CLAIMS

1. A modulatory polynucleotide comprising:

(a) a 5’ flanking region comprising any one of SEQ ID NOs: 1-4;

(b) a loop region comprising any one of SEQ ID NOs: 5-9; and

(c) a 3’ flanking region comprising any one of SEQ ID NOs: 10-14 or 810.

2. The modulatory polynucleotide of claim 1, wherein:

(a) the 5’ flanking region comprises SEQ ID NO: 2 or SEQ ID NO: 3;

(b) the loop region comprises SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 9; and

(c) the 3’ flanking region comprises SEQ ID NO: 11, SEQ ID NO: 12, or SEQ ID NO: 13.

3. The modulatory polynucleotide of claim 1, wherein:

(i) the 5’ flanking region comprises SEQ ID NO: 2, the loop region comprises SEQ ID NO: 5, and the 3’ flanking region comprises SEQ ID NO: 11;

(ii) the 5’ flanking region comprises SEQ ID NO: 2, the loop region comprises SEQ ID NO: 5, and the 3’ flanking region comprises SEQ ID NO: 12;

(iii) the 5’ flanking region comprises SEQ ID NO: 2, the loop region comprises SEQ ID NO: 6, and the 3’ flanking region comprises SEQ ID NO: 11; or

(iv) the 5’ flanking region comprises SEQ ID NO: 3, the loop region comprises SEQ ID NO: 9, and the 3’ flanking region comprises SEQ ID NO: 13.

4. The modulatory polynucleotide of claim 1, wherein the 5’ flanking region comprises SEQ ID NO: 2, the loop region comprises SEQ ID NO: 5, and the 3’ flanking region comprises SEQ ID NO: 11.

5. The modulatory polynucleotide of claim 1, wherein the 5’ flanking region comprises SEQ ID NO: 3, the loop region comprises SEQ ID NO: 9, and the 3’ flanking region comprises SEQ ID NO: 13.

6. The modulatory polynucleotide of any one of claims 1-5, further comprising a passenger

strand and a guide strand.

7. The modulatory polynucleotide of claim 6, wherein the passenger strand and the guide strand are located, respectively, on a 5’ arm and a 3’ arm of a stem loop structure, 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.

8. The modulatory polynucleotide of claim 6 or 7, wherein:

(i) the passenger strand is between 15-30 nucleotides in length; and/or

(ii) the guide strand is between 15-30 nucleotides in length.

9. The modulatory polynucleotide of any one of claims 6-8, wherein the passenger strand is at least 70% complementary to the guide strand.

10. The modulatory polynucleotide of any one of claims 6-9, wherein the guide strand is at least 70% complementary to a target RNA.

11. The modulatory polynucleotide of claim 10, wherein the target RNA is expressed in a neurologic cell, tissue, or organ.

12. A vector encoding the modulatory polynucleotide of any one of claims 1-11.

13. An adeno-associated virus (AAV) viral genome comprising a nucleotide sequence positioned between two inverted terminal repeats (ITRs), wherein the nucleotide sequence encodes the modulatory polynucleotide of any one of claims 1-11.

14. The AAV viral genome of claim 13, which further comprises:

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

(ii) an enhancer;

(iii) an intron region; and/or

(iv) a poly A signal region.

15. A recombinant AAV virus comprising the AAV viral genome of claim 13 or 14 and an AAV capsid protein.

16. The recombinant AAV virus of claim 15, wherein the AAV capsid protein comprises an AAV1 capsid protein or a variant thereof, an AAV5 capsid protein or a variant thereof, or an AAV9 capsid protein or a variant thereof.

17. A cell comprising the modulatory polynucleotide of any one of claims 1-11, the vector of claim 12, the AAV viral genome of claim 13 or 14, or the recombinant AAV virus of claim 15 or 16.

18. The cell of claim 17, wherein the cell is a human cell, an HEK293 cell, a cell of the central nervous system, a motor neuron, or an astrocyte.

19. A pharmaceutical composition comprising the modulatory polynucleotide of any one of claims 1-11, the vector of claim 12, the AAV viral genome of claim 13 or 14, or the recombinant AAV virus of claim 15 or 16, and a pharmaceutically acceptable excipient.

20. Use of a composition comprising the modulatory polynucleotide of any one of claims 1-11, the vector of claim 12, the AAV viral genome of claim 13 or 14, the recombinant AAV virus of claim 15 or 16, or the pharmaceutical composition of claim 19 in the manufacture of a medicament for treating a disease of the central nervous system in a subject.

21. The use of claim 20, wherein the disease of the central nervous system is Huntington's disease or ALS.

22. The use of claim 20 or 21, wherein the composition is formulated for intravenous administration, intracisternal injection, intravascular administration, and/or intraventricular administration.

23. A composition comprising the modulatory polynucleotide of any one of claims 1-11, the vector of claim 12, the AAV viral genome of claim 13 or 14, the recombinant AAV virus of claim 15 or 16, or the pharmaceutical composition of claim 19 for use treating a disease of the central nervous system in a subject.

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 or 24, wherein the composition is formulated for intravenous administration, intracisternal injection, intravascular administration, and/or intraventricular administration.