

CLAIMS

What is claimed is:

1.- ____ An RNAi comprising a first strand and a second strand, wherein

a) the first strand and the second strand form a duplex;

b) the first strand comprises a guide region of at least 19 bases, wherein the guide region comprises a seed region comprising bases 1-N of the guide strand, wherein N=7 or N=8; and

c) the second strand comprises a non-guide region of at least 19 bases, wherein the non-guide region comprises a bulge sequence opposite ~~of any one or more of bases 1-~~ (N+2)base 1 of the guide region in the duplex-, and
wherein the bulge is adjacent to the seed region.

2.- ____ The RNAi of claim 1, wherein ~~N=7 and the bulge is opposite base 1, 2, 3, 4, 5, 6, 7, 8, or 9 of the guide region-;~~

~~3. The RNAi of claim 1, wherein N=8 and the bulge is opposite base 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 of the guide region-~~

~~4. The RNAi of any one of claims 1-3, wherein the bulge is opposite base 1 or base N+2 of the guide region-~~

~~5. An RNAi comprising a first strand and a second strand, wherein~~

~~a) the first strand and the second strand form a duplex;~~

~~b) the first strand comprises a guide region of at least 19 bases, wherein the guide region comprises a seed region comprising bases 1-N of the guide strand, wherein N=7 or N=8; and~~

~~c) the second strand comprises a non-guide region of at least 19 bases, wherein the non-guide region comprises a bulge sequence opposite of any one or more of bases 1-(N+1) of the guide region in the duplex-~~

~~6. The RNAi of claim 5, wherein N=7 and the bulge is opposite base 1, 2, 3, 4, 5, 6, 7, or 8 of the guide region-~~

~~7. The RNAi of claim 5, wherein N=8 and the bulge is opposite base 1, 2, 3, 4, 5, 6, 7, 8, or 9 of the guide region-~~

~~8. The RNAi of any one of claims 5-7, wherein the bulge is opposite base 1 or base N+1 of the guide region.~~

~~9. An RNAi comprising a first strand and a second strand, wherein~~

~~a) the first strand and the second strand form a duplex;~~

~~b) the first strand comprises a guide region of at least 19 bases, wherein the guide region comprises a seed region comprising bases 1-N of the guide strand, wherein N=7 or N=8; and~~

~~c) the second strand comprises a non-guide region of at least 19 bases, wherein the non-guide region comprises a bulge sequence opposite of any one or more of bases 1-N of the guide region in the duplex.~~

~~10. The RNAi of claim 9, wherein N=7 and the bulge is opposite base 1, 2, 3, 4, 5, 6 or 7 of the guide region.~~

~~11. The RNAi of claim 9, wherein N=8 and the bulge is opposite base 1, 2, 3, 4, 5, 6, 7 or 8 of the guide region.~~

~~12. The RNAi of any one of claims 9-11, wherein the bulge is opposite base 1 or base N of the guide region.~~

~~13. The RNAi of any one of claims 1-12, wherein the bulge is opposite base 1 of the guide region.~~

~~14. The RNAi of any one of claims 1-13, wherein a) the bulge is formed by one or more bases of the non-guide strand in the duplex that lack a complementary base on the guide region, wherein the bulge is flanked by bases that do basepair with the guide strand;~~

~~15. The RNAi of any one of claims 1-14, wherein b) the bulge comprises 1 to 10 nucleotides; and/or~~

~~16. The RNAi of any one of claims 1-15, wherein the bulge comprises 1-3 nucleotides.~~

~~17. The RNAi of any one of claims 1-16, wherein c) the RNAi comprises a second bulge, wherein the second bulge is located on the first strand in the guide region located 3'3' to the seed region.~~

3. The RNAi of claim 1 or 2, wherein the bulge comprises 1-3 nucleotides.

4. An RNAi comprising:

(a) a first strand comprising a guide region which comprises the a nucleic acid sequence having about 90% identity to sequence 5'-UAGACAAUGAUUCACACGGU-3'

(SEQ ID NO:1) or has the sequence 5'-UAGACAAUGAUUCACACGGU-3' (SEQ ID NO:1) and a second strand comprising a non-guide region which comprises a nucleic acid sequence having about 90% identity to the sequence 5'-ACCGUGUGUCAUUGUCUAA-3' (SEQ ID NO:2) or has sequence 5'-ACCGUGUGUCAUUGUCUAA-3' (SEQ ID NO:2), wherein the first strand and second strand form a duplex and wherein the A residue at residue 18- or residue 19 of the second strand forms a bulge in the non-guide region;

(b) a first strand comprising a guide region which comprises a nucleic acid sequence having about 90% identity to the sequence 5'-UCGACAAUGAUUCACACGGU-3' (SEQ ID NO:15) or has the sequence 5'-UCGACAAUGAUUCACACGGU-3' (SEQ ID NO:15) and a second strand comprising a non-guide region which comprises a nucleic acid sequence having about 90% identity to the sequence 5'-ACCGUGUGUCAUUGUCGAA-3' (SEQ ID NO:16) or has the sequence 5'-ACCGUGUGUCAUUGUCGAA-3' (SEQ ID NO:16), wherein the first strand and second strand form a duplex and wherein the A residue at residue 18 or residue 19 of the second strand forms a bulge in the non-guide region; or

(c) a first strand comprising a guide region which comprises a nucleic acid sequence having about 90% identity to the sequence 5'-UAGACGAUGAUUCACACGGU-3' (SEQ ID NO:17) or has the sequence 5'-UAGACGAUGAUUCACACGGU-3' (SEQ ID NO:17) and a second strand comprising a non-guide region which comprises a nucleic acid sequence having about 90% identity to the sequence 5'-ACCGUGUGUCAUCGUCUAA-3' (SEQ ID NO:18) or has the sequence 5'-ACCGUGUGUCAUCGUCUAA-3' (SEQ ID NO:18), wherein the first strand and second strand form a duplex and wherein the A residue at residue 18 or residue 19 of the second strand forms a bulge in the non-guide region.

5. The RNAi of claim 4, wherein U residues at residues 11 and 12 of the guide region forms a bulge in the guide region.

6. The RNAi of any one of claims 1-~~17~~5, wherein:

(a) the duplex is between 19 and 25 or 19 and 23 base pairs in length;

~~19. The RNAi of any one of claims 1-18, wherein~~(b) the first and/or second strand further comprises a 3' overhang region, a 5' overhang region, or both 3' and 5' overhang regions-; and/or

~~20. The RNAi of any one of claims 1-19, wherein~~(c) the first strand and the second strand are linked by means of RNA linker capable of forming a loop structure.

~~21-7.~~ The RNAi of claim ~~206~~, wherein:

~~(a)~~ RNA linker comprises from 4 to 50 nucleotides;

~~22. The RNAi of claim, 4 to 20 nucleotides, or 21, wherein 13 nucleotides;~~

~~(b)~~ the loop structure comprises 4 to 20 nucleotides; ~~and/or~~

~~23. The RNAi of any one of claims 20-22, wherein (c) the RNAi comprises 5'5' to 3'3' the second strand, the RNA linker, and the first strand;~~

~~24. The RNAi of any one of claims 20-22, wherein; or~~ the RNAi comprises 5'5' to 3'3' the first strand, the RNA linker, and the second strand.

~~25-8.~~ The RNAi of any one of claims 1-~~247~~, wherein:

~~(a)~~ the sequence is improved to reduce off-target gene silencing;

~~26. The RNAi of any one of claims 1-25, wherein (b) the sequence comprises one or more CpG motifs; and/or~~

~~27. The RNAi of any one of claims 1-26, wherein(c) the sequence comprises one or more CpG motifs in the seed region.~~

~~28-9.~~ The RNAi of any one of claims 1-~~278~~, wherein the RNAi comprises the nucleotide sequence about 90% identical to the nucleotide sequence of SEQ ID NO:3 or has the nucleotide sequence of SEQ ID NO:3.

~~10.~~ The RNAi of any one of claims 1-9, wherein the RNAi is a small inhibitory RNA (siRNA), a microRNA (miRNA), or a small hairpin RNA (shRNA).

~~29-11.~~ The RNAi of any one of claims 1-~~2810~~, wherein the RNAi targets RNA encoding a polypeptide associated with a disorder.

~~30-12.~~ The RNAi of claim ~~2911~~, wherein:

~~(a)~~ the disorder is a CNS disorder;

~~31. The RNAi of claim 29 or 30, wherein(b) the disorder is lysosomal storage disease (LSD), Huntington's disease, epilepsy, Parkinson's disease, Alzheimer's disease, stroke,~~

corticobasal degeneration (CBD), corticogasal ganglionic degeneration (CBGD), frontotemporal dementia (FTD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or cancer of the brain-; and/or

~~32. The RNAi of anyone of claims 29-31, wherein(c)~~ the disorder is ~~Huntington's~~Huntington's disease.

~~33-13.~~ The RNAi of claim ~~3212~~, wherein the polypeptide is huntingtin-, wherein:

~~34. The RNAi of claim 33, wherein(a)~~ the huntingtin comprises a mutation associated with ~~Huntington's~~Huntington's disease-; and/or

~~35. The RNAi of any one of claims 32-34, wherein(b)~~ the guide region comprises the sequence ~~5'-5'~~-UAGACAAUGAUUCACACGGU-~~3'3'~~ (SEQ ID NO:-~~41~~) and the non-guide region comprises the sequence ~~5'-5'~~-ACCGUGUGUCAUUGUCUAA-~~3'3'~~ (SEQ ID NO:2-); or

~~36. The RNAi of any one of claims 32-34, wherein(c)~~ the guide region comprises the sequence ~~5'-5'~~-UCGACAAUGAUUCACACGGU-~~3'3'~~ (SEQ ID NO:-15) and the non-guide region comprises the sequence ~~5'-5'~~-ACCGUGUGUCAUUGUCGAA-~~3'3'~~ (SEQ ID NO: 16-); or

~~37. The RNAi of any one of claims 32-34, wherein(d)~~ the guide region comprises the sequence ~~5'-5'~~-UAGACGAUGAUUCACACGGU-~~3'3'~~ (SEQ ID NO:-17) and the non-guide region comprises the sequence ~~5'-5'~~-ACCGUGUGUCAUCGUCUAA-~~3'3'~~ (SEQ ID NO:-18).

~~38-14.~~ A method to reduce the toxicity of a RNAi comprising introducing a bulge in the non-guide region of the RNAi to generate a RNAi of any one of claims 1-~~37~~13.

~~39-15.~~ An expression construct comprising nucleic acid encoding the RNAi of any one of claims 1-~~38~~13.

~~40-16.~~ The expression construct of claim ~~3915~~ wherein the nucleic acid encoding the RNAi comprises a miRNA scaffold.

~~41-17.~~ The expression construct of claim ~~39-40~~16, wherein the nucleic acid encoding the RNAi comprises a miR-155 scaffold.

18. The expression construct of any one of claims 15-17, wherein the nucleic acid encoding the RNAi is operably linked to a promoter.

~~42-19.~~ The expression construct of claim ~~41~~18, wherein:

(a) the promoter is capable of expressing the RNAi in the brain of a mammal; and/or

(b) the promoter is selected from a cytomegalovirus (CMV) immediate early promoter, an RSV LTR, a MoMLV LTR, a phosphoglycerate kinase- 1 (PGK) promoter, a simian virus 40 (SV40) promoter, a CK6 promoter, a transthyretin promoter (TTR), a TK promoter, a tetracycline responsive promoter (TRE), an HBV promoter, an hAAT promoter, a LSP promoter, a chimeric liver-specific promoter (LSP), an E2F promoter, a telomerase (hTERT) promoter; a cytomegalovirus enhancer/chicken beta-actin/Rabbit β -globin promoter (CAG) promoter, an elongation factor 1 α promoter (EF1 α) promoter, a human β -glucuronidase promoter, a chicken β -actin (CBA) promoter, a retroviral Rous sarcoma virus (RSV) LTR promoter, a dihydrofolate reductase promoter, and a 13-actin promoter.

~~43-20.~~ The expression construct of any one of claims ~~39-42~~15-19, wherein the expression construct further comprises a polyadenylation signal-

~~44. The expression construct of claim 43,~~ wherein optionally the polyadenylation signal is a bovine growth hormone polyadenylation signal, an SV40 polyadenylation signal, or a HSV TK pA.

~~45-21.~~ A vector comprising the expression construct of any one of claims ~~39-44~~15-20.

~~46-22.~~ The vector of claim ~~45~~21, wherein the vector is a recombinant adeno-associated virus (rAAV) vector, a recombinant adenoviral vector, a recombinant lentiviral vector or a recombinant herpes simplex virus (HSV) vector.

~~47-23.~~ The vector of claim ~~46~~22, wherein

(a) the vector is a recombinant adenoviral vector-

~~48. The vector of claim 47, wherein the recombinant adenoviral vector is~~ derived from Adenovirus serotype 2, 1, 5, 6, 19, 3, 11, 7, 14, 16, 21, 12, 18, 31, 8, 9, 10, 13, 15, 17, 19, 20, 22, 23, 24-30, 37, 40, 41, AdHu2, AdHu 3, AdHu4, AdHu24, AdHu26, AdHu34, AdHu35,

AdHu36, AdHu37, AdHu41, AdHu48, AdHu49, AdHu50, AdC6, AdC7, AdC69, bovine Ad type 3, canine Ad type 2, ovine Ad, or porcine Ad type 3;

~~49. The vector of claim 47, wherein the recombinant adenoviral vector is derived from adenovirus serotype 2; or a variant of adenovirus serotype 5.~~

~~50. The vector of claim 46, wherein (b) the vector is a recombinant lentiviral vector;~~

~~51. The vector of claim 50, wherein the recombinant lentiviral vector is derived from a lentivirus pseudotyped with vesicular stomatitis virus (VSV), lymphocytic choriomeningitis virus (LCMV), Ross river virus (RRV), Ebola virus, Marburg virus, Mokala virus, Rabies virus, RD114 or variants therein; or~~

~~52. The vector of claim 46, wherein (c) the vector is a rHSV vector;~~

~~53. The vector of claim 52, wherein the rHSV vector is derived from rHSV-1 or rHSV-2; or~~

~~54. 24. The vector of claim 46, wherein the vector is a rAAV vector;~~

~~55. The rAAV vector of claim 54, and wherein the expression construct is flanked by one or more AAV inverted terminal repeat (ITR) sequences.~~

~~56. 25. The rAAV vector of claim 55, wherein the expression construct is flanked by two AAV ITRs;~~

~~57. The rAAV vector of claim 55; and/or 56;~~

wherein the AAV ITRs are AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, ~~AAVrh10~~AAVrh10, AAV11, ~~AAV12~~AAV12, AAV2R471A, AAV DJ, a goat AAV, bovine AAV, or mouse AAV serotype ITRs.

~~58. 26. The rAAV vector of claim 24 or 25, wherein the rAAV vector comprise 5' to 3' an AAV2 ITR, a promoter, nucleic acid encoding the RNAi, a polyadenylation signal, and an AAV2 ITR; and wherein:~~

~~(a) the promoter is a CBA promoter;~~

~~(b) the polyadenylation signal is a bovine growth hormone polyadenylation signal; and/or~~

~~(c) the rAAV vector comprises 5' to 3' an AAV2 ITR, the CBA promoter, nucleic acid encoding the RNAi, a bovine growth hormone polyadenylation signal, and an AAV2 ITR.~~

~~27.~~ The rAAV vector of any one of claims ~~55-57~~, wherein the AAV ITRs are AAV2 ITRs.

~~59.~~ The rAAV vector of any one of claims ~~54-58~~24-26, wherein the vector further comprises a stuffer nucleic acid.

~~60-28.~~ The rAAV vector of claim ~~59~~27, wherein:

(a) the stuffer nucleic acid is located between the promoter and the nucleic acid encoding the RNAi; and/or

~~61.~~ (b) the stuffer nucleic acid comprises nucleic acid encoding a green fluorescent protein (GFP), a human alpha-1-antitrypsin (AAT) stuffer sequence, or a C16 P1 chromosome 16 P1 clone (human C16) stuffer sequence, wherein optionally the stuffer nucleic acid comprises a nucleic acid sequence from about nucleotide 1692 to nucleotide 2720 of SEQ ID NO: 13.

~~29.~~ The rAAV vector of any one of claims ~~54-60~~24-28, wherein the vector is a self-complementary rAAV vector.

~~62.~~ The rAAV vector of claim ~~61~~, wherein the vector comprises first nucleic acid sequence encoding the RNAi and a second nucleic acid sequence encoding a complement of the RNAi, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

~~63.~~ The rAAV vector of claim ~~62~~, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

~~64-30.~~ A cell comprising the vector of any one of claims ~~45-53~~21-23 or the rAAV vector of any one of claims ~~54-63~~24-29.

~~65-31.~~ A viral particle comprising the vector of claim ~~45~~21, wherein the viral particle is an AAV particle encapsidating the rAAV vector, an adenovirus particle encapsidating the recombinant adenoviral vector, a lentiviral particle encapsidating the recombinant lentiviral vector or an HSV particle encapsidating the recombinant HSV vector.

~~66-32.~~ The viral particle of claim ~~65~~31, wherein:

(a) the viral particle is an adenovirus particle encapsidating the recombinant adenoviral vector;

~~67. The viral particle of claim 66~~, wherein the adenovirus particle comprises a capsid from Adenovirus serotype ~~2~~, 1, 5, 6, 19, 3, 11, 7, 14, 16, 21, 12, 18, 31, 8, 9, 10, 13, 15, 17, 19, 20, 22, 23, 24-30, 37, 40, 41, AdHu2, AdHu 3, AdHu4, AdHu24, AdHu26, AdHu34, AdHu35, AdHu36, AdHu37, AdHu41, AdHu48, AdHu49, AdHu50, AdC6, AdC7, AdC69, bovine Ad type 3, canine Ad type 2, ovine Ad, or porcine Ad type 3~~7~~.

~~68. The viral particle of claim 66, wherein the adenovirus particle comprises an adenovirus serotype 2 capsid; or a variant of an adenoviral serotype 5 capsid.~~

~~69. The viral particle of claim 66, wherein (b)~~ the viral particle is a lentiviral particle encapsidating the recombinant lentiviral vector~~7~~.

~~70. The viral particle of claim 69~~, wherein optionally the lentiviral particle comprises a capsid pseudotyped with vesicular stomatitis virus (VSV), lymphocytic choriomeningitis virus (LCMV), Ross river virus (RRV), Ebola virus, Marburg virus, Mokala virus, Rabies virus, RD114 or variants therein~~7~~; or

~~71. The viral particle of claim 66, wherein (c)~~ the viral particle is a HSV particle~~7~~.

~~72. The viral particle of claim 71~~, wherein the HSV particle is a rHSV-1 particle or a rHSV-2 particle.

~~73-33.~~ A recombinant AAV particle comprising the rAAV vector of any one of claims ~~54-63~~24-29.

~~74-34.~~ The rAAV particle of claim ~~73~~33, wherein the AAV viral particle comprises an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, ~~AAVrh10, AAV11, AAV12~~AAVrh10, AAV11, AAV12, AAV2R471A, AAV2/2-7m8, AAV DJ, AAV2 N587A, AAV2 E548A, AAV2 N708A, AAV V708K, a goat AAV, AAV1/AAV2 chimeric, bovine AAV, or mouse AAV capsid ~~rAAV2/HBoV1~~rAAV2/HBoV1 serotype capsid.

~~75-35.~~ The rAAV particle of claim ~~73~~33 or ~~74~~34, wherein the ITR and the capsid of the rAAV viral particle are derived from the same AAV serotype~~7~~.

~~76. The rAAV particle of claim 73 or 74, wherein the ITR and the capsid of the rAAV viral particle or~~ are derived from different AAV serotypes.

~~77-36.~~ The rAAV particle of ~~claim 76~~any one of claims 33-35, wherein the ITR is derived from AAV2 and the capsid of the rAAV particle is derived from AAV1.

~~78-37.~~ A composition comprising the viral particle of ~~any one of claims 65-72~~claim 31 or 32, or the rAAV particle of any one of claims ~~73-77~~.

~~79.~~ ~~The composition of claim 78, 33-36, optionally~~ wherein the composition further comprises a pharmaceutically acceptable carrier.

~~80-38.~~ A method for inhibiting or reducing the expression of a polypeptide in a ~~mammal~~mammalian disease comprising administering to the mammal the RNAi of any one of claims 1-~~37~~13; the expression construct of any one of claims ~~39-44~~15-20; the vector of any one of claims ~~45-54~~21-23; the rAAV vector of any one of claims ~~55-63~~24-29; the viral particle of ~~any one of claims 65-72; the rAAV particle of any one of claims 73-77; or the composition of claims 78~~claim 31 or 32; the rAAV particle of any one of claims 33-36; or the composition of claim 37, wherein the RNAi targets an RNA encoding the polypeptide.

~~81-39.~~ A method for inhibiting the accumulation of a polypeptide in a cell of a mammal comprising administering to the mammal the RNAi of any one of claims 1-~~37~~13; the expression construct of any one of claims ~~39-44~~15-20; the vector of any one of claims ~~45-53~~21-23; the rAAV vector of any one of claims ~~54-63~~24-29; the viral particle of ~~any one of claims 65-72~~claim 31 or 32; the rAAV particle of any one of claims ~~73-77~~33-36; or the composition of ~~claims 78 or 79~~claim 37, wherein the RNAi targets an RNA encoding the polypeptide.

~~82.~~ ~~The method of claim 80 or 81, wherein the mammal is a human.~~

~~83-40.~~ Use of the RNAi of any one of claims 1-~~37~~13; the expression construct of any one of claims ~~39-44~~15-20; the vector of any one of claims ~~45-53~~21-23; the rAAV vector of any one of claims ~~54-63~~24-29; the viral particle of ~~any one of claims 65-72~~claim 31 or 32; the rAAV particle of any one of claims ~~73-77~~33-36; or the composition of ~~claims 78 or 79~~claim 37, in the manufacture of a medicament for ~~use in the method of any one of claims 80-82~~inhibiting or reducing expression of a polypeptide in a mammalian disease, or inhibiting the accumulation of a polypeptide in a cell of a mammal.

~~84.41. The RNAi of any one of claims 1-3713; the expression construct of any one of claims 39-4415-20; the vector of any one of claims 45-5321-23; the rAAV vector of any one of claims 54-6324-29; the viral particle of any one of claims 65-72claim 31 or 32; the rAAV particle of any one of claims 73-7733-36; or the composition of claims 78 or 79 for use in the method of any one of claims 80-82claim 37 when used in inhibiting or reducing the expression of a polypeptide in a mammalian disease or inhibiting the accumulation of a polypeptide in a cell of a mammal.~~

~~85.42. A kit for inducing RNA interference in a mammal comprising the RNAi of any one of claims 1-3713; the expression construct of any one of claims 39-4415-20; the vector of any one of claims 45-5321-23; the rAAV vector of any one of claims 54-6324-29; the viral particle of any one of claims 65-7231 or 32; the rAAV particle of any one of claims 73-7733-36; or the composition of claims 78 or 79.~~

~~86. The kit of claim 85, wherein the mammal is a human.~~

~~87. A kit for use in the method of any one of claims 80-82 comprising the RNAi of any one of claims 1-37; the expression construct of any one of claims 39-44; the vector of any one of claims 45-53; the rAAV vector of any one of claims 54-63; the viral particle of any one of claims 65-72; the rAAV particle of any one of claims 73-77; or the composition of claims 78 or 79.~~

~~88. An RNAi comprising a first strand comprising a guide region which comprises the sequence 5' UAGACAAUGAUUCACACGGU 3' (SEQ ID NO: 1) and a second strand comprising a non-guide region which comprises the sequence 5' ACCGUGUGUCAUUGUCUAA 3' (SEQ ID NO:2), wherein the first strand and second strand form a duplex and wherein the A residue at residue 18 or residue 19 of the second strand forms a bulge in the non-guide region.~~

~~89. The RNAi of claim 88, wherein the guide region comprises a nucleic acid sequence having about 90% identity to SEQ ID NO:1.~~

~~90. The RNAi of claim 88, wherein the non-guide region comprises a nucleic acid sequence having about 90% identity to SEQ ID NO:2.~~

~~91. The RNAi of any one of claims 88-90, wherein the sequence is improved to reduce off-target gene silencing.~~

~~92. The RNAi of any one of claims 88-91, wherein sequence comprises one or more CpG motifs.~~

~~93. The RNAi of any one of claims 88-92, wherein the sequence comprises one or more CpG motifs in a seed region.~~

~~94. An RNAi comprising a first strand comprising a guide region which comprises the sequence 5' UCGACAAUGAUUCACACGGU 3' (SEQ ID NO: 15) and a second strand comprising a non-guide region which comprises the sequence 5' ACCGUGUGUCAUUGUCGAA 3' (SEQ~~

~~ID NO: 16), wherein the first strand and second strand form a duplex and wherein the A residue at residue 18 or residue 19 of the second strand forms a bulge in the non-guide region.~~

~~95. An RNAi comprising a first strand comprising a guide region which comprises the sequence 5' UAGACGAUGAUUCACACGGU 3' (SEQ ID NO: 17) and a second strand comprising a non-guide region which comprises the sequence 5' ACCGUGUGUCAUCGUCUAA 3' (SEQ ID NO: 18), wherein the first strand and second strand form a duplex and wherein the A residue at residue 18 or residue 19 of the second strand forms a bulge in the non-guide region.~~

~~96. The RNAi of claim wherein the guide region comprises a nucleic acid sequence having about 90% identity to SEQ ID NO: 15 and the non-guide region comprises a nucleic acid sequence having about 90% identity to SEQ ID NO: 16 or a nucleic acid sequence having about 90% identity to SEQ ID NO: 17 and the non-guide region comprises a nucleic acid sequence having about 90% identity to SEQ ID NO: 18.~~

~~97. The RNAi of any one of claims 88-96, wherein U residues at residues 11 and 12 of the guide region forms a bulge in the guide region.~~

~~98. The RNAi of any one of claims 88-97, wherein the duplex is between 19 and 25 or 19 and 23 base pairs in length.~~

~~99. The RNAi of any one of claims 88-98, wherein the first and/or second strand further comprises a 3' overhang region, a 5' overhang region, or both 3' and 5' overhang regions.~~

~~100. The RNAi of any one of claims 88-99, wherein the first strand and the second strand are linked by means of a RNA linker capable of forming a loop structure.~~

~~101. The RNAi of claim 100, wherein RNA linker capable of forming a loop structure comprises from 4 to 50 nucleotides.~~

~~102. The RNAi of claim 100 or 101, wherein RNA linker capable of forming a loop structure comprises from 4 to 20 nucleotides.~~

~~103. The RNAi of any one of claims 100-102, wherein RNA linker capable of forming a loop structure comprises 13 nucleotides.~~

~~104. The RNAi of any one of claims 88-103, wherein the RNAi comprises the nucleotide sequence of SEQ ID NO:3.~~

~~105. The RNAi of claim of any one of claims 88-103, wherein the RNAi comprises a nucleotide sequence about 90% identical to the nucleotide sequence of SEQ ID NO:3.~~

~~106. The RNAi of any one of claims 88-94, wherein the RNAi is a small inhibitory RNA (siRNA), a microRNA (miRNA), or a small hairpin RNA (shRNA).~~

~~107. An expression construct comprising nucleic acid encoding the RNAi of any one of claims 88-106.~~

~~108. The expression construct of claim 107 wherein the nucleic acid encoding the RNAi comprises a miRNA scaffold.~~

~~109. The expression construct of claim 108 wherein the nucleic acid encoding the RNAi comprises a miR-155 scaffold.~~

~~110. The expression construct of any one of claims 107-109, wherein the nucleic acid encoding the RNAi is operably linked to a promoter.~~

~~111. The expression construct of claim 110, wherein the promoter is capable of expressing the RNAi in the brain of a mammal.~~

~~112. The expression construct of claim 110 or 111, wherein the promoter is selected from a cytomegalovirus (CMV) immediate early promoter, an RSV LTR, a MoMLV LTR, a phosphoglycerate kinase 1 (PGK) promoter, a simian virus 40 (SV40) promoter, a CK6 promoter, a transthyretin promoter (TTR), a TK promoter, a tetracycline responsive promoter (TRE), an HBV promoter, an hAAT promoter, a LSP promoter, a chimeric liver specific promoter (LSP), an E2F promoter, a telomerase (hTERT) promoter, a cytomegalovirus enhancer/chicken beta actin/Rabbit β globin promoter (CAG) promoter, an elongation factor 1-alpha promoter (EF1-alpha) promoter, a human β glucuronidase promoter, a chicken β actin (CBA) promoter, a retroviral Rous sarcoma virus (RSV) LTR promoter, a dihydrofolate reductase promoter, and a 13-actin promoter.~~

~~113. The expression construct of any one of claims 110-112, wherein the promoter is a hybrid chicken β actin promoter.~~

~~114. The expression construct of any one of claims 110-113, wherein the expression construct further comprises a polyadenylation signal.~~

~~115. The expression construct of claim 114, wherein the polyadenylation signal is a bovine growth hormone polyadenylation signal.~~

~~116. A vector comprising the expression construct of any one of claims 107-115.~~

~~117. The vector of claim 116, wherein the vector is a recombinant adeno-associated virus (rAAV) vector, a recombinant adenoviral vector, a recombinant lentiviral vector or a recombinant herpes simplex virus (HSV) vector.~~

~~118. The vector of claim 117, wherein the vector is a recombinant adenoviral vector.~~

~~119. The vector of claim 118, wherein the recombinant adenoviral vector is derived from Adenovirus serotype 2, 1, 5, 6, 19, 3, 11, 7, 14, 16, 21, 12, 18, 31, 8, 9, 10, 13, 15, 17, 19, 20, 22, 23, 24-30, 37, 40, 41, AdHu2, AdHu 3, AdHu4, AdHu24, AdHu26, AdHu34, AdHu35, AdHu36, AdHu37, AdHu41, AdHu48, AdHu49, AdHu50, AdC6, AdC7, AdC69, bovine Ad type 3, canine Ad type 2, ovine Ad, or porcine Ad type 3.~~

~~120. The vector of claim 119, wherein the recombinant adenoviral vector is derived from adenovirus serotype 2 or a variant of adenoviral serotype 5.~~

~~121. The vector of claim 117, wherein the vector is a recombinant lentiviral vector.~~

~~122. The vector of claim 121, wherein the recombinant lentiviral vector is derived from a lentivirus pseudotyped with vesicular stomatitis virus (VSV), lymphocytic choriomeningitis~~

~~virus (LCMV), Ross river virus (RRV), Ebola virus, Marburg virus, Mokala virus, Rabies virus, RD114 or variants therein.~~

~~123. The vector of claim 117, wherein the vector is a rHSV vector.~~

~~124. The vector of claim 123, wherein the rHSV vector is derived from rHSV 1 or rHSV 2.~~

~~125. The vector of claim 117, wherein the vector is a recombinant AAV (rAAV) vector.~~

~~126. The rAAV vector of claim 125, wherein the expression construct is flanked by one or more AAV inverted terminal repeat (ITR) sequences.~~

~~127. The rAAV vector of claim 126, wherein the expression construct is flanked by two AAV ITRs.~~

~~128. The rAAV vector of claim 126 or 127, wherein the AAV ITRs are AAV ITRs are AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV 12, AAV2R471A, AAV DJ, a goat AAV, bovine AAV, or mouse AAV serotype ITRs.~~

~~129. The rAAV vector of any one of claims 125-128, wherein the AAV ITRs are AAV2 ITRs.~~

~~130. The rAAV vector of claim 129, wherein the rAAV vector comprises 5' to 3' an AAV2 ITR, a promoter, nucleic acid encoding the RNAi, a polyadenylation signal, and an AAV2 ITR.~~

~~131. The rAAV vector of claim 130 wherein the promoter is a CBA promoter.~~

~~132. The rAAV vector of claim 130 or 131, wherein the polyadenylation signal is a bovine growth hormone polyadenylation signal.~~

~~133. The rAAV vector of any one of claims 130-132, wherein the rAAV vector comprises 5' to 3' an AAV2 ITR, the CBA promoter, nucleic acid encoding the RNAi, a bovine growth hormone polyadenylation signal, and an AAV2 ITR.~~

~~134. The rAAV vector of claim 133, wherein the vector further comprise a stuffer nucleic acid.~~

~~135. The rAAV vector of claim 133, wherein the stuffer nucleic acid comprises nucleic acid encoding a green fluorescent protein (GFP).~~

~~136. The rAAV vector of claim 134 or 135, wherein the stuffer nucleic acid is located between the promoter and the nucleic acid encoding the RNAi.~~

~~137. The rAAV vector of any one of claims 125-136, wherein the RNAi comprises the nucleotide sequence of SEQ ID NO:3.~~

~~138. The rAAV vector of any one of claims 125-136, wherein the RNAi comprises a nucleotide sequence about 90% identical to the nucleotide sequence of SEQ ID NO:3~~

~~139. The rAAV vector of any one of claims 125-138, wherein the vector is a self-complementary vector.~~

~~140. The rAAV vector of claim 139, wherein the vector comprises first nucleic acid sequence encoding the RNAi and a second nucleic acid sequence encoding a complement of the RNAi,~~

wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

~~141. The rAAV vector of claim 140, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.~~

~~142. A cell comprising the vector of any one of claims 116-124 or the rAAV vector of any one of claims 125-141.~~

~~143. The cell of claim 142, wherein the cell is a central nervous system (CNS) cell.~~

~~144. A viral particle comprising the vector of claim 116, wherein the viral particle is an AAV particle encapsidating the rAAV vector, an adenovirus particle encapsidating the recombinant adenoviral vector, a lentiviral particle encapsidating the recombinant lentiviral vector or an HSV particle encapsidating the recombinant HSV vector.~~

~~145. The viral particle of claim 144, wherein the viral particle is an adenovirus particle encapsidating the recombinant adenoviral vector.~~

~~146. The viral particle of claim 145, wherein the adenovirus particle comprises a capsid from Adenovirus serotype 2, 1, 5, 6, 19, 3, 11, 7, 14, 16, 21, 12, 18, 31, 8, 9, 10, 13, 15, 17, 19, 20, 22, 23, 24, 30, 37, 40, 41, AdHu2, AdHu3, AdHu4, AdHu24, AdHu26, AdHu34, AdHu35, AdHu36, AdHu37, AdHu41, AdHu48, AdHu49, AdHu50, AdC6, AdC7, AdC69, bovine Ad type 3, canine Ad type 2, ovine Ad, or porcine Ad type 3.~~

~~147. The viral particle of claim 146, wherein the adenovirus particle comprises an adenovirus serotype 2 capsid or a variant of an adenoviral serotype 5 capsid.~~

~~148. The viral particle of claim 144, wherein the viral particle is a lentiviral particle encapsidating the recombinant lentiviral vector.~~

~~149. The viral particle of claim 148, wherein the lentiviral particle comprises a capsid pseudotyped with vesicular stomatitis virus (VSV), lymphocytic choriomeningitis virus (LCMV), Ross river virus (RRV), Ebola virus, Marburg virus, Mokala virus, Rabies virus, RD114 or variants therein.~~

~~150. The viral particle of claim 144, wherein the viral particle is a HSV particle.~~

~~151. The viral particle of claim 150, wherein the HSV particle is a rHSV-1 particle or a rHSV-2 particle.~~

~~152. A recombinant AAV particle comprising the rAAV vector of any one of claims 125-141.~~

~~153. The rAAV particle of claim 141, wherein the AAV viral particle comprises an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV2/2-7m8, AAV DJ, AAV2 N587A, AAV2 E548A, AAV2 N708A, AAV2 V708K, goat AAV, AAV1/AAV2 chimeric, bovine AAV, mouse AAV, or rAAV2/HBoV1 serotype capsid.~~

~~154. The rAAV particle of claim 152 or 153, wherein the ITR and the capsid of the rAAV viral particle are derived from the same AAV serotype.~~

~~155. The rAAV particle of claim 152 or 153, wherein the ITR and the capsid of the rAAV viral particles are derived from different AAV serotypes.~~

~~156. The rAAV particle of any one of claims 152-155, wherein the rAAV viral particle comprises AAV2 capsid.~~

~~157. The rAAV particle of claim 156, wherein the rAAV viral particle comprises an AAV1 capsid, and wherein the vector comprises AAV2 ITRs.~~

~~158. A composition comprising the viral particle of any one of claims 144-151 or the rAAV particle of any one of claims 152-157.~~

~~159. The composition of claim 158 further comprises a pharmaceutically acceptable carrier.~~

~~160. A method for treating Huntington's disease in a mammal comprising administering to the mammal the composition of claim 158 or 159.~~

~~161. A method for inhibiting the expression of htt in a mammal with Huntington's disease comprising administering to the mammal the composition of claim 158 or 159.~~

~~162. A method for inhibiting the accumulation of htt in a cell of a mammal with Huntington's disease comprising administering to the mammal the pharmaceutical composition of claim 158 or 159.~~

~~163. A method for treating Huntington's disease in a mammal comprising administering to the mammal an RNAi comprising a first strand comprising a first nucleic acid comprising the sequence 5' UAGACAAUGAUUCACACGGU 3' (SEQ ID NO: 1) and a second strand comprising a second nucleic acid comprising the sequence 5' ACCGUGUGUCAUUGUCUAA 3' (SEQ ID NO:2), wherein the A residue at residue 18 or residue 19 of the second strand does not form a basepair with a residue in the first strand.~~

~~164. A method for inhibiting the expression of htt in a mammal with Huntington's disease comprising administering to the mammal an RNAi comprising a first strand comprising a first nucleic acid comprising the sequence 5' UAGACAAUGAUUCACACGGU 3' (SEQ ID NO: 1) and a second strand comprising a second nucleic acid comprising the sequence 5' ACCGUGUGUCAUUGUCUAA 3' (SEQ ID NO:2), wherein the A residue at residue 18 or residue 19 of the second strand does not form a basepair with a residue in the first strand.~~

~~165. A method for inhibiting the accumulation of htt in a cell of a mammal with Huntington's disease comprising administering to the mammal an RNAi comprising a first strand comprising a first nucleic acid comprising the sequence 5' UAGACAAUGAUUCACACGGU 3' (SEQ ID NO: 1) and a second strand comprising a second nucleic acid comprising the sequence 5' ACCGUGUGUCAUUGUCUAA 3' (SEQ ID NO:2), wherein the A residue at residue 18 or residue 19 of the second strand does not form a basepair with a residue in the first strand.~~

~~166. The method of any one of claims 163-165, wherein the first strand comprises a nucleic acid sequence having about 90% identity to SEQ ID NO: 1.~~

~~167. The method of any one of claims 163-165, wherein the second strand comprises a nucleic acid sequence having about 90% identity to SEQ ID NO:2.~~

~~168. The method of any one of claims 163-167, wherein the nucleic acid is improved to reduce off target gene silencing.~~

~~169. The method of any one of claims 163-168, wherein the nucleic acid comprises one or more CpG motifs.~~

~~170. The method of any one of claims 163-169, wherein the nucleic acid comprises one or more CpG motifs in a seed region.~~

~~171. A method for treating Huntington's disease in a mammal comprising administering to the mammal an RNAi comprising a first strand comprising a first nucleic acid comprising the sequence 5' UCGACAAUGAUUCACACGGU 3' (SEQ ID NO: 15) and a second strand comprising a second nucleic acid comprising the sequence 5' ACCGUGUGUCAUUGUCGAA 3' (SEQ ID NO: 16), wherein the A residue at residue 18 or residue 19 of the second strand does not form a basepair with a residue in the first strand.~~

~~172. A method for inhibiting the expression of htt in a mammal with Huntington's disease comprising administering to the mammal an RNAi comprising a first strand comprising a first nucleic acid comprising the sequence 5' UCGACAAUGAUUCACACGGU 3' (SEQ ID NO: 15) and a second strand comprising a second nucleic acid comprising the sequence 5' ACCGUGUGUCAUUGUCGAA 3' (SEQ ID NO: 16), wherein the A residue at residue 18 or residue 19 of the second strand does not form a basepair with a residue in the first strand.~~

~~173. A method for inhibiting the accumulation of htt in a cell of a mammal with Huntington's disease comprising administering to the mammal an RNAi comprising a first strand comprising a first nucleic acid comprising the sequence 5' UCGACAAUGAUUCACACGGU 3' (SEQ ID NO: 15) and a second strand comprising a second nucleic acid comprising the sequence 5' ACCGUGUGUCAUUGUCGAA 3' (SEQ ID NO: 16), wherein the A residue at residue 18 or residue 19 of the second strand does not form a basepair with a residue in the first strand.~~

~~174. The method of any one of claims 171-173, wherein the first strand comprises a nucleic acid sequence having about 90% identity to SEQ ID NO: 15 but maintains the CpG motif.~~

~~175. The method of any one of claims 171-174, wherein the second strand comprises a nucleic acid sequence having about 90% identity to SEQ ID NO: 16 but maintains the CpG motif.~~

~~176. A method for treating Huntington's disease in a mammal comprising administering to the mammal an RNAi comprising a first strand comprising a first nucleic acid comprising the sequence 5' UAGACGAUGAUUCACACGGU 3' (SEQ ID NO: 17) and a second strand comprising a second nucleic acid comprising the sequence 5' ACCGUGUGUCAUCGUCUAA 3' (SEQ ID NO: 18), wherein the A residue at residue 18 or residue 19 of the second strand does not form a basepair with a residue in the first strand.~~

~~177. A method for inhibiting the expression of htt in a mammal with Huntington's disease comprising administering to the mammal an RNAi comprising a first strand comprising a first nucleic acid comprising the sequence 5' UAGACGAUGAUUCACACGGU 3' (SEQ ID NO: 17) and a second strand comprising a second nucleic acid comprising the sequence 5'~~

~~ACCGUGUGUCAUCGUCUAA 3' (SEQ ID NO: 18), wherein the A residue at residue 18 or residue 19 of the second strand does not form a basepair with a residue in the first strand.~~

~~178. A method for inhibiting the accumulation of htt in a cell of a mammal with Huntington's disease comprising administering to the mammal an RNAi comprising a first strand comprising a first nucleic acid comprising the sequence 5' UAGACGAUGAUUCACACGGU 3' (SEQ ID NO: 17) and a second strand comprising a second nucleic acid comprising the sequence 5' ACCGUGUGUCAUCGUCUAA 3' (SEQ ID NO: 18), wherein the A residue at residue 18 or residue 19 of the second strand does not form a basepair with a residue in the first strand.~~

~~179. The method of any one of claims 176-178, wherein the first strand comprises a nucleic acid sequence having about 90% identity to SEQ ID NO: 17 but maintains the CpG motif.~~

~~180. The method of any one of claims 176-179, wherein the second strand comprises a nucleic acid sequence having about 90% identity to SEQ ID NO: 18 but maintains the CpG motif.~~

~~181. The method of any one of claims 163-180, wherein U residues at residues 11 and 12 of the first nucleic acid do not form a basepair with a residue in the second strand.~~

~~182. The method of any one of claims 163-181, wherein the duplex is between 18 and 25 base pairs in length.~~

~~183. The method of any one of claims 163-182, wherein the first and/or second strand further comprises a 3' overhang region, a 5' overhang region, or both 3' and 5' overhang regions.~~

~~184. The method of any one of claims 163-183, wherein the first strand and the second strand are linked by means of an RNA capable of forming a loop structure.~~

~~185. The method of any one of claims 163-184, wherein RNA capable of forming a loop structure comprises from 4 to 50 nucleotides or 4 to 20 nucleotides.~~

~~186. The method of any one of claims 163-185, wherein RNA capable of forming a loop structure comprises 13 nucleotides.~~

~~187. The method of any one of claims 163-186, wherein the RNAi comprises the nucleotide sequence of SEQ ID NO:3.~~

~~188. The method of any one of claims 163-187, wherein the RNAi comprises a nucleotide sequence about 90% identical to the nucleotide sequence of SEQ ID NO:3.~~

~~189. The method of any one of claims 163-188, wherein the first strand of the RNAi is 5' to the second strand.~~

~~190. The method of any one of claims 163-189, wherein the second strand of the RNAi is 5' to the first strand.~~

~~191. The method of any one of claims 163-166, wherein the RNAi is encoded on an expression construct.~~

~~192. The method of any one of claims 163-191, wherein the nucleic acid encoding the RNAi comprises a miRNA scaffold.~~

~~193. The method of claim 192, wherein the miRNA scaffold is a miR-155 scaffold.~~

~~194. The method of any one of claims 163-193, wherein the nucleic acid encoding the RNAi is operably linked to a promoter.~~

~~195. The method of claim 194, wherein the promoter is capable of expressing the RNAi in the brain of a mammal.~~

~~196. The method of claim 195, wherein the promoter is selected from a cytomegalovirus (CMV) immediate-early promoter, a RSV LTR, a MoMLV LTR, a phosphoglycerate kinase-1 (PGK) promoter, a simian virus 40 (SV40) promoter, a CK6 promoter, a transthyretin promoter (TTR), a TK promoter, a tetracycline responsive promoter (TRE), an HBV promoter, an hAAT promoter, a LSP promoter, a chimeric liver-specific promoter (LSP), a E2F promoter, a telomerase (hTERT) promoter, a cytomegalovirus enhancer/chicken beta-actin/Rabbit β globin (CAG) promoter, an elongation factor 1-alpha promoter (EF1-alpha) promoter and a human β -glucuronidase promoter.~~

~~197. The method of any one of claims 194-196, wherein the promoter is a hybrid chicken β -actin promoter.~~

~~198. The method of any one of claims 167-173, wherein the expression construct further comprises a polyadenylation signal.~~

~~199. The method of claim 174, wherein the polyadenylation signal is a bovine growth hormone polyadenylation signal.~~

~~200. The method of any one of claims 191-199, wherein the expression construct is encoded by a vector.~~

~~201. The method of claim 200, wherein the vector is a recombinant adeno-associated virus (rAAV) vector, a recombinant adenoviral vector, a recombinant lentiviral vector or a recombinant herpes simplex virus (HSV) vector.~~

~~202. The method of claim 201, wherein the vector is a recombinant adenoviral vector.~~

~~203. The method of claim 202, wherein the recombinant adenoviral vector is derived from Adenovirus serotype 2, 1, 5, 6, 19, 3, 11, 7, 14, 16, 21, 12, 18, 31, 8, 9, 10, 13, 15, 17, 19, 20, 22, 23, 24, 30, 37, 40, 41, AdHu2, AdHu3, AdHu4, AdHu24, AdHu26, AdHu34, AdHu35, AdHu36, AdHu37, AdHu41, AdHu48, AdHu49, AdHu50, AdC6, AdC7, AdC69, bovine Ad type 3, canine Ad type 2, ovine Ad, or porcine Ad type 3.~~

~~204. The method of claim 203, wherein the recombinant adenoviral vector is derived from adenovirus serotype 2 or a variant of adenovirus serotype 5.~~

~~205. The method of claim 201, wherein the vector is a recombinant lentiviral vector.~~

~~206. The method of claim 205, wherein the recombinant lentiviral vector is derived from a lentivirus pseudotyped with vesicular stomatitis virus (VSV), lymphocytic choriomeningitis virus (LCMV), Ross river virus (RRV), Ebola virus, Marburg virus, Mokala virus, Rabies virus, RD114 or variants therein.~~

~~207. The method of claim 201, wherein the vector is a rHSV vector.~~

~~208. The method of claim 207, wherein the rHSV vector is derived from rHSV 1 or rHSV 2.~~

~~209. The method of claim 201, wherein the vector is a recombinant AAV (rAAV) vector.~~

~~210. The method of claim 209, wherein the expression construct is flanked by one or more AAV inverted terminal repeat (ITR) sequences.~~

~~211. The method of claim 210, wherein the expression construct is flanked by two AAV ITRs.~~

~~212. The method of claim 210 or 211, wherein the AAV ITRs are AAV ITRs are AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV 12, AAV2R471A, AAV DJ, a goat AAV, bovine AAV, or mouse AAV serotype ITRs.~~

~~213. The method of any one of claims 210-212, wherein the AAV ITRs are AAV2 ITRs.~~

~~214. The method of claim 213, wherein the rAAV vector comprises 5' to 3' an AAV2 ITR, a promoter, nucleic acid encoding the RNAi, a polyadenylation signal, and an AAV2 ITR.~~

~~215. The method of claim 214 wherein the promoter is a CBA promoter.~~

~~216. The method of claim 214 or 215, wherein the polyadenylation signal is a bovine growth hormone polyadenylation signal.~~

~~217. The method of claim 213, wherein the rAAV vector comprises 5' to 3' an AAV2 ITR, the CBA promoter, nucleic acid encoding the RNAi, a bovine growth hormone polyadenylation signal, and an AAV2 ITR.~~

~~218. The method of claim 217, wherein the vector further comprise a stuffer nucleic acid.~~

~~219. The method of claim 218, wherein the stuffer nucleic acid comprises nucleic acid encoding a green fluorescent protein (GFP).~~

~~220. The method of claim 218 or 219, wherein the stuffer nucleic acid is located between the promoter and the nucleic acid encoding the RNAi.~~

~~221. The method of any one of claims 214-220, wherein the RNAi comprises the nucleotide sequence of SEQ ID NO:3.~~

~~222. The method of any one of claims 214-220, wherein the RNAi comprises a nucleotide sequence about 90% identical to the nucleotide sequence of SEQ ID NO:3.~~

~~223. The method of any one of claims 209-222, wherein the vector is a self-complementing vector.~~

~~224. The method of claim 223, wherein the vector comprises first nucleic acid sequence encoding the RNAi and a second nucleic acid sequence encoding a complement of the RNAi,~~

wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

~~225. The method of claim 224, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.~~

~~226. The method of claim 200 or 201, wherein the vector is encapsidated in a rAAV particle, the recombinant adenovirus vector is encapsidated in an adenoviral particle, the recombinant lentiviral vector is encapsidated in a lentiviral particle or the recombinant HSV vector is encapsidated in a HSV.~~

~~227. The method of claim 226, wherein the viral particle is an adenovirus particle encapsidating the recombinant adenoviral vector.~~

~~228. The method of claim 227, wherein the adenovirus particle comprises a capsid from Adenovirus serotype 2, 1, 5, 6, 19, 3, 11, 7, 14, 16, 21, 12, 18, 31, 8, 9, 10, 13, 15, 17, 19, 20, 22, 23, 24 30, 37, 40, 41, AdHu2, AdHu3, AdHu4, AdHu24, AdHu26, AdHu34, AdHu35, AdHu36, AdHu37, AdHu41, AdHu48, AdHu49, AdHu50, AdC6, AdC7, AdC69, bovine Ad type 3, canine Ad type 2, ovine Ad, or porcine Ad type 3.~~

~~229. The method of claim 228, wherein the adenovirus particle comprises an adenovirus serotype 2 capsid or a variant of an adenoviral serotype 5 capsid.~~

~~230. The method of claim 226, wherein the viral particle is a lentiviral particle encapsidating the recombinant lentiviral vector.~~

~~231. The method of claim 230, wherein the lentiviral particle comprises a capsid pseudotyped with vesicular stomatitis virus (VSV), lymphocytic choriomeningitis virus (LCMV), Ross river virus (RRV), Ebola virus, Marburg virus, Mokala virus, Rabies virus, RD114 or variants therein.~~

~~232. The method of claim 226, wherein the viral particle is a HSV particle.~~

~~233. The method of claim 232, wherein the HSV particle is a rHSV-1 particle or a rHSV-2 particle.~~

~~234. The method of any one of claims 209-225, wherein the rAAV vector is encapsidated in a recombinant AAV particle.~~

~~235. The method of claim 234, wherein the AAV viral particle comprises an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV2/2-7m8, AAV DJ, AAV2 N587A, AAV2 E548A, AAV2 N708A, AAV2 V708K, goat AAV, AAV1/AAV2 chimeric, bovine AAV, mouse AAV, or rAAV2/HBoV1 serotype capsid.~~

~~236. The method of claim 234 or 235, wherein the ITR and the capsid of the rAAV viral particle are derived from the same AAV serotype.~~

~~237. The method of claim 234 or 235, wherein the ITR and the capsid of the rAAV viral particles are derived from different AAV serotypes.~~

~~238. The method of any one of claims 234-235, wherein the rAAV viral particle comprises AAV2 capsid.~~

~~239. The method of claim 237, wherein the rAAV viral particle comprises an AAV1 capsid, and wherein the vector comprises AAV2 ITRs.~~

~~240. A method of any one of claims 226-239, wherein the viral particle of any one of claims 226-233 or the rAAV particle of any one of claims 234-239 is in a composition.~~

~~241. The method of claim 240, wherein the composition further comprises a pharmaceutically acceptable carrier.~~

~~242. Use of the RNAi of any one of claims 86-106; the expression construct of any one of claims 96-104; the vector of any one of claims 116-124; the rAAV vector of any one of claims 125-141; the viral particle of any one of claims 144-151; the rAAV particle of any one of claims 152-157; or the composition of claims 158 or 159, in the manufacture of a medicament for use in the method of any one of claims 160-241.~~

~~243. The RNAi of any one of claims 86-106; the expression construct of any one of claims 107-115; the vector of any one of claims 116-124; the rAAV vector of any one of claims 125-141; the viral particle of any one of claims 144-151; the rAAV particle of any one of claims 152-157; or the composition of claims 158 or 159, for use in the method of any one of claims 160-241.~~

~~244. A kit for inducing RNA interference in a mammal with Huntington's disease comprising the RNAi of any one of claims 86-106; the expression construct of any one of claims 107-115; the vector of any one of claims 116-124; the rAAV vector of any one of claims 125-141; the viral particle of any one of claims 144-151; the rAAV particle of any one of claims 152-157; or the composition of claims 158 or 159.~~

~~245. The kit of claim 244, wherein the mammal is a human.~~

~~246. A kit for use in the method of any one of claims 160-241 comprising the RNAi of any one of claims 86-106; the expression construct of any one of claims 107-115; the vector of any one of claims 116-124; the rAAV vector of any one of claims 125-141; the viral particle of any one of claims 144-151; the rAAV particle of any one of claims 152-157; or the composition of claims 158 or 159, in the manufacture of a medicament for use in the method of any one of claims 160-241.~~