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 5'-AGUCGGUGUGGUUGACAAGCA-3' (SEQ ID NO:7); and

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

2. The RNAi of claim 1, wherein:

(i) the guide region comprises the nucleic acid sequence 5'-UGGCCGUCCAUCUUGGACCCG-3' (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~~ more than 90% identity to SEQ ID NO: 2; or

(ii) the guide region comprises the nucleic acid sequence 5'-AGUCGGUGUGGUUGACAAGCA-3' (SEQ ID NO:7); and the non-guide region comprises the sequence 5'- UGCUUGUCAACCACACCGACU-3' (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.

4. The RNAi of claim 3, 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

5. The RNAi of claim 3, wherein the 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.

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

7. The RNAi of any one of claims 1-6, wherein the RNAi targets RNA encoding a polypeptide associated with Huntington's disease.

8. The RNAi of any one of claims 1-7, wherein the polypeptide is huntingtin.

9. The RNAi of claim 8, huntingtin comprises a mutation associated with Huntington's disease.

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

11. The expression construct of claim 10, 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; and/or
(ii) the expression construct further comprises an intron; and/or
(iii) the expression construct further comprises a polyadenylation signal.

12. The RNAi of claim 11, 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.

13. The RNAi of claim 11, wherein the intron is a chimeric intron.

14. The RNAi of claim 11, wherein the expression vector is a self-complementary vector and the intron is a delta chimeric intron.

15. The RNAi of claim 11, wherein the polyadenylation signal is a bovine growth hormone polyadenylation signal, an SV40 polyadenylation signal, or a HSV TK pA.

16. A vector comprising the expression construct of any one of claims 10 or 11.

17. The vector of claim 16, wherein:
(i) the vector is a recombinant adenoviral vector; or
(ii) the vector is a recombinant lentiviral vector; or
(iii) the vector is a recombinant herpes simplex virus (HSV) vector.

18. The vector of claim 17, wherein:
(i) the vector is a recombinant adenoviral vector, 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
(ii) the vector is a recombinant lentiviral vector, 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, wherein the rHSV vector is derived from rHSV-1 or rHSV-2.

19. The vector of claim 16, wherein the vector is a rAAV vector.

20. The rAAV vector of claim 19, wherein the expression construct is flanked by one or more AAV inverted terminal repeat (ITR) sequences.

21. The rAAV vector of claim 20, 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.

22. The rAAV vector of claim 19 or 20, wherein the vector further comprises a stuffer nucleic acid, wherein the stuffer nucleic acid is located upstream or downstream of the nucleic acid encoding the RNAi.

23. The rAAV vector of any one of claims 19-22, wherein the vector is a self-complementary rAAV vector.

24. The rAAV vector of claim 23, 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.

25. A cell comprising the vector of claim 16 or 17 or the rAAV vector of any one of claims 19-23.

26. A viral particle comprising the vector of claim 16, wherein:
(i) the viral particle is an AAV particle encapsidating the rAAV vector; or
(ii) the viral particle is an adenovirus particle encapsidating the recombinant adenoviral vector,; or
(iii) the viral particle is a lentiviral particle encapsidating the recombinant lentiviral vector; or
(iv) the viral particle is an HSV particle encapsidating the recombinant HSV vector.

27. The viral particle of claim 26, wherein:
(i) the viral particle is an adenoviral particle encapsidating the recombinant adenoviral vector, 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, 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, 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, wherein the HSV particle is a rHSV-1 particle or a rHSV-2 particle.

28. A recombinant AAV particle comprising the rAAV vector of any one of claims 19-23.

29. The recombinant AAV particle of claim 28, 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.

30. A composition comprising the viral particle of claim 26 or the rAAV particle of claim 28, wherein the composition further comprises a pharmaceutically acceptable carrier.

31. A kit comprising the RNAi of any one of claims 1-6, the viral particle of claim 26, the AAV particle of claim 28, or the composition of claim 30.

32. Use of an RNAi of any one of claims 2-6, a viral particle of claim 26, an AAV particle of claim 28, or a composition of claim 30 in the preparation of a medicament for treating Huntington's disease in a mammal.

33. Use of an RNAi of any one of claims 2-6, a viral particle of claim 26, an AAV particle of claim 28, or a composition of claim 30 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.