.1	40.28	3.07	33.44	4.95	52.85	8.36	66.91	6.58
AD-1019402.1	41.01	6.72	58.59	9.68	75.67	6.36	80.45	48.52
AD-1019441.1	43.13	4.88	42.11	20.87	49.84	11.29	83.77	30.02
AD-1019399.1	44.66	6.75	51.34	3.94	83.68	16.14	85.67	7.63
AD-1019378.1	45.39	6.11	41.34	1.35	64.43	5.63	87.98	16.23
AD-1019419.1	45.70	15.44	47.87	15.97	64.58	24.64	61.93	9.06
AD-1019423.1	46.12	3.60	50.83	12.67	59.80	7.57	78.49	12.61
AD-1019437.1	46.79	2.68	67.22	9.08	64.41	5.28	91.99	18.73
AD-1019376.1	47.24	5.85	45.27	11.35	48.36	7.08	66.50	11.13
AD-1019373.1	48.15	6.89	41.62	12.43	58.13	8.10	68.76	4.30
AD-1019435.1	52.61	4.27	52.59	14.30	71.50	18.95	83.12	30.00
AD-1019411.1	52.82	14.69	58.28	29.31	89.10	24.14	92.75	40.76
AD-1019434.1	53.94	4.86	57.33	16.85	69.25	9.85	73.47	12.55
AD-1019377.1	57.15	11.34	52.68	7.70	77.91	11.93	81.77	11.31
AD-1019412.1	62.07	14.20	88.99	17.66	102.97	21.58	84.96	13.92
AD-1019403.1	64.17	7.55	65.79	13.52	91.61	8.33	78.69	11.47

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD
AD-1019368.1	64.78	8.20	58.57	2.18	65.86	2.46	64.57	20.59
AD-1019404.1	64.98	13.39	89.42	25.45	92.10	13.45	84.96	32.65
AD-1019415.1	67.27	9.53	78.07	17.87	82.38	19.31	77.82	2.74
AD-1019421.1	69.68	26.22	66.48	16.26	88.04	26.99	80.85	17.61
AD-1019400.1	69.82	32.75	98.86	18.21	87.73	31.20	90.88	24.31
AD-1019450.1	70.95	8.42	66.87	9.62	60.36	4.15	74.24	7.35
AD-1019420.1	71.07	8.19	72.14	21.72	75.76	10.39	75.64	7.13
AD-1019429.1	77.16	3.18	90.72	8.30	85.69	8.68	76.60	9.44
AD-1019431.1	77.28	13.02	84.76	20.09	100.34	25.59	105.70	37.13
AD-1019428.1	77.77	17.48	97.53	47.95	103.57	36.26	80.54	9.56
AD-1019364.1	80.17	3.62	81.84	3.20	83.89	5.46	81.75	8.87
AD-1019413.1	80.67	7.77	80.97	20.54	88.80	7.99	119.10	30.63
AD-1019394.1	82.14	16.56	92.68	2.28	90.83	19.90	111.52	47.91
AD-1019398.1	82.85	6.81	97.08	13.06	91.52	2.80	71.62	2.97
AD-1019366.1	82.97	11.84	66.97	7.23	68.08	7.16	80.92	4.98
AD-1019432.1	83.34	10.98	64.39	6.32	64.34	3.93	69.63	8.62
AD-1019380.1	85.03	3.70	63.09	1.84	81.38	13.03	62.93	3.56
AD-1019382.1	85.70	14.67	75.64	7.28	78.99	5.79	87.44	19.58
AD-1019433.1	85.75	8.79	74.83	26.05	75.50	7.52	77.17	6.31
AD-1019424.1	86.03	27.07	111.91	28.13	114.99	40.63	94.47	25.23
AD-1019445.1	87.45	4.61	62.08	7.20	67.40	9.96	83.68	8.22
AD-1019369.1	88.75	2.36	81.44	4.07	80.67	3.48	84.85	6.30
AD-1019416.1	88.97	26.98	108.80	23.13	98.81	15.56	103.92	50.76
AD-1019414.1	89.03	31.13	88.38	23.35	102.76	22.08	76.13	4.19
AD-1019447.1	89.66	8.74	92.05	6.89	89.43	5.66	101.69	11.25

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD
AD-1019430.1	90.85	13.22	90.65	18.57	80.62	5.48	80.44	3.57
AD-1019395.1	91.51	12.21	111.33	32.95	113.73	28.10	127.67	17.84
AD-1019396.1	94.92	23.01	131.79	38.35	115.27	26.56	88.98	30.90
AD-1019425.1	95.56	39.01	125.04	41.22	107.52	38.03	73.18	10.07
AD-1019363.1	95.63	3.09	98.66	7.36	84.59	9.55	83.52	8.42
AD-1019367.1	96.44	1.76	78.39	11.85	79.42	8.52	74.82	4.01
AD-1019362.1	96.52	7.99	88.17	3.46	87.20	3.05	94.83	3.84
AD-1019379.1	96.93	11.61	73.07	12.46	98.79	10.34	104.71	43.49
AD-1019397.1	97.03	16.47	99.20	7.94	103.74	15.25	99.16	16.51
AD-1019392.1	97.50	22.45	111.56	11.32	138.55	20.34	162.41	22.14
AD-1019409.1	98.27	12.80	99.07	45.47	110.14	36.07	134.23	68.21
AD-1019361.1	101.31	14.87	88.47	3.31	83.03	9.78	86.55	9.54
AD-1019449.1	101.70	20.46	78.57	11.74	78.12	4.92	77.69	6.15
AD-1019385.1	101.87	13.51	98.46	12.91	131.69	33.41	115.89	43.86
AD-1019427.1	102.55	21.14	161.66	45.26	103.28	32.72	106.18	5.53
AD-1019390.1	105.47	9.42	92.76	10.07	90.93	13.19	86.69	17.46
AD-1019383.1	105.74	7.88	73.94	4.49	76.20	3.46	73.73	1.51
AD-1019401.1	105.91	15.85	122.03	11.39	137.21	26.94	109.80	41.71
AD-1019393.1	106.21	29.14	105.07	19.55	126.94	46.57	101.66	32.44
AD-1019370.1	106.28	18.22	82.52	11.42	84.49	11.58	76.24	3.39
AD-1019391.1	107.20	42.41	92.50	15.30	110.58	15.64	94.73	13.97
AD-1019446.1	107.77	12.57	91.32	14.53	78.41	9.44	83.59	12.05
AD-1019371.1	109.09	39.35	77.55	9.57	88.12	10.89	94.98	22.84
AD-1019386.1	109.52	12.16	106.26	21.94	124.32	16.83	147.23	17.76
AD-1019389.1	120.92	6.39	89.68	12.49	94.77	10.01	90.44	19.57

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD
AD-1019387.1	135.14	7.97	102.51	12.39	108.16	17.75	95.03	42.80
AD-1019381.1	142.40	16.59	86.79	21.01	106.55	17.10	86.46	17.57

Table 22. HTT Single Dose Screens in Hep3B Cells

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD
AD-1019427	138.10	1.80	106.69	9.66	110.69	6.95	82.33	1.04
AD-1019428	122.96	8.54	123.38	18.73	143.60	19.65	85.92	4.79
AD-1019429	159.97	25.69	127.20	20.43	169.69	7.54	102.37	11.52
AD-1019430	183.50	24.67	141.83	30.68	165.83	16.88	90.68	5.39
AD-1019431	122.49	13.91	99.24	19.93	134.14	12.03	82.93	2.70
AD-1019432	94.78	5.80	81.95	16.55	106.91	10.11	78.58	2.06
AD-1019433	85.34	8.81	70.69	7.49	99.44	9.50	78.06	6.13
AD-1019434	66.47	0.79	49.38	3.88	76.15	9.24	77.24	2.61
AD-1019435	106.08	23.50	77.75	10.92	88.27	2.79	104.29	24.58
AD-1019436	112.04	11.84	119.35	16.71	115.61	11.36	110.74	26.21
AD-1019437	139.88	16.93	130.38	10.92	134.78	14.02	117.90	19.13
AD-1019438	68.19	8.66	71.56	12.22	74.56	10.01	80.95	23.59
AD-1019439	62.16	6.48	50.77	5.23	81.31	7.53	84.51	12.58
AD-1019440	56.89	5.93	46.04	4.27	70.32	11.39	79.98	8.10
AD-1019441	70.06	5.54	42.12	4.50	89.04	2.93	82.56	7.31
AD-1019442	48.73	5.66	34.56	5.17	60.32	6.46	77.28	3.85
AD-1019444	103.32	16.53	71.56	8.89	90.43	14.68	110.64	14.14
AD-1019445	201.07	51.82	144.95	19.20	144.50	22.60	100.27	11.62
AD-1019446	191.30	81.87	137.09	38.39	191.26	8.82	158.08	19.82
AD-1019447	184.26	22.26	167.74	43.07	148.71	32.03	113.94	14.67
AD-1019448	99.85	6.52	75.18	11.48	128.40	10.49	121.88	27.56
AD-1019449	156.40	22.70	114.59	8.29	132.89	16.45	100.24	17.33
AD-1019450	161.29	65.73	92.49	15.35	119.28	11.41	93.35	4.75

Table 23. HTT Single Dose Screens in PCH Cells

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD
AD-1019427	101.37	9.26	156.06	40.24	138.20	35.12	140.07	40.07
AD-1019428	92.49	6.19	135.48	22.38	118.19	5.27	119.47	16.68
AD-1019429	98.97	6.65	131.39	12.98	130.93	6.30	128.81	26.81
AD-1019430	100.45	5.26	129.08	14.59	125.01	11.13	126.55	16.02
AD-1019431	98.21	8.32	145.07	10.68	127.63	7.57	141.36	10.73
AD-1019432	106.29	3.11	168.38	37.13	136.01	22.40	131.93	16.42
AD-1019433	102.70	8.23	161.01	12.53	139.06	5.13	145.64	6.63
AD-1019434	129.67	17.06	154.19	12.23	158.96	23.34	188.71	33.63
AD-1019435	104.54	9.16	131.00	4.95	106.67	10.72	107.91	15.44

AD-1019436	93.90	5.21	119.23	11.41	118.13	13.87	97.48	5.83
AD-1019437	100.62	5.20	119.08	14.80	134.47	18.41	109.63	9.43
AD-1019438	84.11	2.20	117.95	22.08	117.34	12.05	103.38	9.16
AD-1019439	98.67	3.66	135.71	12.20	124.13	7.31	135.45	7.08
AD-1019440	83.61	4.58	99.43	3.05	116.11	3.48	127.08	7.79
AD-1019441	82.45	4.43	137.14	12.07	119.26	6.58	130.27	3.07
AD-1019442	120.65	12.47	153.01	14.74	135.81	15.03	176.38	33.63
AD-1019444	97.66	4.03	120.60	17.75	103.85	6.35	103.97	10.02
AD-1019445	94.35	7.61	120.88	24.22	102.70	4.30	94.75	4.03
AD-1019446	92.74	4.59	107.26	12.05	114.16	5.03	95.74	4.00
AD-1019447	88.37	11.45	108.43	8.25	111.92	15.15	93.29	14.63
AD-1019448	45.33	4.67	62.29	8.67	101.08	7.47	94.82	8.72
AD-1019449	98.22	15.96	112.71	12.36	131.04	8.72	105.94	11.80
AD-1019450	85.07	15.81	97.62	10.72	107.02	2.92	127.99	8.39

Table 26. HTT Single Dose Screens in BE(2)C Cells

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD	Avg % HTT mRNA remaining	SD
AD-1019451	93.29	16.82	79.48	6.60	117.48	21.67	86.30	7.18
AD-1019452	99.01	13.04	95.58	11.01	108.44	12.82	96.63	5.59
AD-1019453	87.05	7.20	113.35	13.73	94.72	2.78	98.74	13.68
AD-1019454	119.73	25.89	106.85	10.68	98.62	4.77	103.14	10.90
AD-1019455	82.82	7.22	103.85	19.64	118.66	29.10	97.17	11.43
AD-1019456	130.50	23.39	97.94	18.86	98.21	6.84	105.81	7.47
AD-1019457	113.79	27.33	98.22	13.18	94.59	15.31	104.74	12.62
AD-1019458	105.55	18.22	81.42	3.46	95.90	9.68	97.59	10.26
AD-1019459	86.39	6.10	82.18	7.18	86.45	7.09	86.03	7.52
AD-1019460	86.54	26.91	73.97	4.97	89.26	22.30	87.31	2.77
AD-1019461	101.49	23.41	102.71	17.25	128.66	12.07	95.42	4.26
AD-1019462	91.96	6.71	107.73	16.29	112.32	21.80	88.42	4.11
AD-1019463	90.33	25.45	88.82	11.53	97.45	10.80	105.73	11.70
AD-1019464	96.47	8.69	105.84	6.30	107.74	8.91	92.45	2.58
AD-1019465	39.56	9.26	44.15	1.46	54.35	15.13	81.22	10.35
AD-1019466	73.77	16.43	58.74	8.97	71.43	15.68	82.76	3.09
AD-1019467	86.04	21.44	63.29	4.25	73.17	11.29	89.01	3.28
AD-1019468	37.14	2.38	40.49	8.69	46.65	3.92	76.47	6.65
AD-1019469	55.50	7.49	58.16	7.02	71.59	3.80	92.31	9.48
AD-1019470	30.87	5.33	42.49	5.00	49.71	8.12	84.22	9.04
AD-1019471	39.47	5.81	38.61	4.32	49.39	4.07	76.09	6.89
AD-1019472	36.94	6.56	38.58	5.74	59.19	9.03	92.89	15.63
AD-1019473	44.28	4.57	41.08	5.92	58.70	14.41	96.29	18.47
AD-1019474	23.10	2.15	26.69	3.41	47.74	11.81	58.58	8.93

AD-1019475	79.15	38.02	75.33	20.13	78.21	15.30	96.03	6.92
AD-1019476	29.76	0.61	34.60	6.18	36.90	9.22	61.84	4.44
AD-1019477	32.07	3.21	37.52	1.42	50.16	16.87	88.20	6.09
AD-1019478	35.78	6.14	46.00	8.07	56.02	5.51	93.58	9.49
AD-1019479	82.43	14.10	79.61	12.60	79.91	1.40	90.84	6.32
AD-1019480	73.10	10.82	64.04	5.81	76.54	2.46	88.44	4.59
AD-1019481	61.17	5.75	50.82	2.01	61.45	4.92	83.66	18.29
AD-1019482	37.37	4.04	46.32	5.39	65.74	8.11	86.94	5.01
AD-1019483	38.58	7.74	36.51	3.09	52.26	5.18	77.39	6.67
AD-1019484	24.49	2.05	30.55	2.75	35.81	8.29	66.74	4.82
AD-1019485	28.44	1.78	32.61	4.65	37.42	6.84	60.91	7.85
AD-1019486	46.24	9.01	45.45	5.18	53.16	7.81	76.82	2.97
AD-1019487	39.72	7.09	41.07	5.67	53.60	9.86	79.86	4.54
AD-1019488	49.71	3.57	45.89	6.61	52.78	5.90	82.82	17.59
AD-1019489	39.41	10.74	30.19	5.45	46.89	3.86	66.60	15.82
AD-1019491	37.54	2.60	38.78	4.86	61.14	10.96	84.32	10.33

Table 31. HTT Single Dose Screens in BE(2)C Cells

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % HTT mRNA remaining**	**SD**	**Avg % HTT mRNA remaining**	**SD**	**Avg % HTT mRNA remaining**	**SD**	**Avg % HTT mRNA remaining**	**SD**
AD-1255829.1	42.96	5.68	43.85	2.29	66.98	1.37	87.40	4.66
AD-1289804.1	51.24	11.22	49.88	3.32	74.10	3.11	112.44	7.55
AD-1255847.1	56.33	5.48	53.42	4.55	73.16	9.69	86.04	11.02
AD-1255846.1	60.91	8.58	54.43	5.62	76.71	5.58	88.90	9.21
AD-1255842.1	71.67	8.66	57.02	6.91	82.51	3.37	88.66	8.57
AD-1255826.1	63.03	13.87	61.10	6.07	81.42	7.45	106.67	5.54
AD-1255828.1	58.25	8.33	61.99	2.58	62.19	9.96	95.71	14.52
AD-1255844.1	77.81	19.83	62.45	3.32	93.71	5.93	94.62	11.51
AD-1289792.1	63.07	19.66	62.71	7.40	70.83	2.95	97.30	8.23
AD-1255825.1	61.98	11.14	62.99	5.30	82.22	8.57	113.33	9.73
AD-1255822.1	54.95	8.25	63.21	7.99	73.10	6.20	94.27	7.33
AD-1255839.1	79.41	19.00	63.82	10.25	78.93	6.77	92.85	7.99
AD-1255827.1	66.37	7.51	66.77	10.38	76.46	6.28	93.56	8.78
AD-1255824.1	70.91	12.73	67.84	12.01	79.52	3.88	104.18	6.96
AD-1255845.1	71.58	5.96	68.53	5.24	99.80	7.33	102.28	15.66
AD-1255830.1	55.81	5.08	72.00	4.27	85.56	3.31	107.28	6.84
AD-1289806.1	73.43	5.18	76.80	10.37	92.52	7.68	102.29	4.29
AD-1255836.1	124.80	23.77	81.79	12.98	107.34	3.39	93.98	7.73
AD-1289807.1	77.24	10.72	87.68	14.15	82.46	0.99	99.67	4.22
AD-1289805.1	88.02	4.90	90.31	4.52	97.27	3.91	121.40	4.20
AD-1255840.1	105.83	14.38	90.46	4.13	80.88	15.34	82.60	12.65
AD-1289808.1	122.86	14.70	92.14	2.12	102.50	3.56	96.30	8.50

AD-1289800.1	76.52	4.81	93.52	5.12	90.00	4.51	95.56	2.21
AD-1255838.1	89.17	8.94	93.90	18.11	108.49	11.18	94.09	9.61
AD-1255843.1	107.35	9.98	93.92	6.81	109.57	7.77	93.99	4.85
AD-1255837.1	117.27	34.77	93.96	7.45	98.71	18.19	100.51	7.76
AD-1255833.1	99.27	6.98	94.69	17.28	101.75	10.49	88.41	2.89
AD-1289797.1	80.55	6.78	98.81	6.21	74.29	18.16	104.59	7.71
AD-1255823.1	105.66	24.48	98.93	13.66	86.06	9.79	100.05	8.60
AD-1289810.1	92.87	20.76	100.62	6.60	97.46	4.56	122.30	16.77
AD-1289811.1	93.41	6.43	102.94	1.79	96.52	6.13	98.20	6.21
AD-1289812.1	90.48	4.72	104.24	15.15	83.21	3.00	96.73	22.75
AD-1255841.1	101.07	13.00	104.75	7.36	100.13	18.24	96.25	9.73
AD-1289799.1	91.60	17.43	104.76	10.87	85.06	17.47	85.10	10.35
AD-1255834.1	125.74	10.44	106.54	6.84	94.34	21.58	97.11	4.22
AD-1289809.1	124.27	17.95	108.22	12.24	99.43	0.97	103.04	5.39
AD-1289801.1	98.11	7.63	109.29	5.74	98.62	7.63	111.41	15.08
AD-1289793.1	98.72	9.25	110.46	9.91	116.62	26.19	103.92	5.03
AD-1289798.1	94.79	16.26	110.50	7.33	88.92	11.12	104.76	15.05
AD-1289796.1	81.94	6.56	110.65	15.00	87.24	7.53	121.12	19.77
AD-1289803.1	109.67	9.57	115.61	26.44	88.09	26.87	110.34	2.77
AD-1255835.1	97.25	6.52	116.18	25.86	102.10	12.39	101.26	5.04
AD-1289802.1	99.88	5.45	122.93	13.24	98.52	8.59	115.30	12.06
AD-1289794.1	86.59	6.59	130.53	22.85	95.85	8.83	118.93	12.22
AD-1289795.1	92.81	12.98	132.84	25.18	101.37	16.37	108.22	9.88

Table 34. HTT Single Dose Screens in BE(2)C Cells

	50 nM		10 nM		1 nM		0.1 nM	
Duplex	**Avg**	**SD**	**Avg**	**SD**	**Avg**	**SD**	**Avg**	**SD**
AD-1289928.1	26.86	1.60	19.55	4.52	22.39	2.15	24.14	1.37
AD-1289833.1	23.91	3.07	17.68	4.58	23.55	2.74	27.27	2.74
AD-1289929.1	23.77	2.47	15.37	2.70	24.10	4.62	24.65	2.18
AD-1289927.1	27.09	5.65	18.06	2.62	24.84	1.66	28.64	2.32
AD-1289826.1	25.34	2.46	16.35	1.53	25.52	5.56	25.98	2.57
AD-1289831.1	30.21	1.67	36.35	7.86	26.09	3.74	30.90	2.30
AD-1289925.1	25.68	4.12	20.60	4.16	27.36	3.07	39.34	7.40
AD-1289824.1	32.57	4.27	38.34	6.20	29.00	2.92	34.38	5.30
AD-1289832.1	32.44	3.57	35.65	5.85	29.89	2.64	37.93	10.68
AD-1289825.1	39.83	17.90	26.65	9.54	30.69	2.01	34.00	4.25
AD-1289852.1	29.07	4.82	35.54	5.97	30.92	7.56	49.11	2.59
AD-1289867.1	28.36	2.80	31.88	7.37	31.98	12.26	56.00	5.83
AD-1289924.1	26.70	1.03	24.41	1.78	32.66	3.15	39.48	5.92
AD-1289853.1	34.66	4.96	28.99	3.10	35.62	5.35	47.55	8.03
AD-1289860.1	30.85	1.81	33.63	6.59	36.85	9.35	47.87	13.74
AD-1289931.1	27.24	1.71	29.84	4.12	36.93	5.95	52.53	23.19
AD-1289926.1	20.74	1.73	21.36	3.76	37.21	10.19	33.30	5.90
AD-1289851.1	29.04	4.65	46.37	10.68	37.41	7.70	59.15	8.97
AD-1289930.1	28.14	3.09	27.85	5.73	37.82	7.73	51.47	21.21
AD-1289859.1	32.10	2.80	36.95	3.88	39.64	2.26	51.16	3.87
AD-1289932.1	38.64	15.28	32.51	2.70	40.87	5.61	57.50	9.85

	50 nM		10 nM		1 nM		0.1 nM	
Duplex	**Avg**	**SD**	**Avg**	**SD**	**Avg**	**SD**	**Avg**	**SD**
AD-1019405.3	32.37	3.41	27.02	4.04	40.92	2.74	27.48	2.39
AD-1289861.1	28.13	4.06	21.27	3.46	41.31	5.09	49.50	12.59
AD-1107447.5	37.70	10.79	43.44	9.88	41.46	7.19	49.31	3.36
AD-1289948.1	30.97	2.76	40.28	4.17	41.80	7.23	66.69	15.51
AD-1289864.1	29.78	3.77	39.21	7.89	42.69	5.07	89.93	14.78
AD-1289913.1	31.72	5.80	34.84	8.88	42.95	10.68	73.21	7.08
AD-1289923.1	59.24	10.74	39.10	6.46	45.24	7.48	32.36	10.02
AD-1289921.1	53.68	1.92	58.15	6.99	45.73	4.52	65.30	17.40
AD-1289865.1	31.87	5.72	40.91	4.15	45.75	10.10	79.13	17.89
AD-1107442.5	32.33	6.49	43.54	11.06	46.70	8.32	64.81	14.58
AD-1289830.1	42.03	13.79	33.46	8.03	46.86	4.86	59.66	10.81
AD-1289866.1	36.51	6.26	41.19	8.95	46.89	11.53	71.88	7.53
AD-1289947.1	38.31	1.99	49.21	5.64	48.00	8.18	83.10	17.67
AD-1289933.1	32.81	4.00	35.67	2.53	48.04	7.15	69.06	9.73
AD-1289950.1	27.26	3.33	34.49	6.62	48.53	8.09	69.57	3.80
AD-1289868.1	30.84	5.79	42.94	4.23	52.80	8.22	61.31	3.51
AD-1289946.1	46.68	5.83	46.28	8.49	54.50	7.35	68.13	7.41
AD-1289960.1	35.30	1.65	35.68	3.55	54.94	9.28	65.79	5.26
AD-1289956.1	27.84	2.18	36.44	6.74	55.13	12.30	71.89	7.68
AD-1289827.1	28.82	5.84	29.88	4.99	55.28	10.84	52.68	11.79
AD-1289829.1	40.71	2.43	53.32	13.95	56.16	7.42	85.09	20.29
AD-1289850.1	68.59	4.01	72.52	15.97	58.55	10.21	83.76	7.50
AD-1289945.1	59.40	11.93	40.74	8.64	59.54	12.43	76.72	22.59
AD-1289835.1	37.25	4.53	52.77	8.52	60.32	12.83	112.64	25.83
AD-1289828.1	39.08	9.24	50.27	6.14	60.38	8.94	85.28	13.09
AD-1289949.1	48.48	15.67	46.75	6.41	60.71	7.90	74.31	4.00
AD-1289871.1	31.65	7.54	50.42	4.81	60.78	10.75	76.82	20.33
AD-1289914.1	31.82	1.51	36.43	2.73	60.93	9.49	76.70	18.34
AD-1289911.1	36.55	3.76	52.21	4.79	61.12	6.82	96.29	13.51
AD-1289857.1	37.65	1.30	54.22	7.43	62.08	12.37	112.67	7.11
AD-1289944.1	41.93	6.76	38.97	6.75	62.30	6.63	103.47	5.76
AD-1289957.1	28.01	4.91	33.18	4.70	63.87	9.58	81.23	11.07
AD-1289955.1	35.33	2.36	39.61	7.12	64.57	6.39	83.55	12.05
AD-1289834.1	38.03	15.96	41.29	5.72	66.11	14.38	70.25	14.42
AD-1289855.1	47.03	10.61	45.38	6.17	66.56	9.83	113.47	25.72
AD-1019402.3	51.50	11.45	78.69	14.18	67.31	12.68	108.20	11.66
AD-1289954.1	53.07	5.81	56.54	15.91	69.08	10.97	81.29	11.70
AD-1289920.1	59.99	6.29	76.06	5.44	72.04	7.85	83.88	18.77
AD-1019426.3	35.72	4.46	39.52	5.34	72.10	11.86	105.24	4.97
AD-1289862.1	35.67	5.88	38.24	6.53	72.61	22.46	94.79	2.43
AD-1289854.1	49.03	11.42	48.86	5.36	73.01	13.83	88.95	28.52
AD-1289914.2	30.03	5.23	33.37	2.93	73.79	12.67	88.84	7.72
AD-1289915.1	51.74	11.74	41.21	11.76	74.00	18.84	103.91	17.51
AD-1107449.5	41.89	7.53	42.32	2.51	74.27	4.96	117.23	13.14
AD-1289870.1	48.95	10.27	49.15	12.60	74.52	14.88	105.14	20.17
AD-1289953.1	35.31	3.01	45.74	4.87	74.71	7.89	107.34	16.59
AD-1107451.5	48.67	4.47	55.46	6.57	76.65	14.88	114.80	16.96
AD-1289961.1	52.85	13.96	49.17	9.57	77.13	6.98	84.90	17.73
AD-1289951.1	31.47	8.60	45.99	5.14	77.78	9.98	102.83	16.18
AD-1289915.2	37.75	9.20	40.82	2.69	79.15	10.39	99.07	23.10
AD-1289912.1	82.10	12.60	95.77	23.45	79.51	11.95	88.10	11.79
AD-1289958.1	49.85	10.86	43.74	4.02	79.96	21.58	106.79	13.72
AD-1289869.1	41.54	14.67	48.99	10.01	81.83	10.93	95.34	11.88
AD-1289916.2	38.11	12.11	30.92	6.77	83.06	27.70	89.95	11.93
AD-1289858.1	77.51	8.31	98.31	11.66	83.94	4.52	88.77	13.74
AD-1289789.1	57.63	5.94	59.15	10.78	86.59	17.72	91.84	14.11

	50 nM		10 nM		1 nM		0.1 nM	
Duplex	**Avg**	**SD**	**Avg**	**SD**	**Avg**	**SD**	**Avg**	**SD**
AD-1255821.1	69.16	8.85	82.13	11.58	89.11	12.53	97.77	12.97
AD-1289959.1	42.26	5.22	40.42	4.96	90.44	16.55	71.09	18.49
AD-1289790.1	73.58	9.37	78.35	21.25	90.71	28.57	82.85	26.71
AD-1289952.1	52.77	12.63	56.28	12.30	94.30	5.79	131.73	12.58
AD-1289791.1	74.62	17.99	119.43	34.26	99.39	20.30	98.65	23.07
AD-1289922.1	83.30	14.91	69.35	9.41	100.96	15.26	98.87	18.45
AD-1289919.1	84.61	7.92	93.30	16.27	100.99	12.77	98.84	16.16
AD-1289916.1	51.67	8.05	54.39	2.65	102.21	17.34	146.47	25.74
AD-1289863.1	96.63	15.42	129.19	8.00	146.62	21.26	154.53	20.81

Example 2. HTT *in vivo* screen using RNAi agents targeting HTT exon1 – AAV

Duplexes of interest targeting HTT exon 1, identified from the above *in vitro* studies, were evaluated *in vivo*.

In particular, at pre-dose day -14 wild-type mice (C57BL/6) were transduced by retororbital administration of 2 x 10^{10} viral particles of an adeno-associated virus 8 (AAV8) vector encoding a portion of wild type human HTT. Exemplary AAV vectors are provided in the Table below.

Construct	**Region**	**Start**	**End**	**Insert (bp)**	**Length (bp)**
AAV1	5' UTR+ORF	1	2655	200	2855
AAV2	ORF	2656	5310	200	2855
AAV3	ORF	5311	7965	200	2855
AAV4	ORF+3'UTR	7966	10820	-	2855
AAV5	3'UTR	10821	13475	200	2855

In this experiment, mice were administered an AAV8 encoding a portion of wild-type HTT (AAV1).

At day 0, groups of three mice were subcutaneously administered a single 3 mg/kg dose of the agents of interest or PBS control. At day 14 post-dose animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen. Tissue mRNA was extracted and analyzed by the RT-QPCR method. Human HTT mRNA levels were compared to housekeeping gene GAPDH. The values were then normalized to the average of AAV control group. The data were expressed as percent of baseline value, and presented as mean ± standard deviation. The results, shown in **FIGS. 1** and **2**, demonstrate that the exemplary duplex agents tested effectively reduce the level of the human HTT messenger RNA *in vivo*.

Example 3. HTT *in vivo* screen with RNAi agents targeting HTT Exon1

Duplexes of interest targeting exon 1 of human HTT were evaluated in an art-recognized mouse model of Huntington disease (HD), the YAC128 mouse model of HD. YAC128 mice harbor a yeast artificial chromosome (YAC) containing the entire human HD gene containing 128 CAG repeats in their genomes. YAC128 mice develop motor abnormalities and age-dependent brain atrophy including cortical and striatal atrophy associated with striatalneuronal loss. YAC128 mice exhibit initial hyperactivity, followed by the onset of a motor deficit and finally hypokinesis (see, *e.g.*, Slow, *et al.* (2003) *Human Molecular Genetics* 12(13):1555; Van Raamsdonk, *et al.* (2005), 2 *Human Molecular Genetics* 14(24):3823; and Carroll, *et al.* (2011) *Neurobiology of Disease* 43:257–265).

At Day 0, YAC128 mice (7-13 weeks of age, 27.7 ± 3.4 grams, n=36) were subcutaneously administered a single 10 mg/kg dose of the agents of interest or PBS control. At day 7 post-dose, animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen. Liver mRNA was extracted and analyzed by the RT-QPCR method.

The effect of these agent on full-length wild-type human HTT mRNA is shown in **FIG. 3A**. These data demonstrate that the exemplary duplex agents tested effectively reduce the level of the human HTT messenger RNA *in vivo*.

Human mutant HTT protein levels were determined using Western Blot analysis.

Briefly, livers were homogenized in RIPA buffer along with protease inhibitors. Total protein was quantified using Pierce BCA kit following manufacturer's instructions. Eighty µg of total cell lysates were denatured by boiling in 4x LDS buffer and were subjected to SDS-PAGE in a 3-8% tris acetate gradient gel and transferred to PVDF membranes. The blots were blocked with Odyssey blocking buffer for 1 hour at room temperature and hybridized to specific antibodies overnight at 4°C. The following antibodies were used: HTT (Millipore, Catalog #MAB2166), Calnexin (Millipore-Sigma, catalog # C4731, Fluorescence conjugated secondary antibodies (Licor, Goat anti-rabbit, Catalog #926–32211 and Donkey anti-mouse, Catalog #926–680721:5000). Detection of protein bands was carried out using the Biorad Chemidoc MP Imaging system. The density of each HTT band was normalized to Calnexin loading control and the normalized intensities were used to quantify HTT knockdown in siRNA treated samples relative to vehicle (1X PBS) treated controls.

The effect of these agents on mutant human HTT protein levels is shown in **FIGS. 3B-3C**. These data demonstrate that the exemplary duplex agents tested effectively reduce the level of the full-length wild-type human HTT messenger RNA **(FIG. 3A)** as well as mutant human HTT protein *in vivo*.

In another set of experiments, YAC128 mice (7-13 weeks of age, 27.7 ± 3.4 grams, n=36) were subcutaneously administered a single 10 mg/kg dose of the agents of interest or PBS control at Day 0. At day 7 post-dose, animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen. Liver mRNA was extracted and analyzed by the RT-QPCR method.Full-length mutant HTT mRNA levels and full-length mutant HTT protein levels were analyzed as described

above. The results are shown in **FIGS. 4A-4B** and demonstrate that the exemplary duplex agents tested effectively reduce the level of the mutant human HTT protein *in vivo*.

Additional duplexes of interest targeting exon 1 of human HTT were also assessed for the ability to inhibit human full-length wild-type HTT expression *in vivo* in mice of varying ages and weights. Specifically, at Day 0, mice (10-16 week of age, 28.2 ± 3.7 grams, n=84) were subcutaneously administered a single 10 mg/kg dose of the agents of interest or PBS control. At day 7 post-dose, animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen. Liver mRNA was extracted and analyzed by the RT-QPCR method.

Full-length wild-type human HTT mRNA levels were measured as described herein, and the results are shown in **FIG. 5** and demonstrate that the exemplary duplex agents tested effectively reduce the level of the full-lenth wild-type human HTT mRNA *in vivo*.

Example 4. Structural Activity Relationship Analysis

Duplexes of interest targeting exon 1 of human HTT were selected for further structural activity relationship (SAR) analysis and assessed for the ability to inhibit mutant HTT expression *in vivo*.

Specifically, at Day 0, YAC128 mice (6-9 weeks of age, n=4 per group) were subcutaneously administered a single 10 mg/kg dose of the agents of interest or PBS control. At day 7 post-dose, animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen. Liver mRNA was extracted and analyzed by the RT-QPCR method.

FIG. 6 shows the effect of these agents on full-length mutant human HTT mRNA levels and full-length mutant human protein levels. The data demonstrate that the agents inhibit expression of mutant exon 1 of human HTT and full-length mutant human HTT mRNA and full-length human protein *in vivo*.

Additional duplexes of interest were also assessed in YAC128 mice (6 weeks of age, n=4 per group). At Day 0, mice were subcutaneously administered a single 10 mg/kg dose of the agents of interest or PBS control. At day 7 post-dose, animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen. Liver mRNA was extracted and analyzed by the RT-QPCR method.

FIG. 7 shows the effect of these agents on full-length mutant human HTT mRNA levels.

Example 5. *In Vitro* Screen in Human HD Patient Fibroblasts.

The effect of duplexes of interest on the expression of full-length wild type human HTT and full-length mutant HTT was also assessed in human fibroblasts. Fibroblasts were obtained from Coriell, adult healthy control patient (”Control”, GM02153), an HD patient with adult disease onset (“Adult”, GM04478”) and an HD patient with juvenile disease onset (”Juvenile”, GM09197”). Fibroblasts were transfected with either 10 nM or 50 nM of duplexes targeting exon 1 of the HTT gene or the full length HTT gene.

The results are shown in **FIGS. 8A-8B, FIGS. 9A-9B, FIGS. 10A-10D** and **FIGS. 11A-11D** and demonstrate that the agents targeting exon 1 of the HTT gene or the full length HTT gene inhibit expression of the full-length mutant human HTT mRNA in patient samples *in vitro*.

Example 6. HTT *in vivo* screen with RNAi agents targeting full length human HTT

Duplexes of interest targeting full length human HTT, identified from the above *in vitro* studies, were evaluated *in vivo* using both the YAC128 mouse model and the AAV approaches, as described herein.

At pre-dose day -14 wild-type mice (C57BL/6, 7-13 weeks of age, 27.7 ± 3.4 grams, n=36) were transduced by retro-orbital administration of 2 x 10^{10} viral particles of an adeno-associated virus 8 (AAV8) vector encoding a portion of human HTT, including AAV1, AAV2, AAV3, or AAV4, as described in Example 2 above.

At Day 0, the transduced mice and YAC128 mice were subcutaneously administered a single 3 mg/kg or a 10 mg/kg dose of the agents of interest or PBS control. At Day 7 or Day 14 post-dose, animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen. Liver mRNA was extracted and analyzed by the RT-QPCR method.

As shown in **FIG 12**, the agents inhibit expression of full-length human HTT or full-length mutant human HTT mRNA *in vivo* using both experimental models.

Additional duplexes of interest targeting full-length human HTT were also assessed for their ability to inhibit wild-type human HTT *in vivo*.

At pre-dose day -14 wild-type mice (C57BL/6, 7-13 weeks of age, 27.7 ± 3.4 grams, n=36) were transduced by intravenous administration of 2 x 10^{10} viral particles of AAV1, AAV2, AAV3, or AAV4 (see Table above in Example 2).

At Day 0, the transduced mice were subcutaneously administered a single 3 mg/kg dose of the agents of interest or PBS control. At Day 14 post-dose, animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen. Liver mRNA was extracted and analyzed by the RT-QPCR method.

As shown in **FIGS. 13A-13D**, the agents inhibit expression of full-length wild-type human HTT mRNA *in vivo* and numerous duplexes targeting full-length human HTT transcript were determined to have an efficacy of greater than 90%.

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Huntingtin (HTT), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 6, and

wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one of the sense strand or the antisense strand.

2. The dsRNA agent of claim 1, wherein the nucleotide sequence of the sense strand comprises any one of the sense strand nucleotide sequences in any one of Tables 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 or 33.

3. The dsRNA agent of claim 1 or 2, wherein the lipophilic moiety is conjugated *via* a linker or a carrier.

4. A double stranded ribonucleic acid (dsRNA) 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 an mRNA encoding HTT, 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, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 or 33.

5. The dsRNA agent of claim 4, wherein the sense strand, the antisense strand, or both the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

6. The dsRNA agent of claim 5, wherein the lipophilic moiety is conjugated to one or more internal positions in the double stranded region of the dsRNA agent.

7. The dsRNA agent of claim 5 or 6, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on the antisense strand.

8. The dsRNA agent of claim 5 or 6, 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.

9. The dsRNA agent of any one of claims 1-3 and 5-8, wherein lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

10. The dsRNA agent of any one of claims 1-3 and 5-9, 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.

11. The dsRNA agent of claim 10, wherein the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

12. The dsRNA agent of any one of claims 1-3 and 7-11, wherein the internal positions include all positions except the terminal two positions from each end of the sense strand or the antisense strand.

13. The dsRNA agent of claim 12, wherein the internal positions include all positions except the terminal three positions from each end of the sense strand or the antisense strand.

14. The dsRNA agent of any one of claims 1-3 and 5-13, wherein the internal positions exclude a cleavage site region of the sense strand.

15. The dsRNA agent of claim 14, wherein the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.

16. The dsRNA agent of claim 14, wherein the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.

17. The dsRNA agent of any one of claims 1-3 and 5-13, wherein the internal positions exclude a cleavage site region of the antisense strand.

18. The dsRNA agent of claim 17, wherein the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.

19. The dsRNA agent of any one of claims 1-3 and 5-18, 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.

20. The dsRNA agent of any one of claims 1-3 and 5-19, 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.

21. The dsRNA agent of claim 20, 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.

22. The dsRNA agent of claim 6, wherein the positions in the double stranded region exclude a cleavage site region of the sense strand.

23. The dsRNA agent of any one of claims 1-3 and 5-22, 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.

24. The dsRNA agent of any one of claims 5-22, 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.

25. The dsRNA agent of any one of claims 1-3 and 5-24, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

26. The dsRNA agent of claim 25, 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.

27. The dsRNA agent of claim 26, 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.

28. The dsRNA agent of claim 27, wherein the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

29. The dsRNA agent of claim 28, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

30. The dsRNA agent of claim 29, wherein the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

31. The dsRNA agent of any one of claims 1-3 and 5-30, 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.

32. The dsRNA agent of claim 31, 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.

33. The dsRNA agent of any one of claims 1-3 and 5-32, 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.

34. The double-stranded iRNA agent of any one of claims 1-3 and 5-33, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

35. The dsRNA agent of any one of claims 1-34, wherein the dsRNA agent comprises at least one modified nucleotide.

36. The dsRNA agent of claim 35, 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

37. The dsRNA agent of claim 35, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

38. The dsRNA agent of any one of claims 35-37, 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 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, 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.

39. The dsRNA agent of claim 38, 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.

40. The dsRNA of claim 38, 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.

41. The dsRNA of claim 38, wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification.

42. The dsRNA of claim 41, 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).

43. The dsRNA agent of claim 38, wherein the modified nucleotide comprises a short sequence of 3'-terminal deoxy-thymine nucleotides (dT).

44. The dsRNA agent of claim 38, wherein the modifications on the nucleotides are 2'-O-methyl, GNA and 2'fluoro modifications.

45. The dsRNA agent of any one of claims 1-44, further comprising at least one phosphorothioate internucleotide linkage.

46. The dsRNA agent of claim 45, wherein the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

47. The dsRNA agent of any one of claims 1-45, wherein each strand is no more than 30 nucleotides in length.

48. The dsRNA agent of any one of claims 1-47, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

49. The dsRNA agent of any one of claims 1-47, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

50. The dsRNA agent of any one of claims 1-49, wherein the double stranded region is 15-30 nucleotide pairs in length.

51. The dsRNA agent of claim 50, wherein the double stranded region is 17-23 nucleotide pairs in length.

52. The dsRNA agent of claim 50, wherein the double stranded region is 17-25 nucleotide pairs in length.

53. The dsRNA agent of claim 50, wherein the double stranded region is 23-27 nucleotide pairs in length.

54. The dsRNA agent of claim 50, wherein the double stranded region is 19-21 nucleotide pairs in length.

55. The dsRNA agent of claim 50, wherein the double stranded region is 21-23 nucleotide pairs in length.

56. The dsRNA agent of any one of claims 1-55, wherein each strand has 19-30 nucleotides.

57. The dsRNA agent of any one of claims 1-55, wherein each strand has 19-23 nucleotides.

58. The dsRNA agent of any one of claims 1-55, wherein each strand has 21-23 nucleotides.

59. The dsRNA agent of any one of claims 1-58, further comprising a targeting ligand that targets a liver tissue.

60. The dsRNA agent of claim 59, wherein the targeting ligand is a GalNAc conjugate.

61. The dsRNA agent of any one of claims 1-3 and 5-60, 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.

62. The dsRNA agent of any one of claims 1-3 and 5-61, 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.

63. The dsRNA agent of any one of claims 1-62 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.

64. The dsRNA agent of any one of claims 1-62 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.

65. The dsRNA agent of any one of claims 1-62 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.

66. The dsRNA agent of any one of claims 1-62 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.

67. The dsRNA agent of any one of claims 1-62 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.

68. The dsRNA agent of any one of claims 1-67, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

69. The dsRNA agent of claim 68, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

70. The dsRNA agent of any one of claims 1-69, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

71. The dsRNA agent of any one of claims 1-70, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

72. A cell containing the dsRNA agent of any one of claims 1-71.

73. A pharmaceutical composition for inhibiting expression of a gene encoding HTT, comprising the dsRNA agent of any one of claims 1-71.

74. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-71 and a lipid formulation.

75. 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 1-71, or the pharmaceutical composition of claim 73 or 74; 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.

76. The method of claim 75, wherein the cell is within a subject.

77. The method of claim 76, wherein the subject is a human.

78. The method of any one of claims 75-77, wherein the expression of HTT is inhibited by at least 50%.

79. The method of claim 77, wherein the subject has been diagnosed with a HTT-associated disease.

80. The method of claim 79, wherein the nucleotide repeat expansion disease is Huntington's disease.

81. 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 dsRNA agent of any one of claims 1-71, or the pharmaceutical composition of claim 73 or 74, thereby treating the subject.

82. The method of claim 81, wherein treating comprises amelioration of at least on sign or symptom of the disease.

83. The method of claim 81, where treating comprises prevention of progression of the disease.

84. The method of claim 81, wherein the HTT-associated disease is Huntington's disease.

85. The method of any one of claims 81-84, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

86. The method of any one of claims 81-85, wherein the dsRNA agent is administered to the subject intrathecally.

87. The method of any one of claims 81-86, further comprising measuring a level of HTT in a sample obtained from the subject.

88. The method of any one of claims 81-87, further comprising administering to the subject an additional agent suitable for treatment or prevention of an HTT-associated disorder.

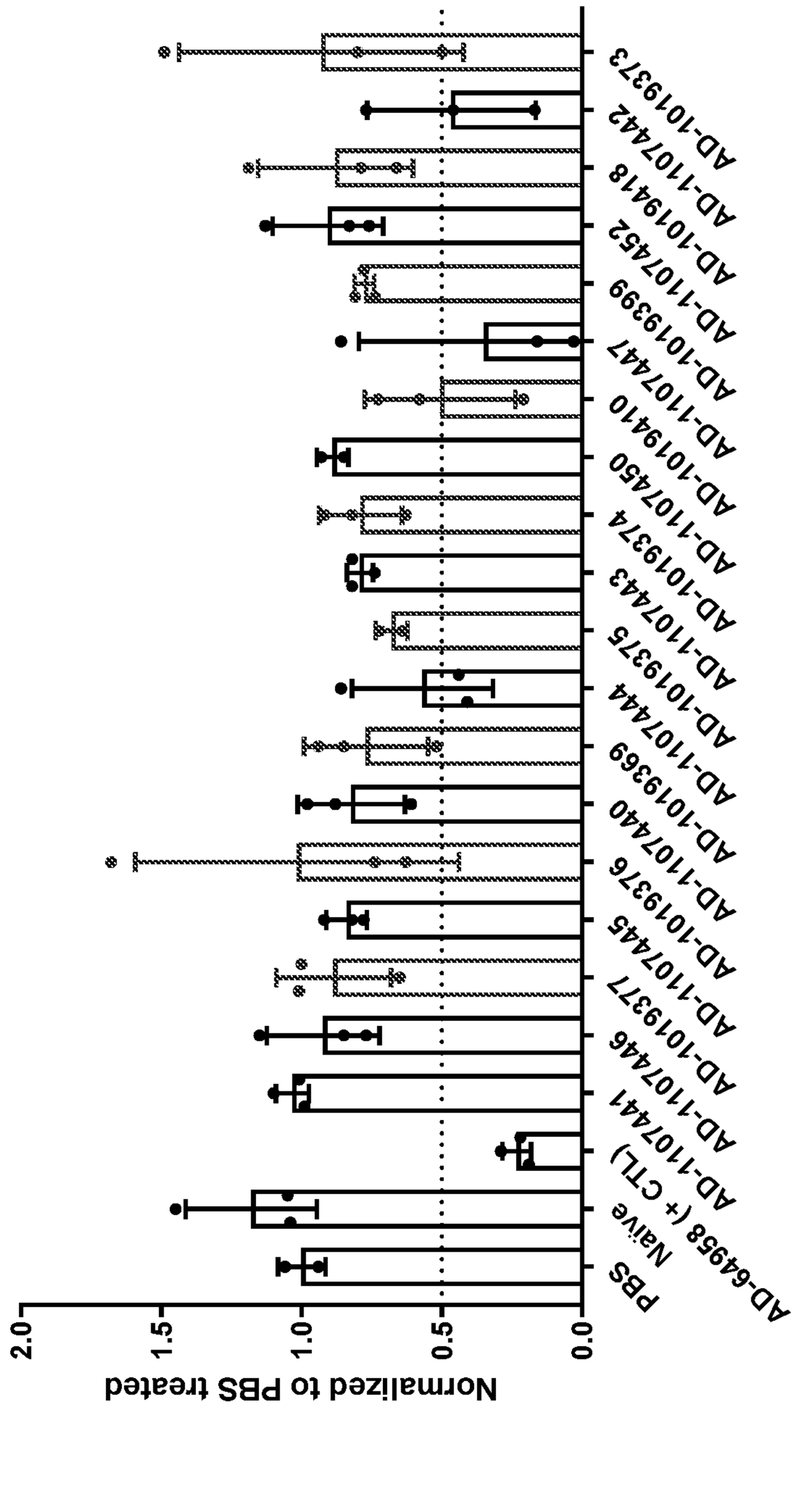

Normalized to PBS treated
0.0
0.5
1.0
1.5
2.0
PBS
Naïve
AD-64958 (+ CTL)
AD-1074A1
AD-1074A6
AD-1193A7
AD-1074A5
AD-1193A6
AD-1074A0
AD-1193A9
AD-1074A4
AD-1193A5
AD-1074A3
AD-1193A4
AD-1074A5
AD-1193A3
AD-1074A0
AD-1194A0
AD-1074A7
AD-1193A9
AD-1074A2
AD-1194A8
AD-1074A2
AD-1193A7

FIG.1

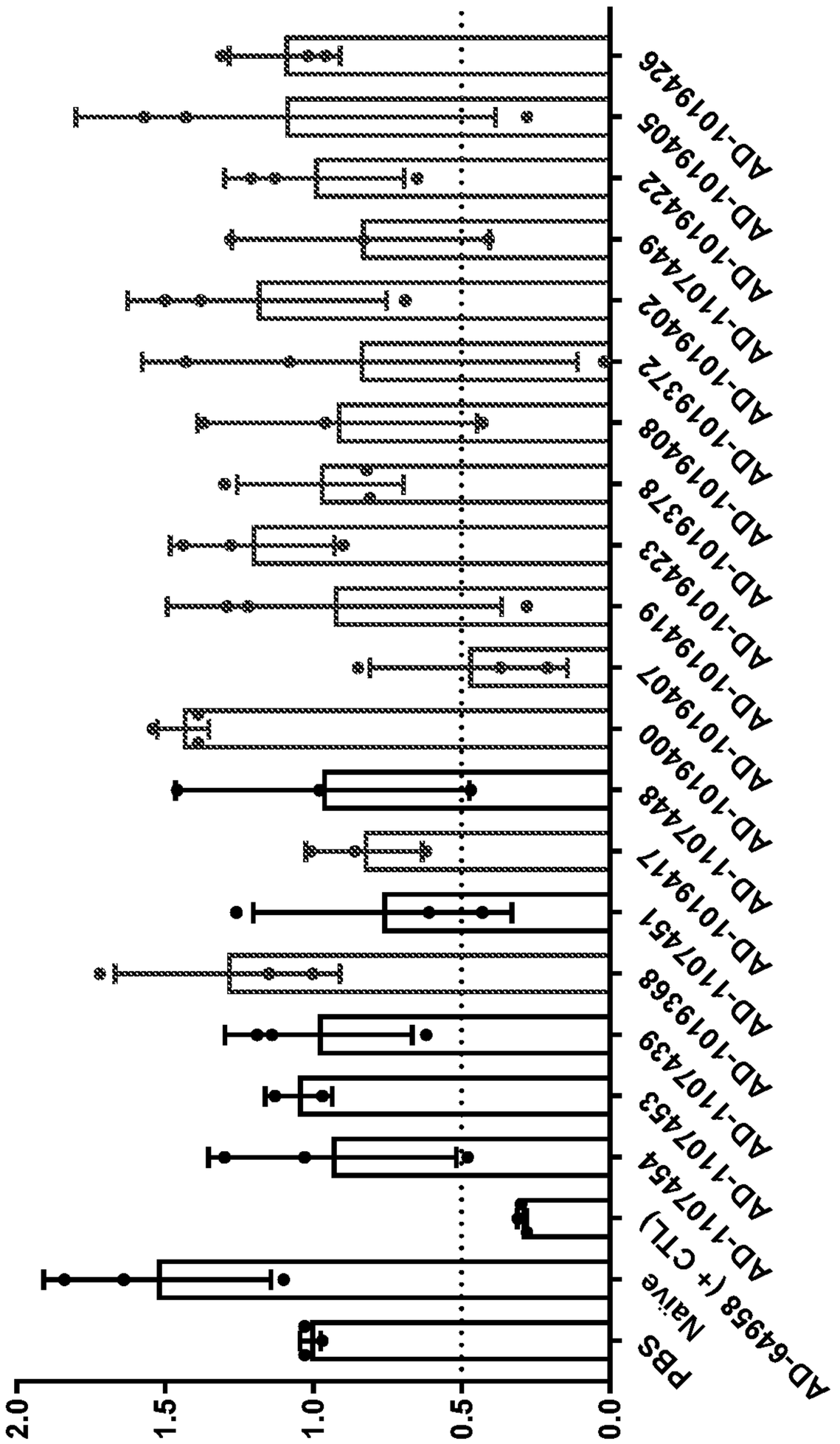

PBS
Naïve
AD-64958 (+ CTL)
AD-1074454
AD-1074453
AD-1074439
AD-1193568
AD-1074451
AD-1194171
AD-1074448
AD-1194000
AD-1194407
AD-1194419
AD-1194423
AD-1193578
AD-1194408
AD-1193572
AD-1194402
AD-1074449
AD-1194422
AD-1194405
AD-1194426
0.0
0.5
1.0
1.5
2.0
Normalized to PBS treated

FIG.2

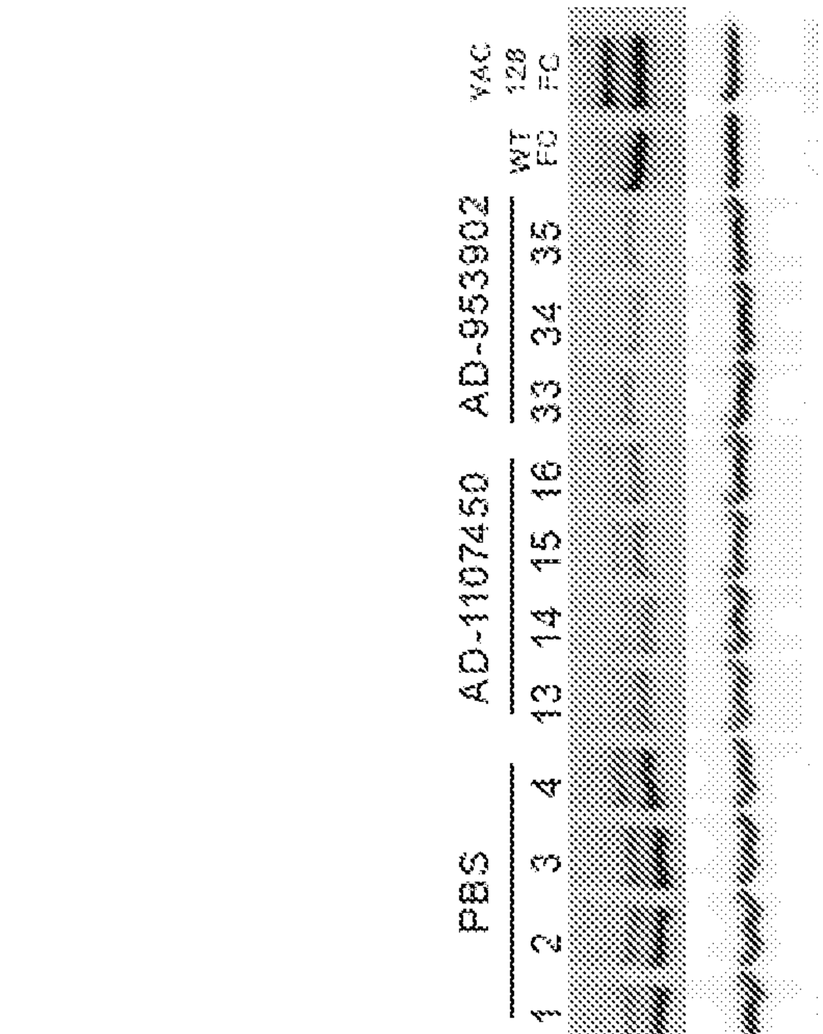


FIG.3B

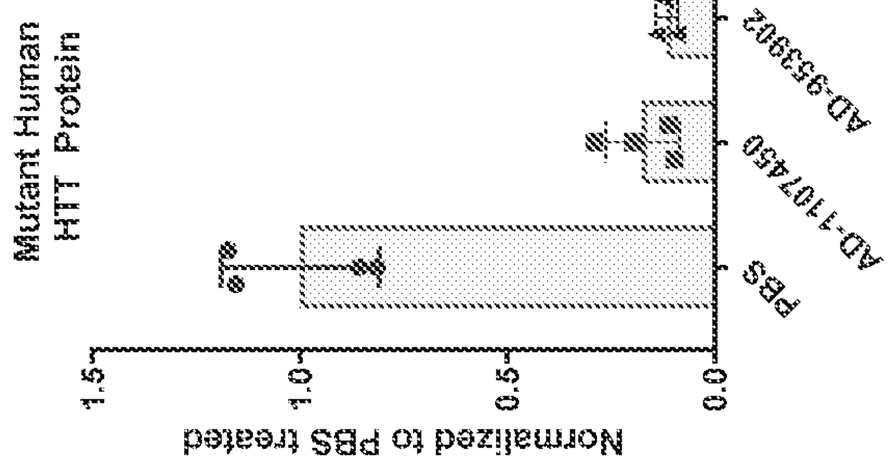


FIG.3C

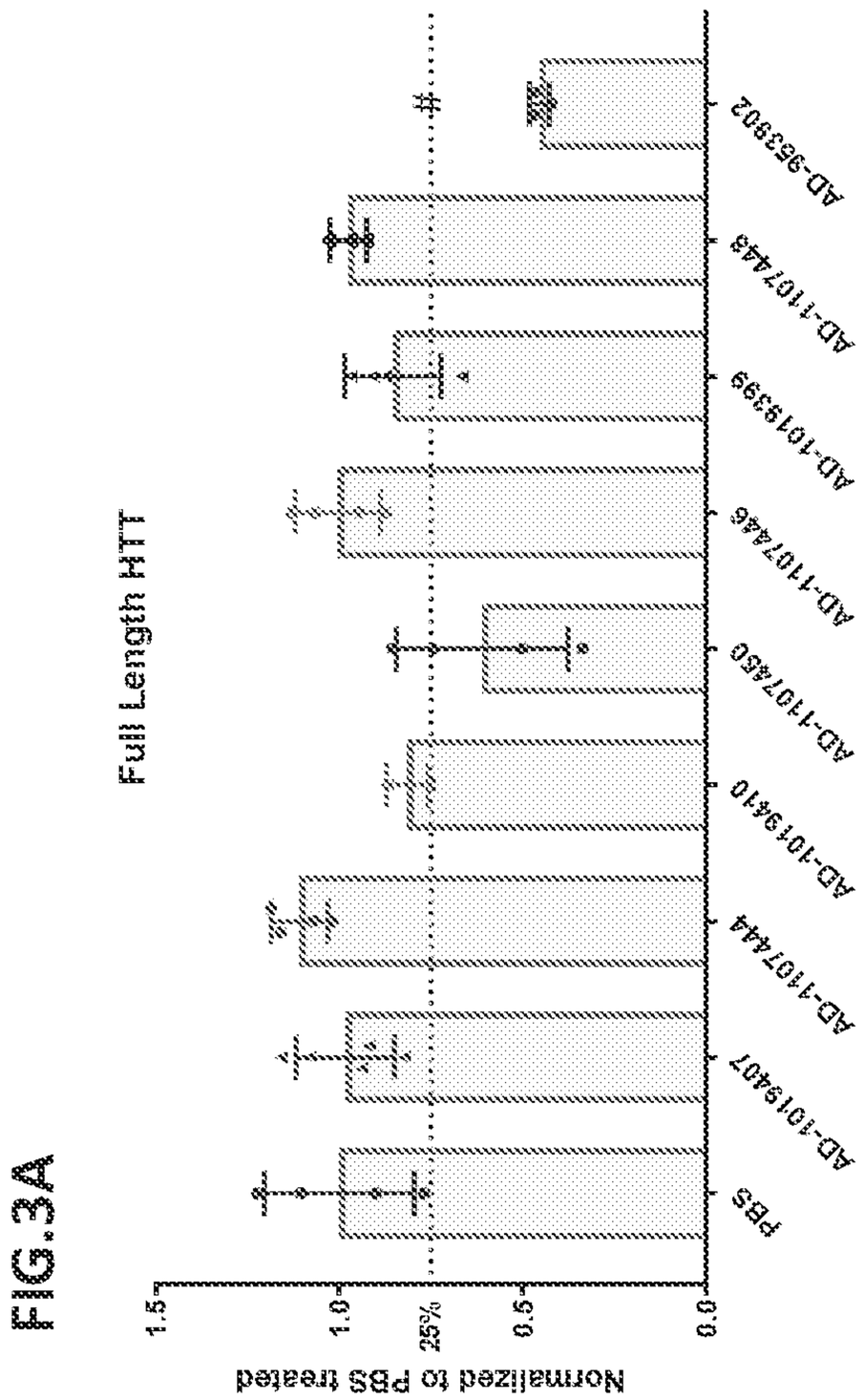


FIG.3A

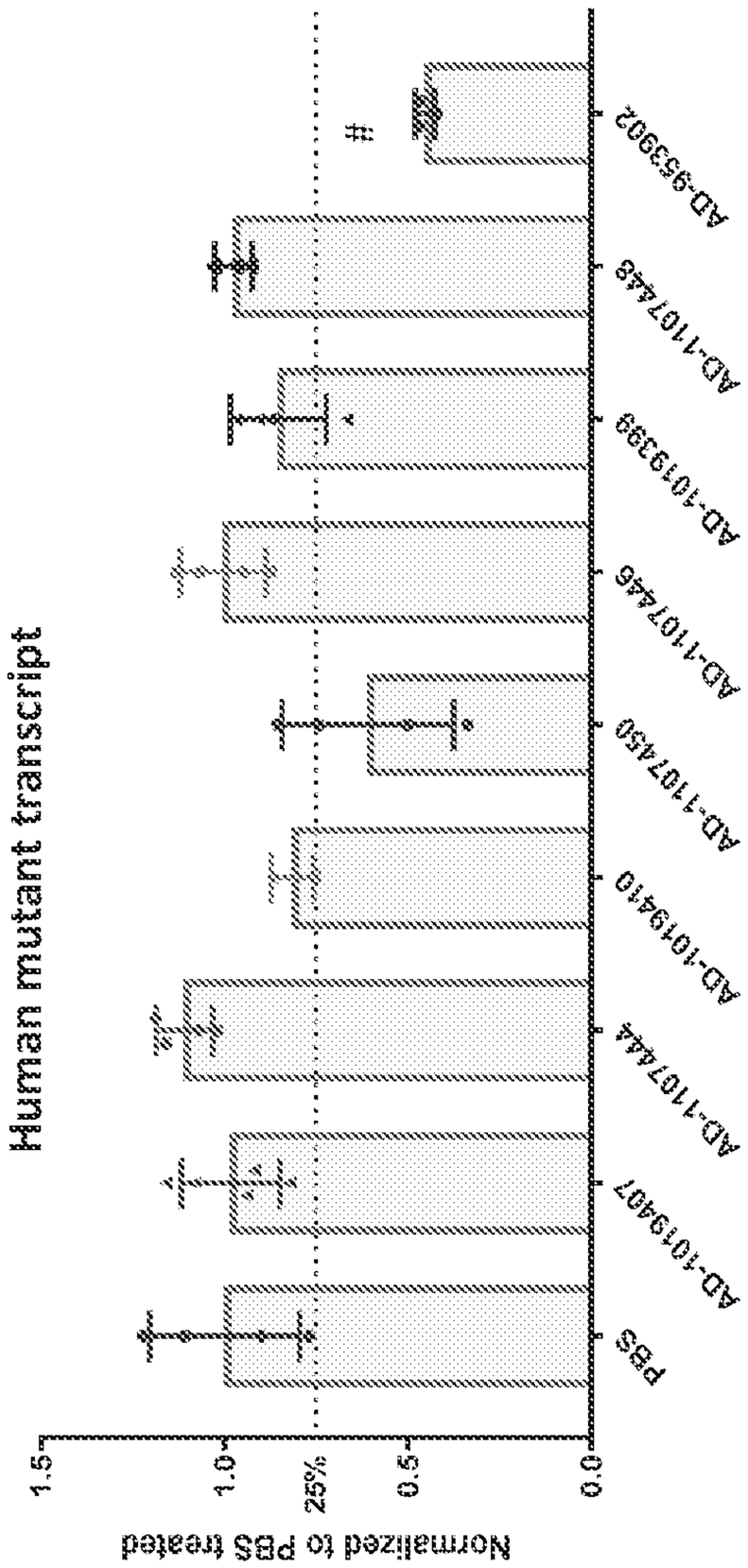

Human mutant transcript
Normalized to PBS treated
1.5
1.0
25%
0.5
0.0
PBS
AD-1019407
AD-1107444
AD-1019410
AD-1107450
AD-1019399
AD-1107448
AD-953902
#
*

FIG.4A

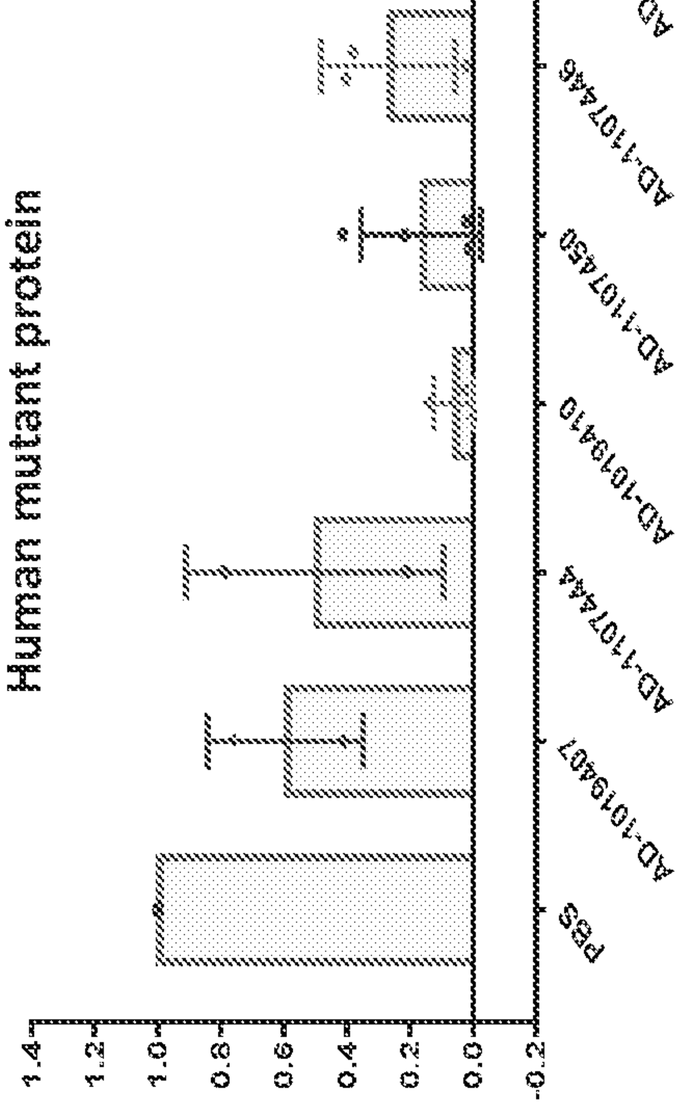

Human mutant protein
Normalized to PBS treated
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
PBS
AD-1019407
AD-1107444
AD-1019410
AD-1107450
AD-1019399
AD-1107448
AD-953902
*

FIG.4B

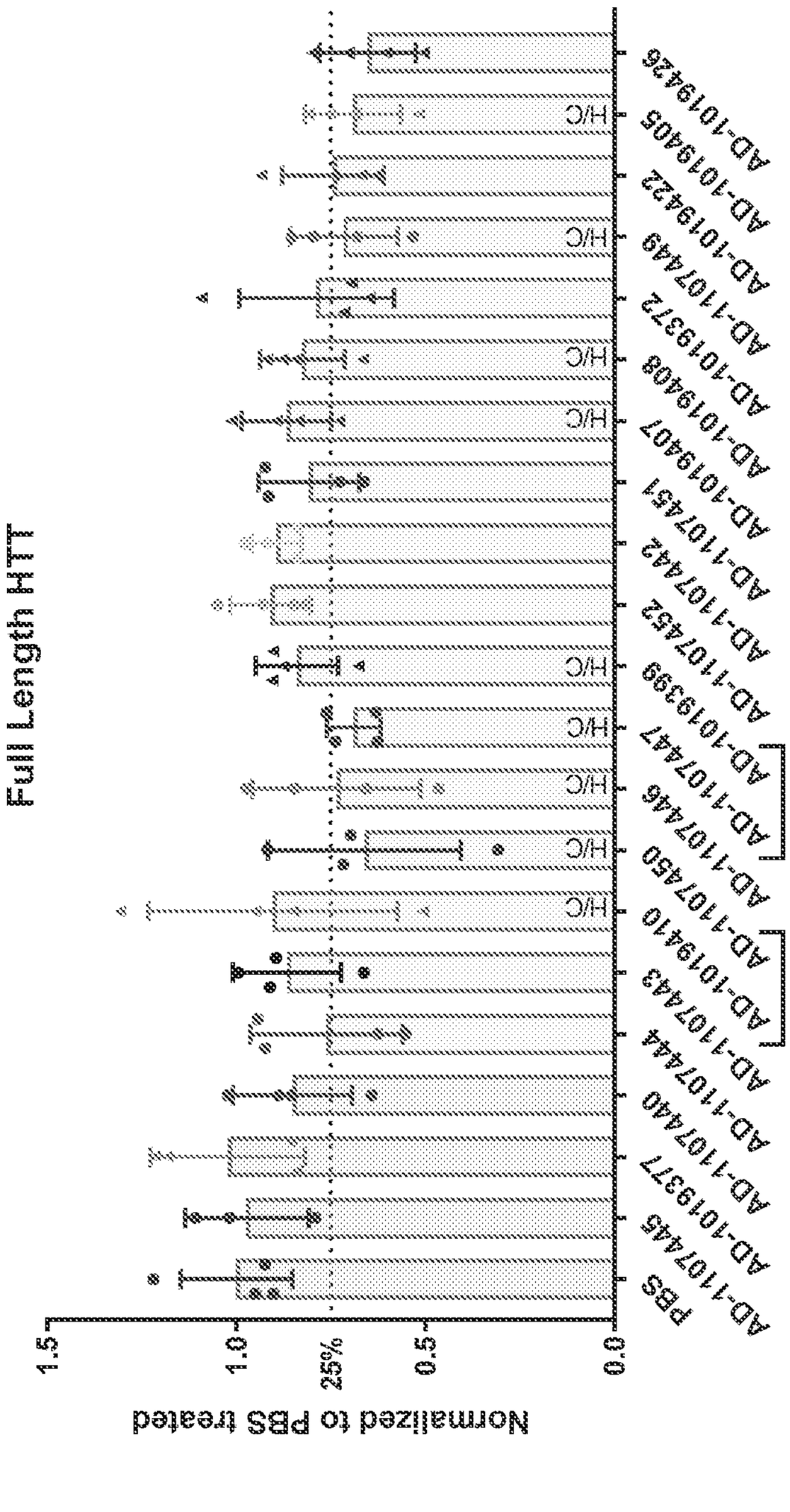

Full Length HTT
Normalized to PBS treated
1.5
1.0
25%
0.5
0.0
PBS
AD-1107445
AD-1019377
AD-1107440
AD-1107444
AD-1107443
AD-1019410
AD-1107450
AD-1107446
AD-1107447
AD-1019399
AD-1107452
AD-1107442
AD-1107451
AD-1019407
AD-1019408
AD-1019372
AD-1107449
AD-1019422
AD-1019405
AD-1019426
H/C

FIG. 5

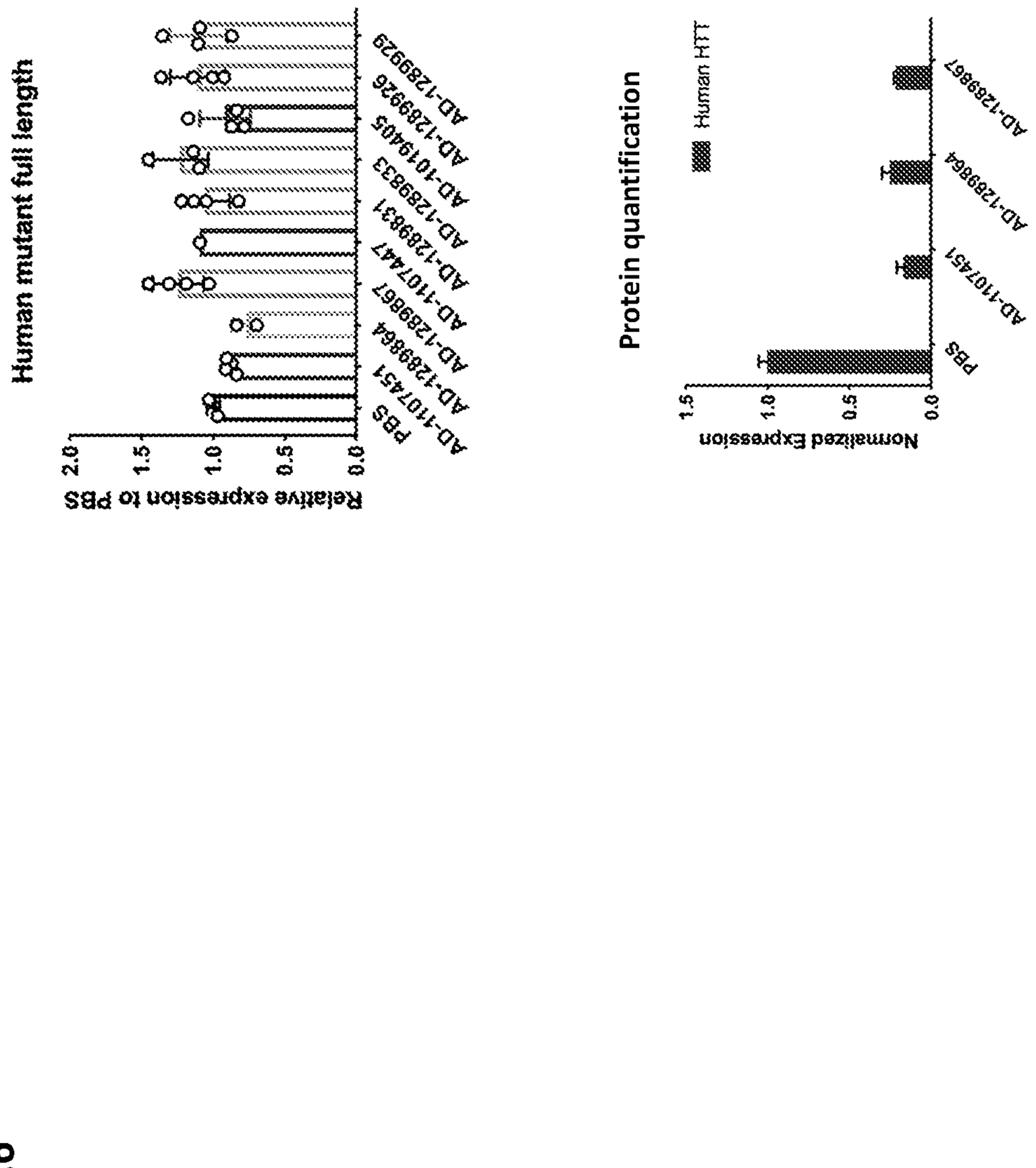

Human mutant full length
Relative expression to PBS
2.0
1.5
1.0
0.5
0.0
PBS
AD-1107451
AD-1289864
AD-1289867
AD-1107447
AD-1289831
AD-1289833
AD-1019405
AD-1289926
AD-1289929
Protein quantification
Human HTT
Normalized Expression
1.5
1.0
0.5
0.0
PBS
AD-1107451
AD-1289864
AD-1289867

FIG.6

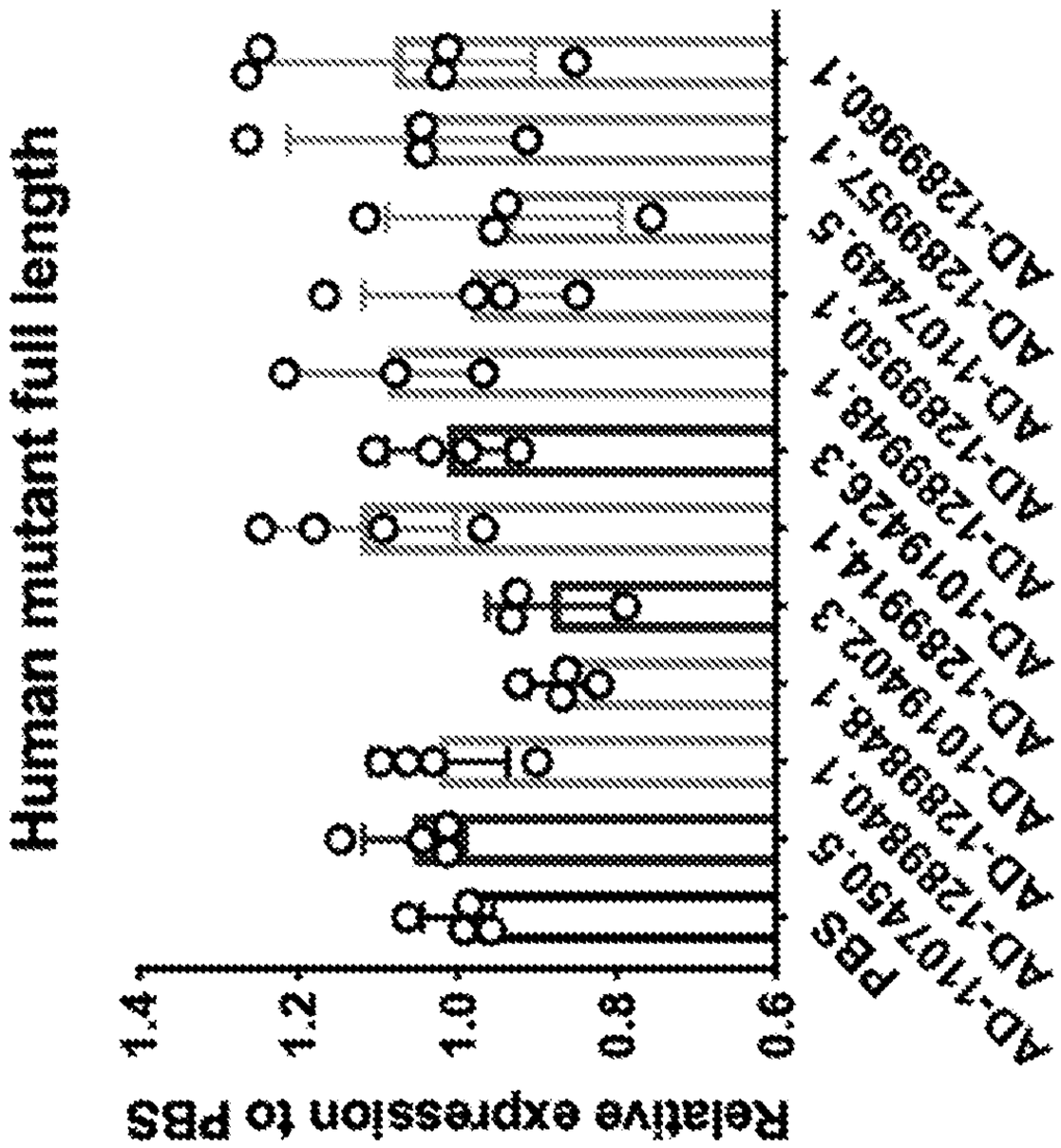

Human mutant full length
Relative expression to PBS
1.4
1.2
1.0
0.8
0.6
PBS
AD-1107450.5
AD-1289840.1
AD-1289848.1
AD-1019402.3
AD-1289914.1
AD-1019426.3
AD-1289948.1
AD-1107449.5
AD-1289957.1
AD-1289960.1

FIG.7

FIG.8B

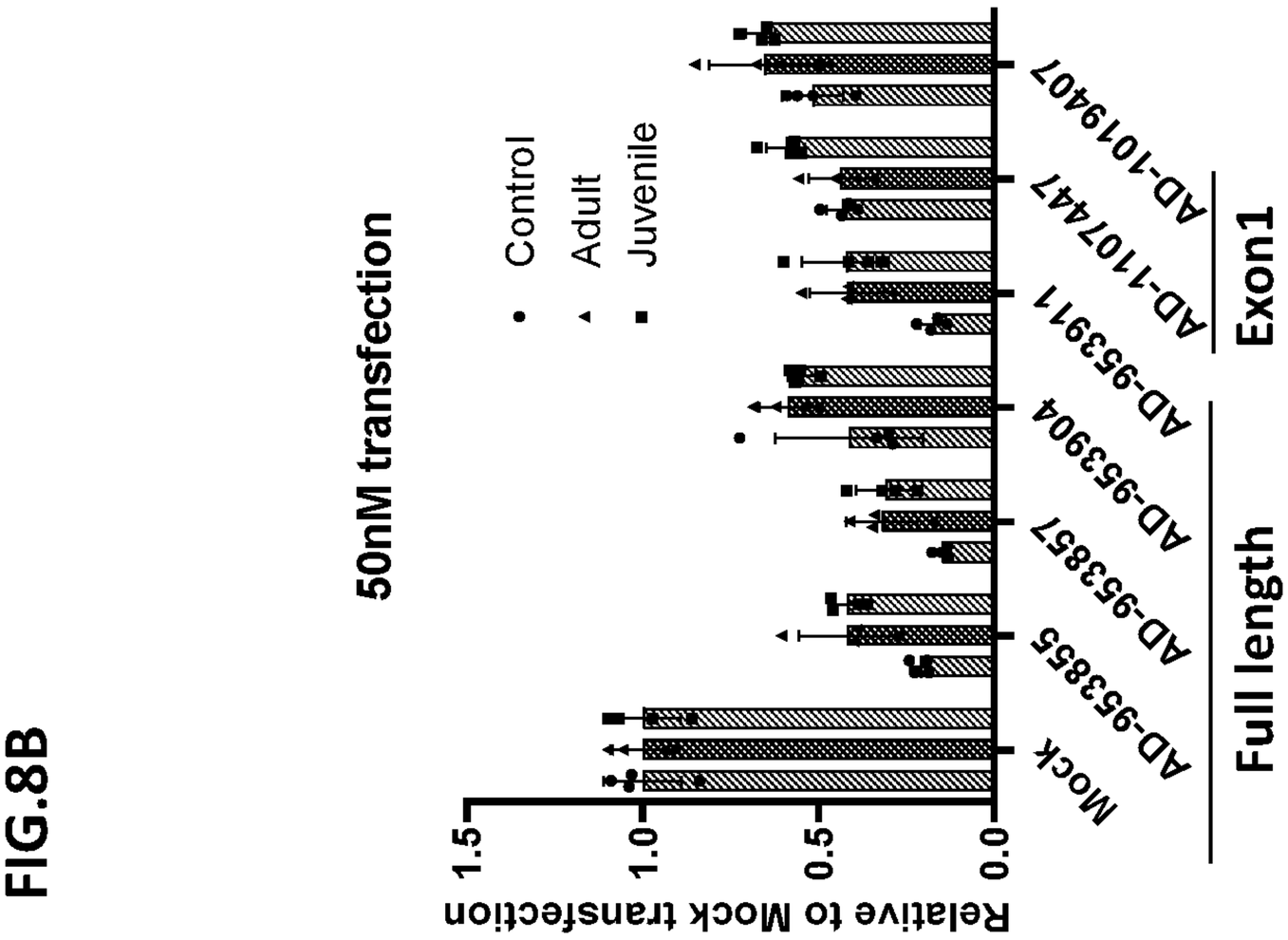
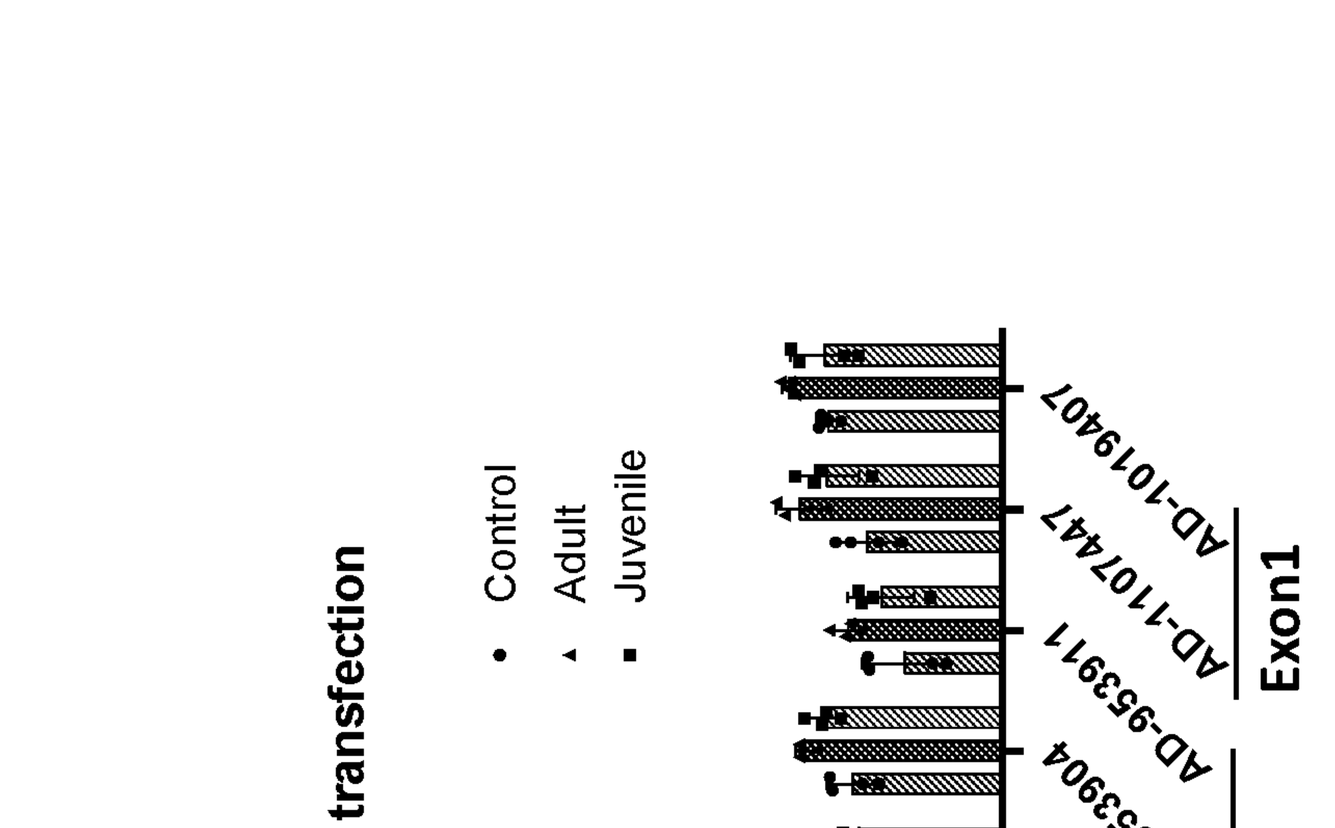

50nM transfection
Control
Adult
Juvenile
Relative to Mock transfection
1.5
1.0
0.5
0.0
Mock
AD-953855
AD-953857
AD-953904
AD-953911
AD-1107447
AD-1019407
Full length
Exon1

FIG.8A


10nM transfection
Control
Adult
Juvenile
Relative to Mock transfection
2.0
1.5
1.0
0.5
0.0
Mock
AD-953855
AD-953857
AD-953904
AD-953911
AD-1107447
AD-1019407
Full length
Exon1

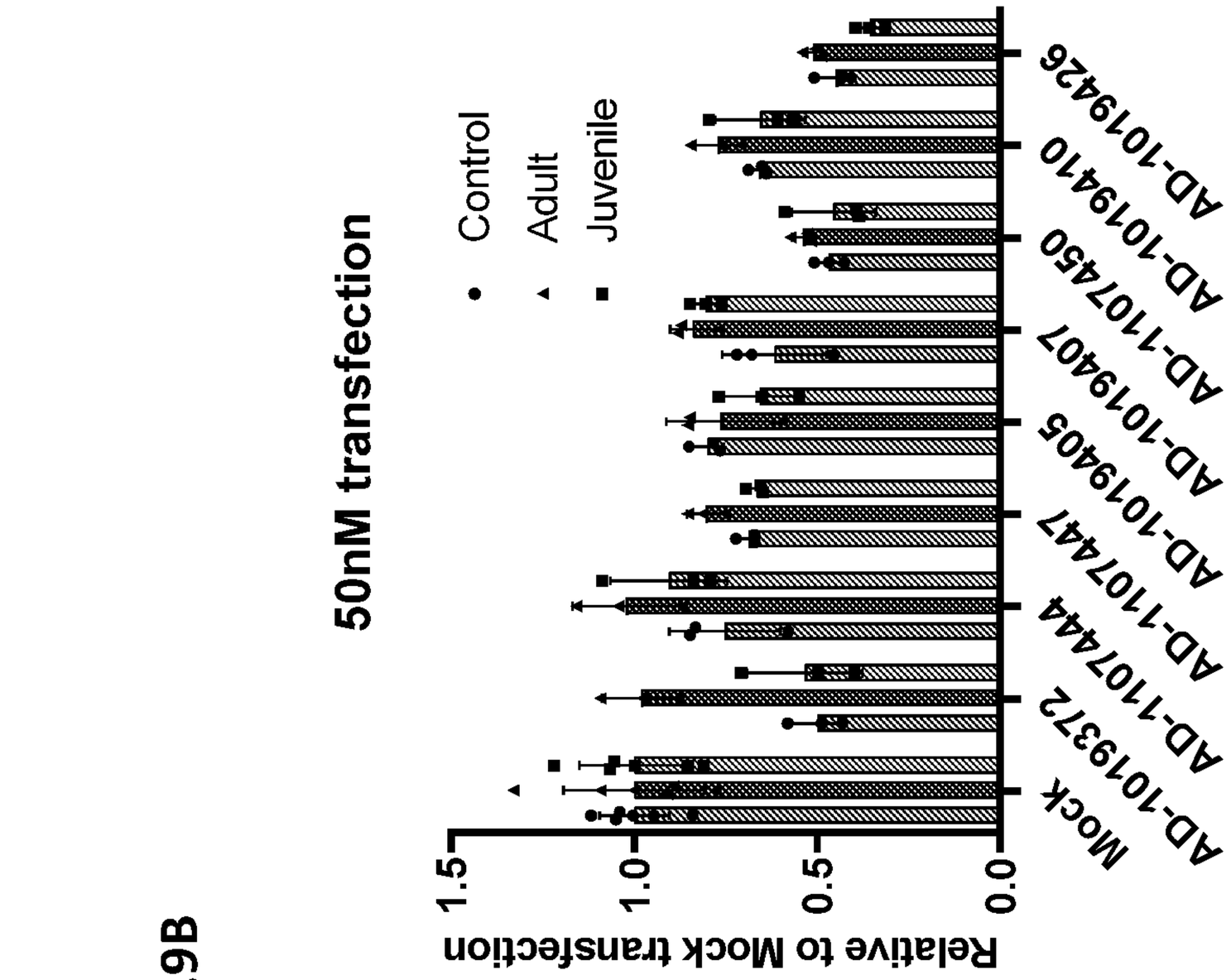

50nM transfection
Control
Adult
Juvenile
Relative to Mock transfection
1.5
1.0
0.5
0.0
Mock
AD-1019372
AD-1074A4
AD-1074A7
AD-1019405
AD-1019407
AD-1074B0
AD-1019410
AD-1019426

FIG.9B

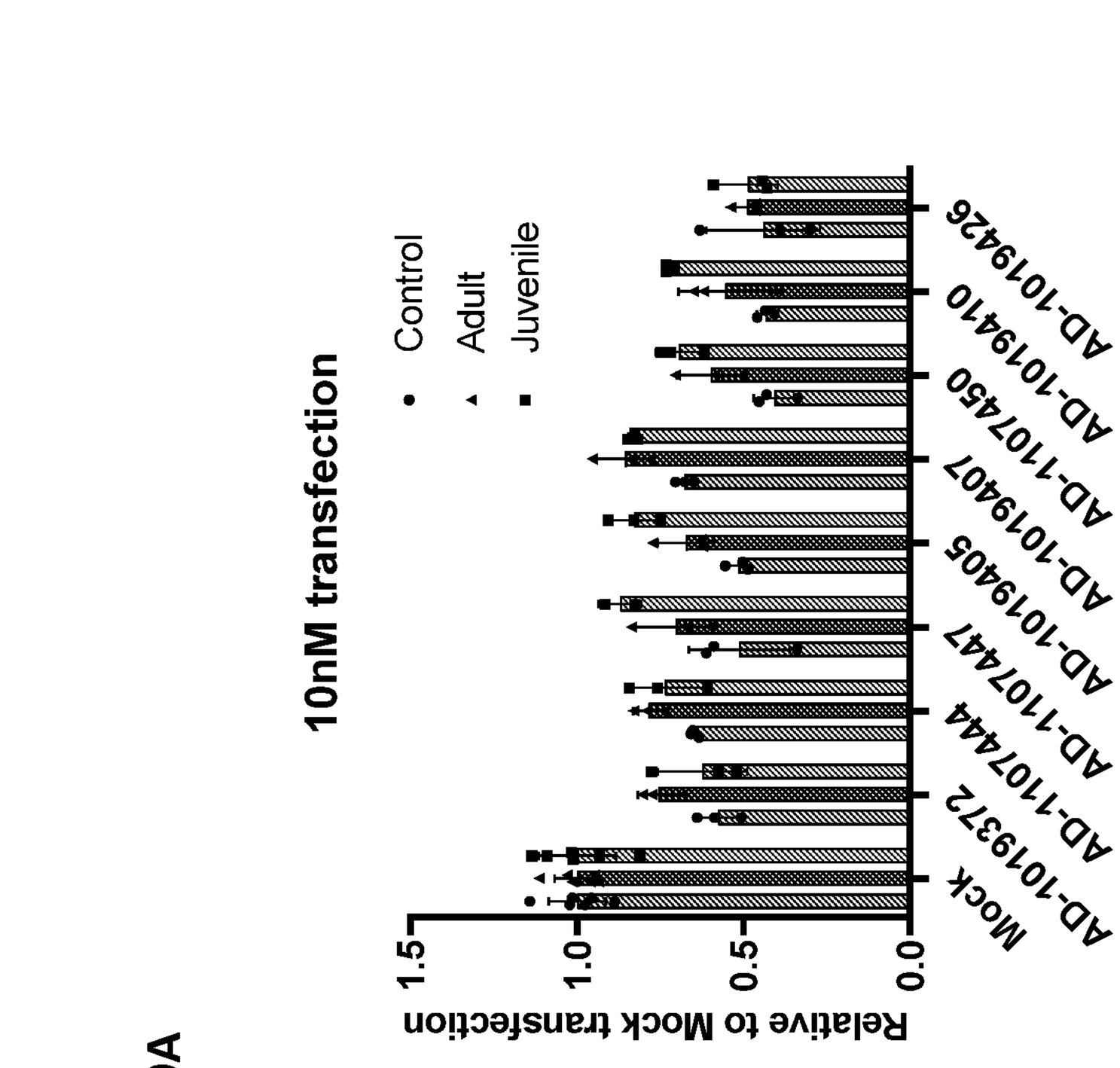

10nM transfection
Control
Adult
Juvenile
Relative to Mock transfection
1.5
1.0
0.5
0.0
Mock
AD-1019372
AD-1074A4
AD-1074A7
AD-1019405
AD-1019407
AD-1074B0
AD-1019410
AD-1019426

FIG. 9A

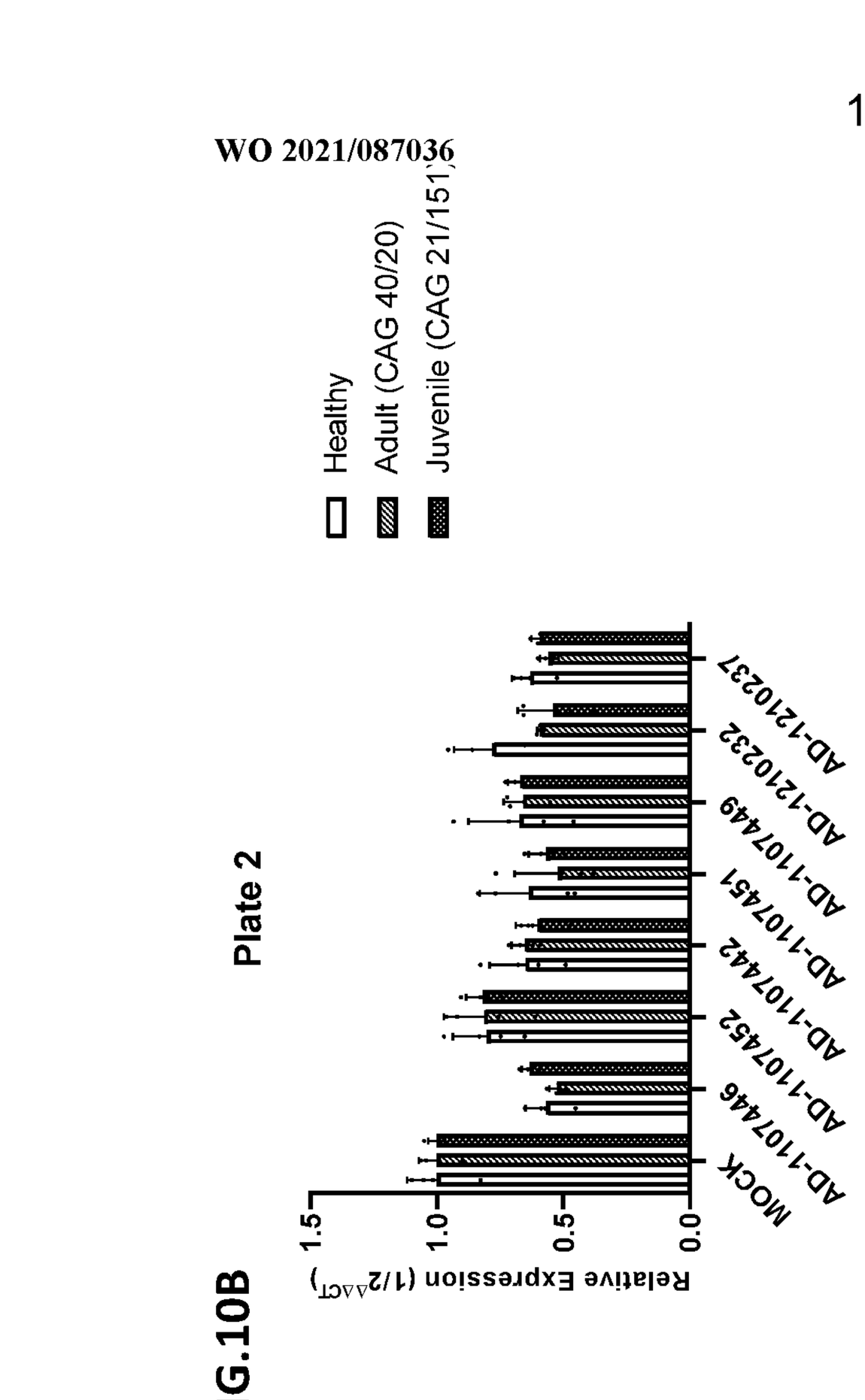


FIG.10A

FIG.10B

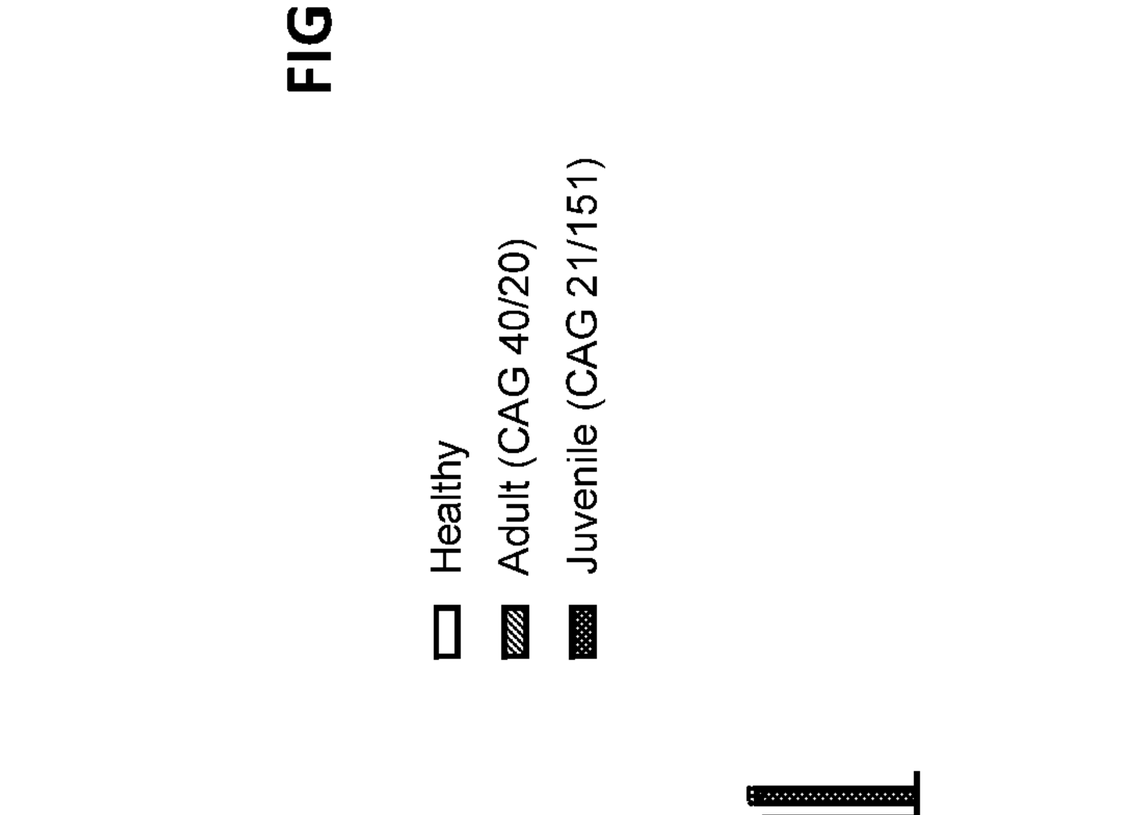


FIG.10C

FIG.10D

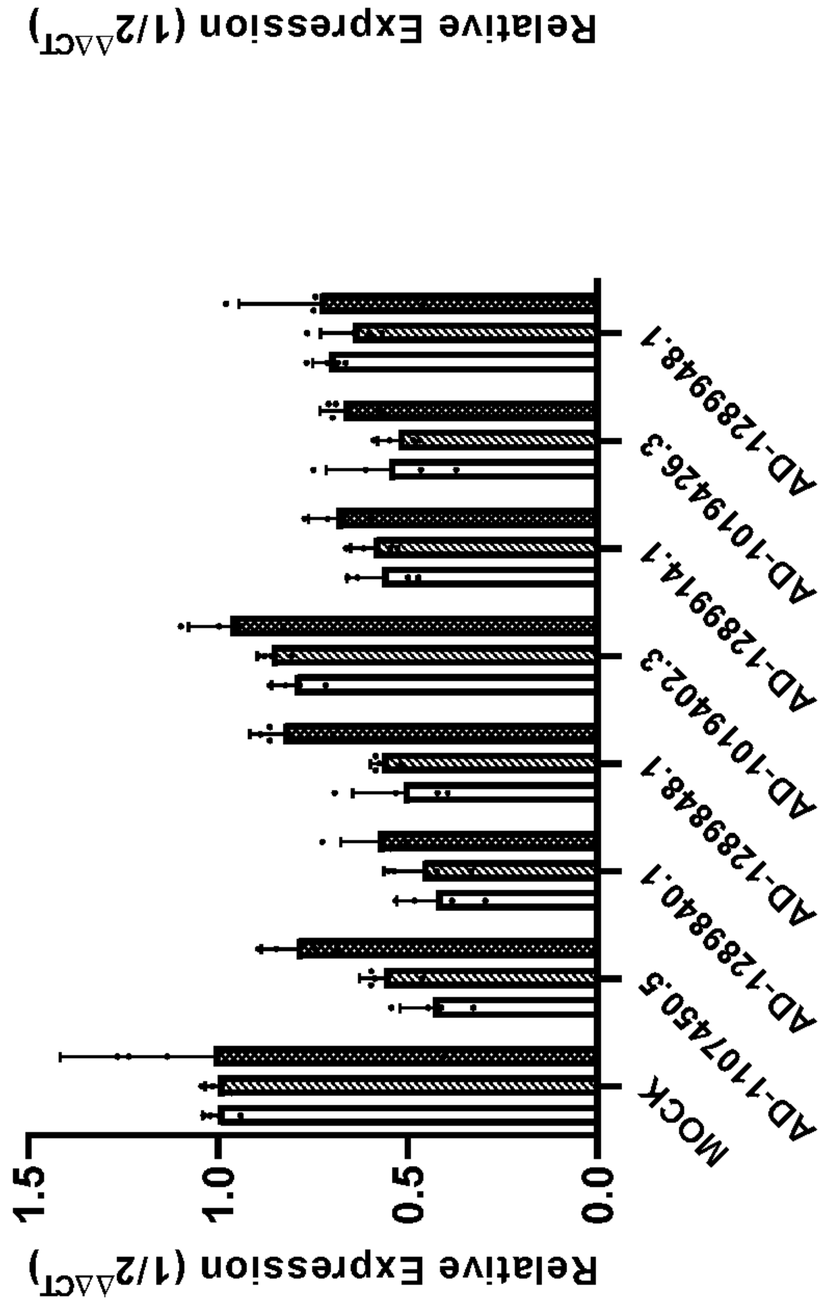


FIG.11B

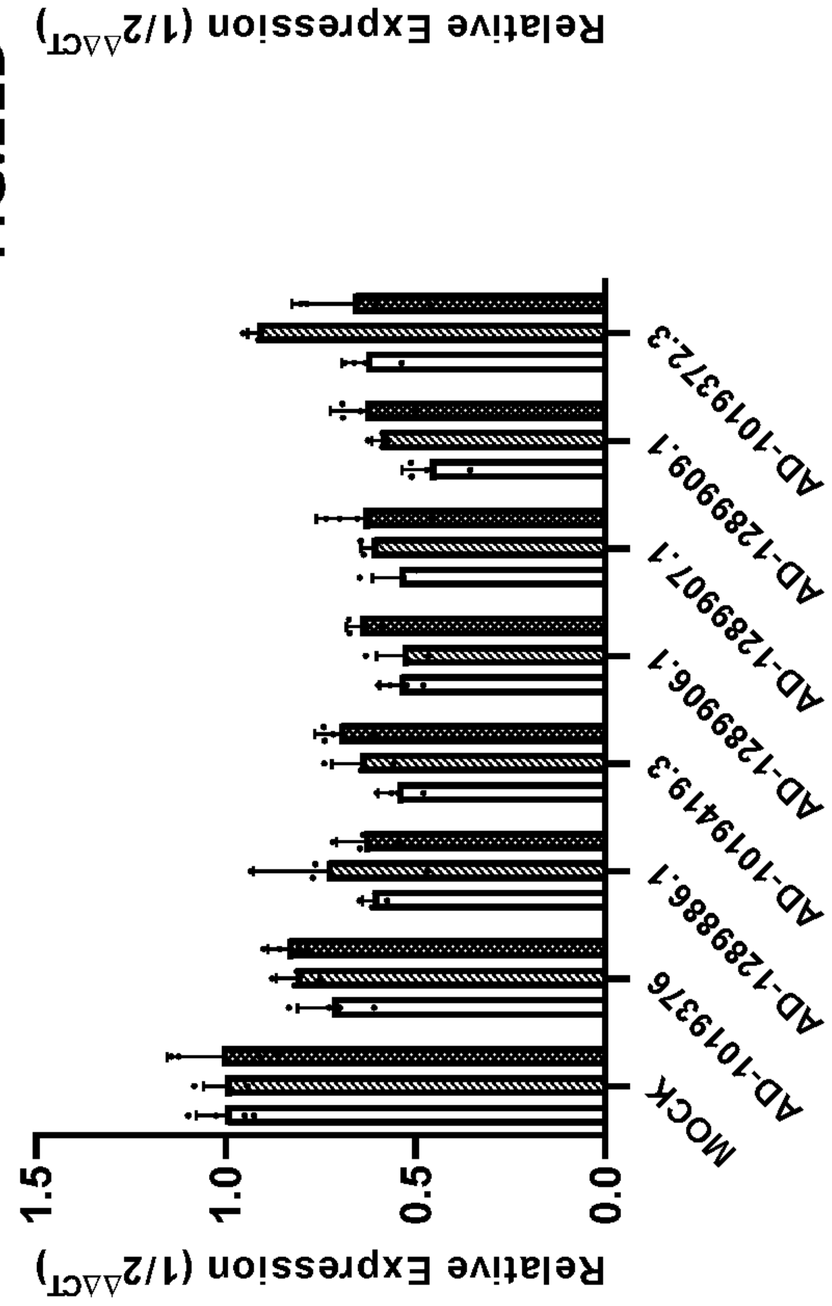


FIG.11D

FIG.11A

FIG.11C

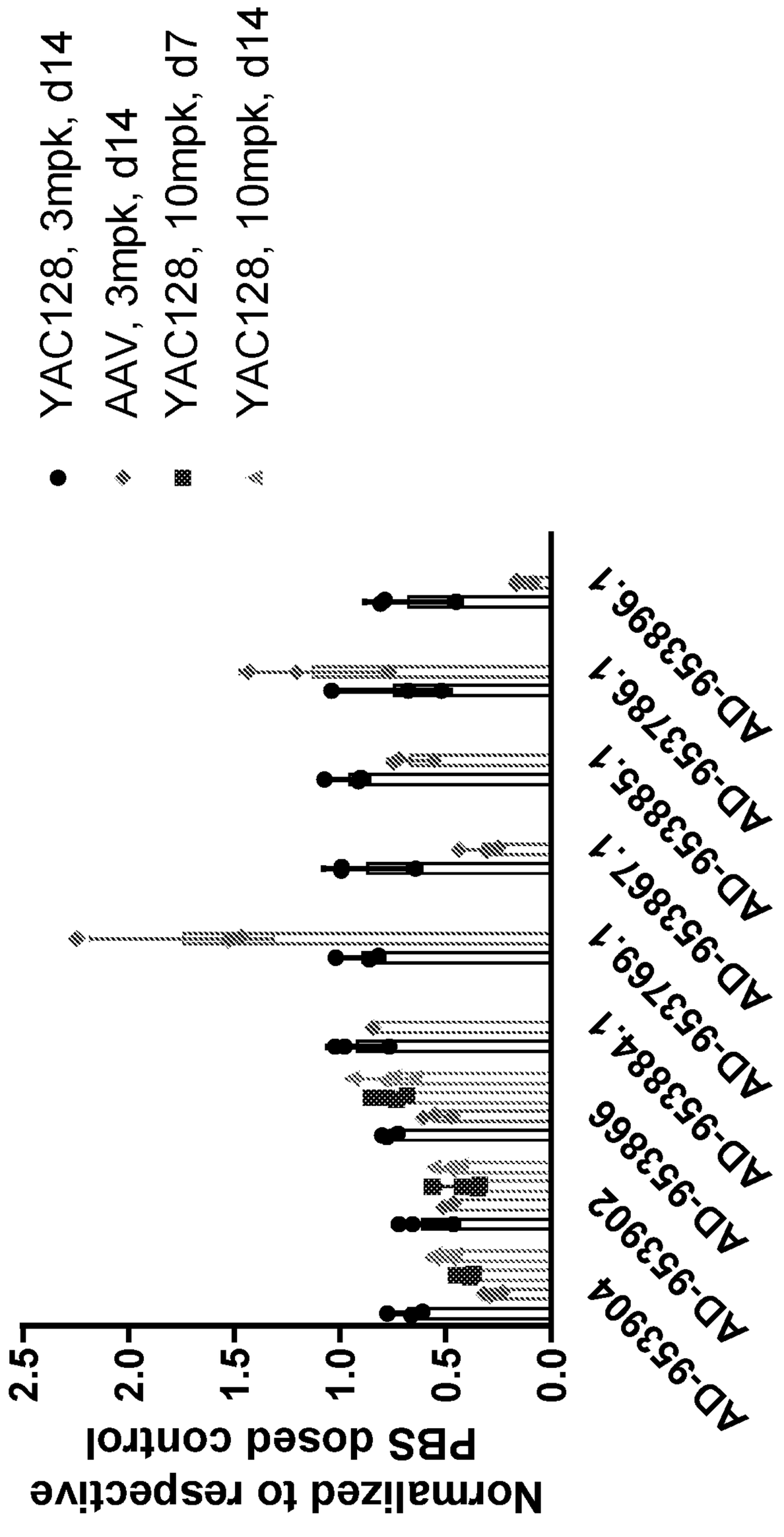

YAC128, 3mpk, d14
AAV, 3mpk, d14
YAC128, 10mpk, d7
YAC128, 10mpk, d14
AD-953904
AD-953902
AD-953866
AD-953884.1
AD-953769.1
AD-953867.1
AD-953885.1
AD-953786.1
AD-953896.1
0.0
0.5
1.0
1.5
2.0
2.5
PBS dosed control
Normalized to respective

FIG. 12

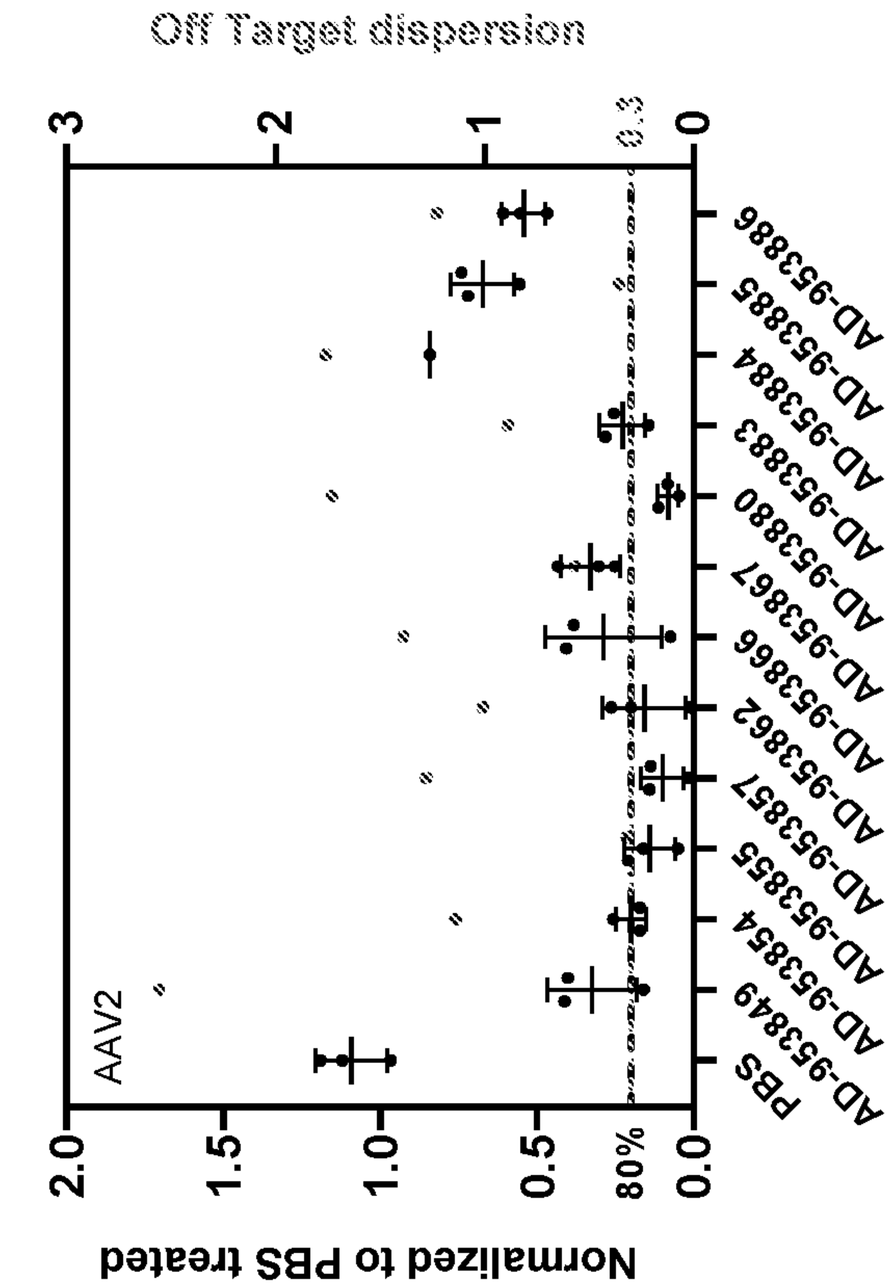


FIG.13B

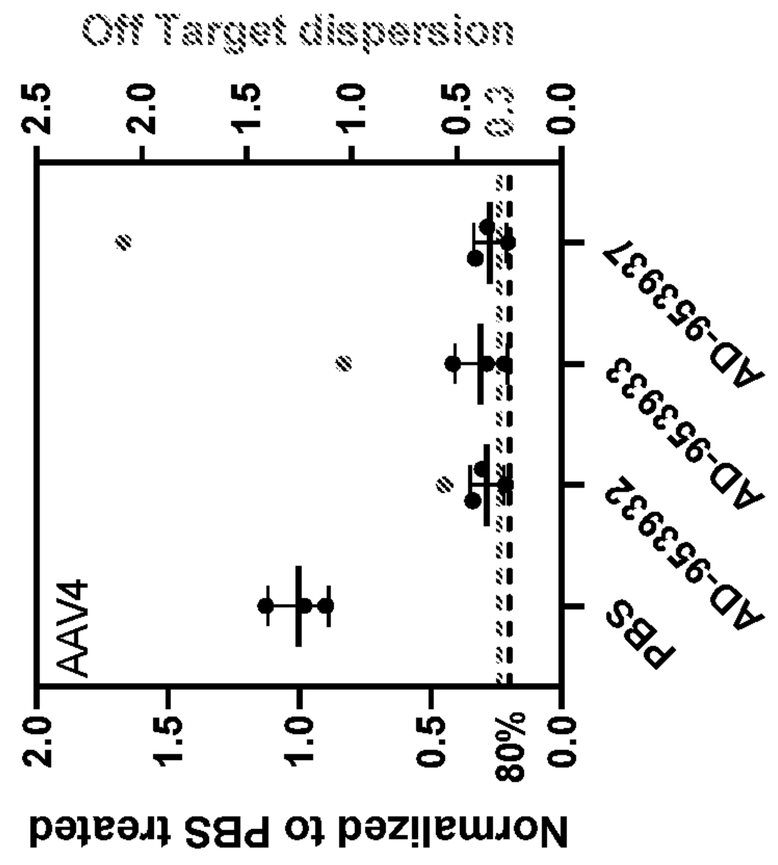


FIG.13D

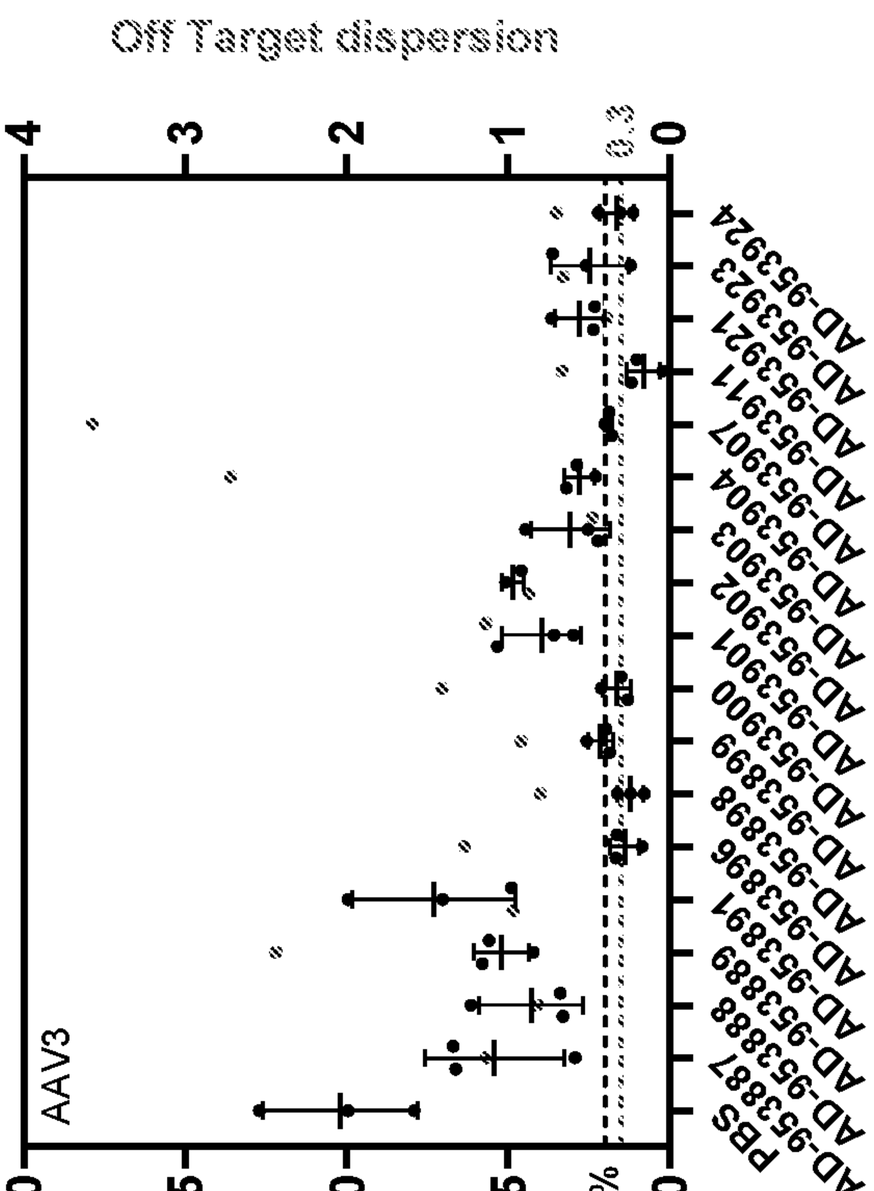


FIG.13C

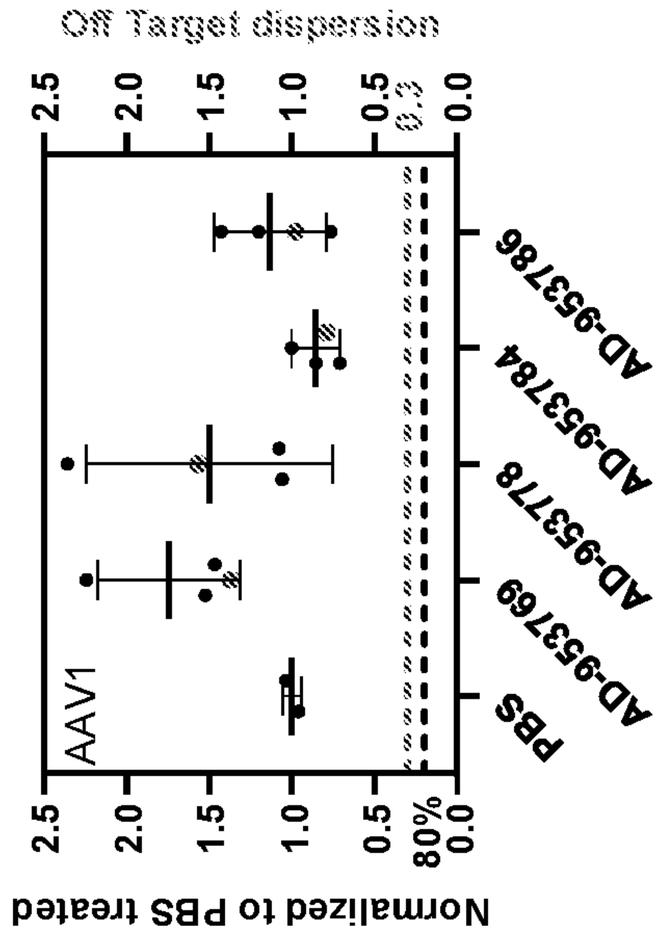


FIG.13A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/057849

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/051045 A2 (ALNYLAM PHARMACEUTICALS, INC. [US]) 3 May 2007 (2007-05-03) page 55; sequences 794, 795 page 19 page 33 - page 34 page 57 page 71 - page 75 ----- -/--	1-88

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2021	22/03/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Macchia, Giovanni

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/057849

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DIFIGLIA M. ET AL.: "Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA, vol. 104, no. 43, 23 October 2007 (2007-10-23), pages 17204-17209, XP002526486, ISSN: 0027-8424, DOI: 10.1073/PNAS.0708285104 the whole document -----	1
A	BRANDON J. PEEL ET AL.: "Conjugation and evaluation of small hydrophobic molecules to triazole-linked siRNAs", ACS MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 2, 12 February 2015 (2015-02-12), pages 117-122, XP055288657, US ISSN: 1948-5875, DOI: 10.1021/ml500260j the whole document -----	1
A	WO 2004/094595 A2 (ALNYLAM PHARMACEUTICALS, INC. [US]) 4 November 2004 (2004-11-04) claim 53 page 216 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/057849

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a. [X] forming part of the international application as filed:

[X] in the form of an Annex C/ST.25 text file.

[ ] on paper or in the form of an image file.

b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

[ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

[ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/057849

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-88(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-88(partially)

A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Huntingtin (HTT),
wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,
wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 6, wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one of the sense strand or the antisense strand
and
wherein the nucleotide sequence of the sense strand comprises the first of the sense strand nucleotide sequences in Table 2 which matches with SEQ ID NO:1 (AS-379380.1, SEQ ID NO:91 on page 139), as well as sequences overlapping thereto.
A double stranded ribonucleic acid (dsRNA) 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 an mRNA encoding HTT, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the first antisense nucleotide sequence in Table 2 which is complementary to SEQ ID NO:1 (AS-379380.1, SEQ ID NO:292 on page 139), as well as sequences overlapping thereto.
dsRNA agents related thereto, as in claims 2, 3, 5-71, cells, pharmaceutical compositions and methods related thereto.

2-500. claims: 1-88(partially)

as invention 1, but referring to the second, third, fourth, ..., (last) of the sense/antisense nucleotide sequences in any one of Tables 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 24, 25, 27-30, 32 or 33, which match with SEQ ID NO:1, then with the remaining sequences which match SEQ ID NOs:2 to 5.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/057849

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007051045 A2	03-05-2007	AU 2006305886 A1	03-05-2007
		AU 2010241477 A1	09-12-2010
		CA 2627025 A1	03-05-2007
		CN 101365801 A	11-02-2009
		EP 1941059 A2	09-07-2008
		EP 2325315 A1	25-05-2011
		JP 5111385 B2	09-01-2013
		JP 2009513144 A	02-04-2009
		US 2007099860 A1	03-05-2007
		US 2008221055 A1	11-09-2008
		US 2010298405 A1	25-11-2010
		US 2012095076 A1	19-04-2012
		WO 2007051045 A2	03-05-2007
WO 2004094595 A2	04-11-2004	AU 2004233092 A1	04-11-2004
		AU 2009213011 A1	08-10-2009
		CA 2522637 A1	04-11-2004
		DK 1620544 T3	14-01-2019
		EP 1620544 A2	01-02-2006
		EP 2660322 A2	06-11-2013
		EP 2664672 A1	20-11-2013
		EP 2666858 A1	27-11-2013
		EP 2669377 A2	04-12-2013
		ES 2702942 T3	06-03-2019
		JP 4597976 B2	15-12-2010
		JP 2007525454 A	06-09-2007
		US 2005107325 A1	19-05-2005
		US 2005119214 A1	02-06-2005
		US 2005164235 A1	28-07-2005
		US 2010179309 A1	15-07-2010
		US 2010292455 A1	18-11-2010
		WO 2004094595 A2	04-11-2004