CLAIMS

1. A modulatory polynucleotide comprising:
   (a) a 5’ flanking region comprising the nucleotide sequence of SEQ ID NO: 5;
   (b) a loop region comprising the nucleotide sequence of SEQ ID NO: 16; and
   (c) a 3’ flanking region comprising the nucleotide sequence of SEQ ID NO: 21.

2. The modulatory polynucleotide of claim 1, further comprising a passenger strand and a guide strand.

3. The modulatory polynucleotide of claim 2, wherein the passenger strand is located between the 5’ flanking region and the loop region and the guide strand is located between the loop region and the 3’ flanking region.

4. The modulatory polynucleotide of claim 2, wherein the guide strand is located between the 5’ flanking region and the loop region and the passenger strand is located between the loop region and the 3’ flanking region.

5. The modulatory polynucleotide of claim 2, wherein the guide strand comprises a microRNA seed sequence comprising positions 2-7, 2-8, or 2-9.

6. The modulatory polynucleotide of claim 2, wherein the guide strand, passenger strand, or both the guide strand and the passenger strand are each between 15-22 nucleotides in length.

7. The modulatory polynucleotide of claim 2, wherein the guide strand and passenger strand are each 21 nucleotides in length.

8. The modulatory polynucleotide of claim 2, wherein the passenger strand is at least 70% complementary to the guide strand.

9. The modulatory polynucleotide of claim 2, wherein the guide strand is at least 60% complementary to a target RNA, and wherein the target RNA is a mammalian coding mRNA expressed in a cell of the central nervous system.

10. The modulatory polynucleotide of claim 1, wherein the modulatory polynucleotide targets the expression of an Htt gene.

11. The modulatory polynucleotide of claim 1, wherein the modulatory polynucleotide is a pri-mRNA.

12. The modulatory polynucleotide of claim 1, wherein the modulatory polynucleotide targets the expression of a SOD1 gene.

13. A viral genome which comprises a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein the nucleic acid sequence encodes the modulatory polynucleotide of any one of claims 1-12.

14. The viral genome of claim 13, which further comprises one, two, three, or all of:

(i) a promoter operably linked to the nucleotide sequence encoding the modulatory polynucleotide;

(ii) an enhancer;

(iii) an intron region; and

(iv) a poly A signal region.

15. The viral genome of claim 14, wherein:

(i) the promoter is a CBA promoter or an H1 promoter;

(ii) the enhancer is a CMV enhancer; or

(iii) the intron is an SV40 intron.

16. The viral genome of claim 13, wherein the viral genome is single stranded or self-complementary.

17. A recombinant adeno-associated virus (rAAV) comprising the viral genome of claim 13, and an AAV capsid protein.

18. The rAAV of claim 17, comprising an AAV1 capsid protein, an AAV5 capsid protein, and AAV9 capsid protein, or a variant thereof.

19. A vector comprising the modulatory polynucleotide of any one of claims 1-12.

20. A cell comprising the rAAV of claim 17.

21. The cell of claim 20, which is a mammalian cell, an HEK293 cell, an insect cell, an Sf9 cell, a cell of the central nervous system, a neuron, medium spiny neuron, a motor neuron, or an astrocyte.

22. A pharmaceutical composition comprising the rAAV of claim 17, and a pharmaceutically acceptable excipient for use in treating Huntington's disease.

23. A composition comprising the rAAV of claim 17 for use in a method of treating a disease of the central nervous system.

24. The composition for use of claim 23, wherein the disease of the central nervous system is Huntington's disease or ALS.

25. The composition for use of claim 23, where the composition is formulated for administration via intravenous administration or via intracisternal administration.

26. A method of producing a recombinant AAV, comprising providing a cell with a polynucleotide comprising the viral genome of claim 13, at least one polynucleotide encoding AAV rep genes, and at least one polynucleotide encoding AAV cap genes; and harvesting the recombinant AAV from the cell.