

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

5 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.

10 In one aspect, the present disclosure refers to 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 antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complement of nucleotides 142-195 of SEQ ID NO:1, 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.

15 In another aspect, the present disclosure refers to 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.

20 In another aspect, the present disclosure refers to 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.

25 In yet another aspect, the present disclosure refers to a cell containing the dsRNA agent as disclosed herein.

30 In yet another aspect, the present disclosure refers to a pharmaceutical composition for inhibiting expression of a gene encoding HTT, comprising the dsRNA agent as disclosed herein.

35 In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the dsRNA agent as disclosed herein and a lipid formulation.

In yet another aspect, the present disclosure refers to an *in vitro* method of inhibiting expression of a huntingtin (HTT) gene in a cell, the method comprising: (a) contacting the cell with the dsRNA agent as disclosed herein, or the pharmaceutical composition as disclosed herein; 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.

In yet another aspect, the present disclosure refers to the use of the dsRNA agent as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject diagnosed with an HTT-associated disease.

In one ~~aspect~~example, the present ~~invention~~disclosure 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the antisense strand comprises at least 15 contiguous nucleotides differing by no 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 ~~embodiment~~examples, the lipophilic moiety is conjugated *via* a linker or a carrier.

In another ~~aspect~~example, the present ~~invention~~disclosure 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

In some ~~embodiment~~examples, the internal positions include all positions except the terminal two positions from each end of the sense strand or the antisense strand. In other ~~embodiment~~examples, the internal positions include all positions except the terminal three positions from each end of the sense strand or the antisense strand.

In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the internal positions exclude a cleavage site region of the antisense strand. In other ~~embodiment~~examples, the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the positions in the double stranded region exclude a cleavage site region of the sense strand.

In some ~~embodiment~~examples, 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.

5 In other ~~embodiment~~examples, 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 ~~embodiment~~examples, the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

In some ~~embodiment~~examples, 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, geranyloxyhexanol, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

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

In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazoliny, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxaliny, pyridazinonyl, tetrahydrofuranyl, and decaliny; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

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

In some ~~embodiment~~examples, the dsRNA agent comprises at least one modified nucleotide. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In some embodimentexamples, 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-tetrahydrofuran-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 embodimentexamples, 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 embodimentexamples, 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 embodimentexamples, at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification. In some embodimentexamples, 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 embodimentexamples, the modified nucleotide comprises a short sequence of 3'-terminal deoxy-thymine nucleotides (dT).

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

In some embodimentexamples, the dsRNA agent further comprises at least one phosphorothioate internucleotide linkage. In some embodimentexamples, the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages. In one embodimentexample, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. Optionally, the strand is the antisense strand. In another embodimentexample, the strand is the sense strand. In a related embodimentexample, the

phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. Optionally, the strand is the antisense strand. In another [embodimentexample](#), the strand is the sense strand. In another [embodimentexample](#), 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 [embodimentexample](#), the strand is the sense strand.

In some [embodimentexamples](#), each strand is no more than 30 nucleotides in length.

In some [embodimentexamples](#), at least one strand comprises a 3' overhang of at least 1 nucleotide or a 3' overhang of at least 2 nucleotides.

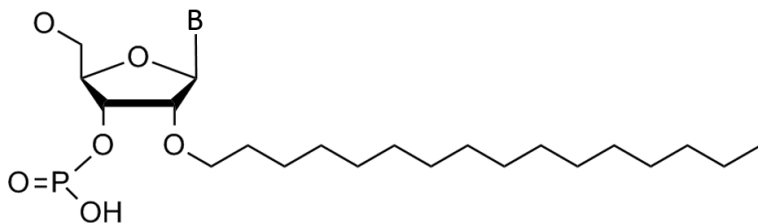
The double stranded region may be 15-30 nucleotide pairs in length; 17-23 nucleotide pairs in length; 17-25 nucleotide pairs in length; 23-27 nucleotide pairs in length; 19-21 nucleotide pairs in length; or 21-23 nucleotide pairs in length.

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

In some [embodimentexamples](#), the dsRNA agent further comprises a targeting ligand that targets a liver tissue. In some [embodimentexamples](#), the targeting ligand is a GalNAc conjugate.

In certain [embodimentexamples](#), 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 [embodimentexamples](#), the targeting ligand is a C16 ligand. In one [embodimentexample](#), 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 [embodimentexamples](#), the lipophilic moiety or targeting ligand is conjugated *via* a bio-cleavable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

In some [embodimentexamples](#), 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 [embodimentexamples](#), 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.

5 In some ~~embodiment~~examples, 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
10 internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some ~~embodiment~~examples, 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
15 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 ~~embodiment~~examples, 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
20 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 ~~embodiment~~examples, 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
30 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 ~~embodiment~~examples, the dsRNA agent further comprises a phosphate or phosphate mimic at the 5'-end of the antisense strand. In some ~~embodiment~~examples, the phosphate mimic is a
35 5'-vinyl phosphonate (VP).

In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the sense strand has a total of 21 nucleotides and the antisense
40 strand has a total of 23 nucleotides.

An additional ~~aspect~~example 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~~example 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~~example 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~~example, 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 embodimentexample, the RNAi agent includes four or more PS modifications, optionally six to ten PS modifications, optionally eight PS modifications.

In an additional embodimentexample, 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 embodimentexample, 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 embodimentexample, 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 embodimentexample, 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 embodimentexample, 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.

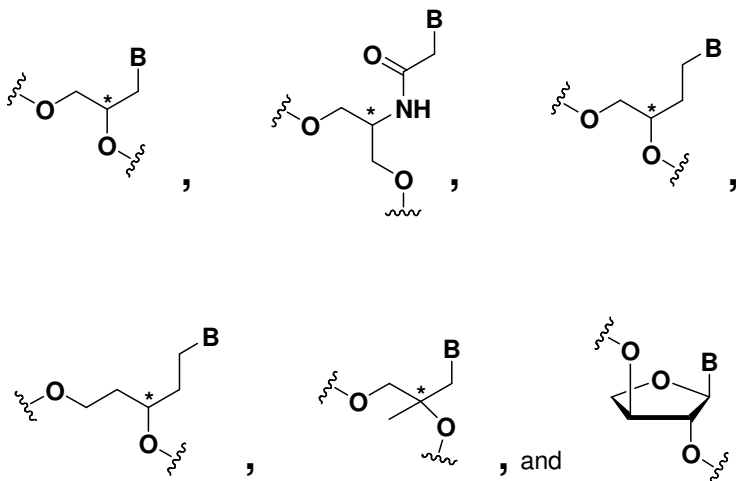
In another embodimentexample, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes two or more 2'-O-methyl modified nucleotides. Optionally, the RNAi agent includes 2'-O-methyl modified nucleotides at all nucleobase 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~~example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

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

In certain ~~embodiment~~examples, 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



where B is nucleobase.

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

15 In one ~~embodiment~~example, the double stranded RNAi agent is in an unbuffered solution. Optionally, the unbuffered solution is saline or water. In another ~~embodiment~~example, 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~~example, the buffer solution is phosphate buffered saline (PBS). Another ~~aspect~~example 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~~example, the lipid formulation includes a lipid nanoparticle (LNP).

20 An additional ~~aspect~~example 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 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.

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

30 In certain ~~embodiment~~examples, the subject is a rhesus monkey, a cynomolgous monkey, a mouse, or a rat. In certain ~~embodiment~~examples HTT expression is inhibited by at least about 50% by the RNAi agent.

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

Another ~~aspect~~example 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~~example, treating comprises amelioration of at least one sign or symptom of the disease. In another ~~embodiment~~example, treating comprises prevention of progression of the disease.

In some ~~embodiment~~examples, the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

In some ~~embodiment~~examples, the dsRNA agent is administered to the subject intrathecally. In one ~~embodiment~~example, 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 ~~embodiment~~examples, the method further comprises measuring a level of HTT in a sample obtained from the subject.

Another ~~aspect~~example 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~~example, 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.

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 antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complement of nucleotides 142-195 of SEQ ID NO:1, 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.
- ~~1~~2. 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~~3. The dsRNA agent of claim ~~1~~2, 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~~4. The dsRNA agent of any one of claims 1-3 ~~or 2~~, wherein the lipophilic moiety is conjugated via a linker or a carrier.
- ~~4~~5. 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~~6. The dsRNA agent of claim 45, 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~~7. The dsRNA agent of claim 56, wherein the lipophilic moiety is conjugated to one or more internal positions in the double stranded region of the dsRNA agent.

78. The dsRNA agent of claim ~~56~~ or ~~67~~, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on the antisense strand.

89. The dsRNA agent of claim ~~56~~ or ~~67~~, 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 logK_{ow}, 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~~10. The dsRNA agent of any one of claims ~~1–3~~ and ~~5–19~~1–4, 6 and 9, 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~~11. The dsRNA agent of claim ~~20~~10, 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~~12. The dsRNA agent of any one of claims ~~1–34~~ and ~~56–24~~11, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

~~26~~13. The dsRNA agent of claim ~~25~~12, 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, geranyloxyhexanol, hexadecylglycerol,

borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

~~27~~14. The dsRNA agent of claim ~~26~~13, 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~~15. The dsRNA agent of claim ~~27~~14, wherein the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

~~29~~16. The dsRNA agent of claim ~~28~~15, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

~~30~~17. The dsRNA agent of claim ~~29~~16, wherein the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

~~31~~18. The dsRNA agent of any one of claims 1-~~43~~ and ~~56~~-~~30~~17, 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~~19. The dsRNA agent of claim ~~31~~18, 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 decaliny; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

~~33~~20. The dsRNA agent of any one of claims 1-~~43~~ and ~~65~~-~~32~~19, 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~~21. The ~~double-stranded iRNA~~ dsRNA agent of any one of claims 1-~~34~~ and ~~56~~-~~33~~20, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

~~35~~22. The dsRNA agent of any one of claims 1-~~34~~21, wherein the dsRNA agent comprises at least one modified nucleotide.

3623. The dsRNA agent of claim 3522, 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

3724. The dsRNA agent of claim 3522, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

3825. The dsRNA agent of any one of claims 3522-3724, 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-tetrahydrofuran-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.

3926. The dsRNA agent of claim 3825, 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.

4027. The dsRNA of claim 3825, 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~~28. The dsRNA of claim ~~38~~25, 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~~29. The dsRNA agent of any one of claims 1-~~44~~28, further comprising at least one phosphorothioate internucleotide linkage.

~~46~~30. The dsRNA agent of claim ~~45~~29, wherein the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

~~47~~31. The dsRNA agent of any one of claims 1-~~45~~30, wherein each strand is no more than 30 nucleotides in length.

~~48~~32. The dsRNA agent of any one of claims 1-~~47~~31, 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~~33. The dsRNA agent of any one of claims 1-~~49~~32, 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~~³⁴. The dsRNA agent of any one of claims 1-~~55~~³³, wherein each strand ~~has~~ is independently 19-30 nucleotides in length.

~~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 moiety or targeting ligand is conjugated via a bio-cleavable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.~~

~~62~~³⁵. The dsRNA agent of any one of claims 1-~~34~~ and ~~56-61~~³⁴, 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.~~

~~6836.~~ The dsRNA agent of any one of claims 1-~~6735~~, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

~~6937.~~ The dsRNA agent of claim ~~6836~~, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

~~7038.~~ The dsRNA agent of any one of claims 1-~~6937~~, 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.~~

~~7239.~~ A cell containing the dsRNA agent of any one of claims 1-~~7138~~.

~~7340.~~ A pharmaceutical composition for inhibiting expression of a gene encoding HTT, comprising the dsRNA agent of any one of claims 1-~~7138~~.

~~7441.~~ A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-~~7138~~ and a lipid formulation.

~~7542.~~ An *in vitro* 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-~~7138~~, or the pharmaceutical composition of claim ~~7340~~ or ~~7441~~; 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~~43. The method of ~~any one of claims 75-77~~42, 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~~44. ~~Use of 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~~38, or the pharmaceutical composition of claim ~~73~~40 or ~~74~~41 in the manufacture of a medicament for treating a subject diagnosed with an HTT-associated disease, thereby treating the subject.

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

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

~~84~~45. The ~~method-use~~ of claim ~~81~~44, wherein the HTT-associated disease is Huntington's disease.

~~85~~46. The ~~method-use~~ of any one of claims ~~81-84~~44 or ~~45~~, wherein the dsRNA agent is to be administered to the subject at a dose of ~~about~~ 0.01 mg/kg to ~~about~~ 50 mg/kg.

~~86~~47. The ~~method-use~~ of any one of claims ~~81-85~~44-46, wherein the dsRNA agent is to be 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~~48. The ~~method-use~~ of any one of claims ~~81-87~~44-47, further comprising ~~administering to the subject that~~ an additional agent is to be administered to the subject ~~suitable~~ for treatment or prevention of an HTT-associated disorder.