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, wherein the guide region comprises the nucleic acid sequence 5'-UGGCCGUCCAUCUUGGACCCG-3' (SEQ ID NO:1), or a nucleic acid sequence having about 90% identity to SEQ ID NO: 1; or 5'-AGUCGGUGUGGUUGACAAGCA-3' (SEQ ID NO:7), or a nucleic acid sequence having about 90% identity to SEQ ID NO: 7; and

c) the second strand comprises a non-guide region.

2. The RNAi of claim 1, wherein:

(i) the nucleic the guide region comprises the nucleic acid sequence 5'-UGGCCGUCCAUCUUGGACCCG-3' (SEQ ID NO:1), or a nucleic acid sequence having about 90% identity to SEQ ID NO: 1; and the non-guide region comprises the sequence 5'-CGGGUCCAAGAUGGACGGCCA-3' (SEQ ID NO:2), or a nucleic acid sequence having about 90% identity to SEQ ID NO: 2; or

(ii) the nucleic the guide region comprises the nucleic acid sequence 5'-AGUCGGUGUGGUUGACAAGCA-3' (SEQ ID NO:7), or a nucleic acid sequence having about 90% identity to SEQ ID NO: 7; and the non-guide region comprises the sequence 5'-UGCUUGUCAACCACACCGACU-3' (SEQ ID NO:8), or a nucleic acid sequence having about 90% identity to SEQ ID NO: 8.

3. The RNAi of claim 1 or 2, wherein the first strand and the second strand are linked by means of a RNA linker capable of forming a loop structure, optionally wherein:

(i) the RNA linker comprises from 4 to 50 nucleotides; and/or

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

(iii) the RNAi comprises 5' to 3' the second strand, the RNA linker, and the first strand; or

(iv) the RNAi comprises 5' to 3' the first strand, the RNA linker, and the second strand.

4. The RNAi of claim 3, wherein he RNAi comprises 5' to 3' the first strand, the RNA linker, and the second strand, and wherein the RNAi comprises the nucleic acid sequence of SEQ ID NO:4 or SEQ ID NO:10, or a nucleotide sequence about 90% identical to the nucleotide sequence of SEQ ID NO:4 or SEQ ID NO:10.

5. The RNAi of any one of claims 1-4, wherein the RNAi is a small inhibitory RNA (siRNA), a microRNA (miRNA), or a small hairpin RNA (shRNA).

6. The RNAi of any one of claims 1-5, wherein the RNAi targets RNA encoding a polypeptide associated with Huntington's disease, optionally wherein the polypeptide is huntingtin, and optionally wherein the huntingtin comprises a mutation associated with Huntington's disease.

7. An expression construct comprising nucleic acid encoding the RNAi of any one of claims 1-6.

8. The expression construct of claim 7, wherein:
(i) the nucleic acid encoding the RNAi comprises a miRNA scaffold; and/or
(ii) the nucleic acid encoding the RNAi is operably linked to a promoter, optionally 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 (EFl-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; and/or
(ii) the expression construct further comprises an intron, optionally wherein the intron is a chimeric intron, and optionally wherein the expression vector is a self-complementary vector and the intron is a delta chimeric intron; and/or

(iii) the expression construct further comprises a polyadenylation signal, optionally wherein the polyadenylation signal is a bovine growth hormone polyadenylation signal, an SV40 polyadenylation signal, or a HSV TK pA.

9. A vector comprising the expression construct of any one of claims 7 or 8.

10. The vector of claim 9, wherein:

(i) the vector is a recombinant adenoviral vector, and optionally 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; or

(ii) the vector is a recombinant lentiviral vector, optionally 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

(iii) the vector is a recombinant herpes simplex virus (HSV) vector, optionally wherein the rHSV vector is derived from rHSV-1 or rHSV-2.

11. The vector of claim 9, wherein the vector is a rAAV vector.

12. The rAAV vector of claim 11, wherein the expression construct is flanked by one or more AAV inverted terminal repeat (ITR) sequences, optionally wherein:

(i) the expression construct is flanked by two AAV ITRs; and/or

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

13. The rAAV vector of claim 11 or 12, wherein the vector further comprises a stuffer nucleic acid, optionally whereinthe stuffer nucleic acid is located upstream or downstream of the nucleic acid encoding the RNAi.

14. The rAAV vector of any one of claims 11-13, wherein the vector is a self-complementary rAAV vector, optionally 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, and optionally 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.

15. A cell comprising the vector of claim 9 or 10 or the rAAV vector of any one of claims 11-14.

16. A viral particle comprising the vector of claim 9, wherein:
(i) the viral particle is an AAV particle encapsidating the rAAV vector, optionally 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; or
(ii) the viral particle is an adenovirus particle encapsidating the recombinant adenoviral vector, optionally wherein the adenovirus particle comprises an adenovirus serotype 2 capsid or a variant of an adenoviral serotype 5 capsid; or
(iii) the viral particle is a lentiviral particle encapsidating the recombinant lentiviral vector, optionally 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; or
(iv) the viral particle is an HSV particle encapsidating the recombinant HSV vector, optionally wherein the HSV particle is a rHSV-1 particle or a rHSV-2 particle.

17. A recombinant AAV particle comprising the rAAV vector of any one of claims 11-14, optionally wherein:

(i) 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, AAV V708K, AAV2-HBKO, AAVDJ8, AAVPHP.B, AAVPHP.eB, AAVBR1, AAVHSC15, AAVHSC17, a goat AAV, AAV1/AAV2 chimeric, bovine AAV, or mouse AAV capsid rAAV2/HBoV1 serotype capsid; and/or
(ii) the ITR and the capsid of the rAAV viral particle are derived from the same AAV serotype; or
(iii) the ITR and the capsid of the rAAV viral particle are derived from different AAV serotypes, optionally wherein the ITR is derived from AAV2 and the capsid of the rAAV particle is derived from AAV1.

18. A composition comprising the viral particle of claim 16 or the rAAV particle of claim 17, optionally wherein the composition further comprises a pharmaceutically acceptable carrier.

19. A kit comprising the RNAi of any one of claims 1-6, the viral particle of claim 16, the AAV particle of claim 17, or the composition of claim 18, optionally wherein the kit further comprises instructions for use.

20. Use of an RNAi of any one of claims 2-6, a viral particle of claim 16, an AAV particle of claim 17, or a composition of claim 18 in the preparation of a medicament for treating Huntington's disease in a mammal.

21. Use of an RNAi of any one of claims 2-6, a viral particle of claim 16, an AAV particle of claim 17, or a composition of claim 18 in the preparation of a medicament for inhibiting the expression of htt or inhibiting the accumulation of htt in a cell in a mammal with Huntington's disease.