CLAIMS

We claim:

1. An adeno-associated virus (AAV) viral genome comprising a nucleic acid sequence positioned between a first inverted terminal repeat (ITR) and a second ITR, wherein said nucleotide sequence encodes a modulatory polynucleotide, wherein the modulatory polynucleotide comprises from 5′ to 3′:

(a) a 5′ flanking region, wherein the nucleotide sequence encoding the 5′ flanking region comprises a nucleotide sequence selected from SEQ ID NOs: 1255-1263;

(b) an antisense sequence at least 80% identical to a nucleotide sequence selected from SEQ ID NOs: 916-1084;

(c) a loop region, wherein the nucleotide sequence encoding the loop region comprises a nucleotide sequence selected from SEQ ID NOs: 1264-1273;

(d) a sense strand sequence at least 80% identical to a nucleotide sequence selected from SEQ ID NOs: 1085-1253, wherein the sense strand sequence is complementary to the antisense strand sequence; and

(e) a 3′ flanking region, wherein the nucleotide sequence encoding the 3′ flanking region comprises a nucleotide sequence selected from SEQ ID NOs: 1274-1280.

2. The AAV viral genome of claim 1, wherein:

(a) the nucleotide sequence encoding the 5′ flanking region comprises SEQ ID NO: 1259;

(b) the nucleotide sequence encoding the loop region comprises SEQ ID NO: 1268;

(c) the nucleotide sequence encoding the 3′ flanking region comprises SEQ ID NO: 1277; and

(d) the antisense strand sequence is at least 80% identical to the nucleotide sequence of SEQ ID NO: 963, and the sense strand sequence is at least 80% identical to the nucleotide sequence of SEQ ID NO: 1132.

3. The AAV viral genome of claim 1, wherein the antisense strand sequence comprises nucleotides 1-19 of SEQ ID NO: 963, and the sense strand sequence comprises nucleotides 1-18 of SEQ ID NO: 1132.

4. The AAV viral genome of claim 1, wherein the antisense strand sequence is at least 85% identical to SEQ ID NO: 963, and the sense strand sequence is at least 85% identical to SEQ ID NO: 1132.

5. The AAV viral genome of claim 1, wherein the sense strand sequence and/or antisense strand sequence are, independently, between 20-22 nucleotides in length.

6. The AAV viral genome of claim 1, wherein the sense strand sequence and the antisense strand sequence comprise a 3′ overhang of 1-2 nucleotides.

7. An AAV viral genome, comprising a nucleic acid sequence positioned between a first inverted terminal repeat (ITR) and a second ITR, wherein said nucleotide sequence encodes a modulatory polynucleotide, wherein the modulatory polynucleotide comprises from 5′ to 3′:

(i) a 5′ flanking region, wherein the nucleotide sequence encoding the 5′ flanking region comprises SEQ ID NO: 1259;

(ii) a sense strand sequence, which comprises nucleotides 1-18 of SEQ ID NO: 1132;

(iii) a loop region, wherein the nucleotide sequence encoding the loop region comprises SEQ ID NO: 1268;

(iv) an antisense strand sequence, which comprises nucleotides 1-19 of SEQ ID NO: 963; and

(v) a 3′ flanking region, wherein the nucleotide sequence encoding the 3′ flanking region comprises SEQ ID NO: 1277.

8. The AAV viral genome of claim 7, wherein:

(i) the first ITR comprises a nucleotide sequence selected from SEQ ID NOs: 1370-1373, and is positioned 5′ relative to the nucleotide sequence encoding the modulatory polynucleotide; and

(ii) the second ITR comprises a nucleotide sequence selected from SEQ ID NOs: 1370-1372, and is positioned 3′ relative to the nucleotide sequence encoding the modulatory polynucleotide.

9. The AAV viral genome of claim 7, wherein the first ITR comprises the nucleotide sequence of SEQ ID NO: 1371 and is positioned 5′ relative to the nucleotide sequence encoding the modulatory polynucleotide, and the second ITR comprises the nucleotide sequence of SEQ ID NO: 1373, and is positioned 3′ relative to the nucleotide sequence encoding the modulatory polynucleotide.

10. A recombinant adeno-associated virus (AAV) particle comprising the AAV viral genome of claim 7, and an AAV capsid, wherein the AAV capsid comprises an AAV9 capsid or variant thereof, an AAV5 capsid or variant thereof, or an AAVrh10 capsid or variant thereof.

11. A pharmaceutical composition comprising the recombinant AAV particle of claim 10, and a pharmaceutically acceptable excipient.

12. Use of the pharmaceutical composition of claim 11 in the manufacture of a medicament for inhibiting or suppressing the expression of SOD1 gene in a cell, wherein the medicament is to be administered to the cell.

13. The use of claim 12, wherein the cell is:

(i) a mammalian cell, a motor neuron, or an astrocyte; and/or

(ii) in a subject, wherein the subject has amyotrophic lateral sclerosis (ALS).

14. The use of claim 12, wherein the SOD1 gene comprises a wild type SOD1 gene, a mutated SOD1 gene, or a combination thereof.

15. Use of the pharmaceutical composition of claim 11 in the manufacture of a medicament for the treatment of amyotrophic lateral sclerosis (ALS) in a subject, wherein a therapeutically effective amount of the medicament is to be administered to the subject.

16. The use of claim 15, wherein the ALS is:
(i) familial ALS;
(ii) sporadic ALS;
(iii) early stage ALS;
(iv) middle stage ALS; and/or
(v) late stage ALS.

17. A modulatory polynucleotide targeting a SOD1 gene comprising from 5′ to 3′:
(i) a 5′ flanking region, wherein the nucleotide sequence encoding the 5′ flanking region comprises a nucleotide sequence selected from SEQ ID NOs: 1255-1263;
(ii) an antisense strand at least 80% identical to a nucleotide sequence selected from SEQ ID NOs: 916-1084;
(iii) a loop region, wherein the nucleotide sequence encoding the loop region comprises a nucleotide sequence selected from SEQ ID NOs: 1264-1273;
(iv) a sense strand at least 80% identical to a nucleotide sequence selected from SEQ ID NOs: 1085-1253, wherein the sense strand sequence is complementary to the antisense strand sequence; and
(v) a 3′ flanking region, wherein the nucleotide sequence encoding the 3′ flanking region comprises a nucleotide sequence selected from SEQ ID NOs: 1274-1280.

18. A modulatory polynucleotide targeting a SOD1 gene comprising from 5′ to 3′:
(i) a 5′ flanking region, wherein the nucleotide sequence encoding the 5′ flanking region comprises the nucleotide sequence of SEQ ID NO: 1259;
(ii) an antisense strand sequence at least 80% identical to the nucleotide sequence of SEQ ID NO: 963;
(iii) a loop region, wherein the nucleotide sequence encoding the loop region comprises the nucleotide sequence of SEQ ID NO: 1268;
(iv) a sense strand sequence at least 80% identical to the nucleotide sequence of SEQ ID NO: 1132, wherein the sense strand sequence is complementary to the antisense strand sequence; and
(v) a 3′ flanking region, wherein the nucleotide sequence encoding the 3′ flanking region comprises the nucleotide sequence of SEQ ID NO: 1277.

19. An adeno-associated virus (AAV) viral genome comprising a nucleic acid sequence positioned between a first inverted terminal repeat (ITR) and a second ITR, wherein said nucleotide sequence encodes the modulatory polynucleotide of claim 18.

20. The AAV viral genome of claim 19, further comprising:
(i) a promoter;

(ii) an enhancer;
(iii) an intron; and/or
(iv) a poly A sequence region.

21. The AAV viral genome of claim 20, wherein the promoter is a CMV promoter, a CBA promoter, a EF-1α promoter, a PGK promoter, a synapsin promoter, an H1 promoter, or a truncation thereof.

22. The AAV viral genome of claim 20, wherein the poly A sequence region comprises the nucleotide sequence of SEQ ID NO: 1410.

23. The AAV viral genome of claim 7, further comprising:
(i) a promoter;
(ii) an enhancer;
(iii) an intron; and/or
(iv) a poly A sequence region.

24. The AAV viral genome of claim 23, wherein the promoter is a CMV promoter, a CBA promoter, a EF-1α promoter, a PGK promoter, a synapsin promoter, an H1 promoter, or a truncation thereof.

25. The AAV viral genome of claim 23, wherein the poly A sequence region comprises the nucleotide sequence of SEQ ID NO: 1410.

26. The use of claim 15, wherein the medicament is to be administered to the subject via intravenous administration, intracisternal magna administration, or combination thereof.

27. The modulatory polynucleotide of claim 18, wherein the antisense strand sequence is at least 85% identical to SEQ ID NO: 963, and the sense strand sequence is at least 85% identical to SEQ ID NO: 1132.

28. The modulatory polynucleotide of claim 18, wherein the antisense strand sequence comprises nucleotides 1-19 of SEQ ID NO: 963, and the sense strand sequence comprises nucleotides 1-18 of SEQ ID NO: 1132.

29. The pharmaceutical composition of claim 11 for use in therapy.

30. The AAV particle of claim 10 for use in therapy.