CLAIMS

1. An adeno-associated viral (AAV) vector genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs); wherein said nucleic acid sequence encodes a sense strand sequence and an antisense strand sequence; wherein the sense strand sequence comprises at least 15 contiguous nucleotides differing by no more than 6 nucleotides from SEQ ID NO. 51; wherein the antisense strand sequence comprises at least 15 contiguous nucleotides differing by no more than 6 nucleotides from SEQ ID NO. 220; and wherein said sense strand sequence and antisense strand sequence share a region of complementarity of at least seven nucleotides in length.

2. The AAV vector genome of claim 1, wherein the nucleic acid sequence encodes a sense strand sequence and an antisense strand sequence of an siRNA duplex; wherein the sense strand sequence has at least 80% identity to SEQ ID NO. 51; and wherein the antisense strand sequence has at least 80% identity to SEQ ID NO. 220.

3. The AAV vector genome of claim 1, wherein the nucleic acid sequence encodes a sense strand sequence and an antisense strand sequence of an siRNA duplex; wherein the sense strand sequence has at least 85% identity to SEQ ID NO. 51; and wherein the antisense strand sequence has at least 85% identity to SEQ ID NO. 220.

4. The AAV vector genome of claim 1, wherein the nucleic acid sequence encodes a sense strand sequence and an antisense strand sequence of an siRNA duplex; wherein the sense strand sequence comprises nucleotides 1-18 of SEQ ID NO. 51; and wherein the antisense strand sequence comprises nucleotides 1-19 of SEQ ID NO. 220.

5. The AAV vector genome of claim 1, wherein the region of complementarity is at

least 17 nucleotides in length.

6. The AAV vector genome of claim 1, wherein the region of complementarity is 17-20 nucleotides in length.

7. The AAV vector genome of claim 1, wherein the region of complementarity is 18 nucleotides in length.

8. The AAV vector genome of claim 1, wherein the sense strand sequence and the antisense strand sequence are, independently, 30 nucleotides or less in length.

9. The AAV vector genome of claim 3, wherein at least one of the sense strand sequence and the antisense strand sequence comprise a 3’ overhang of at least 1 nucleotide.

10. The AAV vector genome of claim 3, wherein at least one of the sense strand sequence and the antisense strand sequence comprise a 3’ overhang of at least 2 nucleotides.

11. An AAV particle comprising the AAV vector genome of claim 4 and an AAVrh10 capsid.

12. A method for inhibiting the expression of SOD1 gene in a cell comprising administering to the cell a composition comprising an AAV vector genome of claim 4.

13. The method of claim 12, wherein the cell is a mammalian cell.

14. The method of claim 13, wherein the mammalian cell is a motor neuron.

15. The method of claim 13, wherein the mammalian cell is an astrocyte.

16. Use of an AAV particle of claim 11 in the manufacture of a pharmaceutical composition for treating amyotrophic lateral sclerosis (ALS) in a subject in need of treatment.

17. The use of claim 16, wherein the expression of SOD1 mRNA is inhibited or suppressed by up to 93%.

18. The use of claim 16, wherein the expression of SOD1 mRNA is inhibited or suppressed by about 20% to about 93.

19. The use of claim 16, wherein the expression of SOD1 mRNA is inhibited or suppressed by about 50% to about 93%.

20. The use of claim 16, wherein the ALS is familial ALS with an identified SOD1 gene mutation.

21. The use of claim 16, wherein the ALS is sporadic ALS.

22. The use of claim 16, wherein the SOD1 gene embraces a mutation that causes a gain of function effect inside the cell.

23. The use of claim 22, wherein the pharmaceutical composition is to be administered to the subject by intraparenchymal spinal administration.

24. The use of claim 16, wherein the pharmaceutical composition is to be administered to the subject by intraparenchymal spinal administration.

25. The AAV vector genome of claim 1, wherein the sense strand sequence has at

least 80% identity to SEQ ID NO. 51.

26. The AAV vector genome of claim 1, wherein the sense strand sequence has at least 85% identity to SEQ ID NO. 51.

27. The AAV vector genome of claim 1, wherein the sense strand sequence comprises nucleotides 1-18 of SEQ ID NO. 51.

28. The AAV vector genome of claim 1, wherein the antisense strand sequence has at least 80% identity to SEQ ID NO. 220.

29. The AAV vector genome of claim 1, wherein the antisense strand sequence has at least 85% identity to SEQ ID NO. 220.

30. The AAV vector genome of claim 1, wherein the antisense strand sequence comprises nucleotides 1-18 of SEQ ID NO. 220.

31. The AAV vector genome of claim 1, wherein the antisense strand sequence comprises nucleotides 1-19 of SEQ ID NO. 220.

32. The AAV vector genome of claim 1, wherein the sense strand sequence and the antisense strand sequence are, independently, 20 nucleotides in length.

CLAIMS

1. An siRNA duplex for inhibiting expression of SOD1 comprising a sense strand sequence and antisense strand sequence; wherein the sense strand sequence comprises nucleotides 1-18 of SEQ ID NO: 51 and the antisense strand sequence comprises nucleotides 1-19 of SEQ ID NO: 220.

2. The siRNA duplex of claim 1, wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity, wherein the region of complementarity is between 17-20 nucleotides in length.

3. The siRNA duplex of claim 1, wherein the sense strand sequence and the antisense strand sequence are, independently, 20, 21 or 22 nucleotides in length.

4. The siRNA duplex of claim 1, wherein at least one of the sense strand sequence and the antisense strand sequence comprise a 3' overhang of at least 1 or 2 nucleotides.

5. A modulatory polynucleotide for inhibiting expression of SOD1 comprising the siRNA duplex of claim 1.

6. The modulatory polynucleotide of claim 5, which comprises:
(i) a 5’ flanking region;
(ii) a loop region; and
(iii) a 3’ flanking region.

7. An adeno-associated viral (AAV) vector genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein the nucleic acid sequence encodes the modulatory polynucleotide of claim 5.

8. An adeno-associated viral (AAV) vector genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs); wherein said nucleic acid sequence encodes a sense strand sequence and an antisense strand sequence of an siRNA duplex; wherein

the sense strand sequence comprises nucleotides 1-18 of SEQ ID NO: 51, and the antisense strand sequence comprises nucleotides 1-19 of SEQ ID NO: 220.

9. The AAV vector genome of claim 8, wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity, wherein the region of complementarity is between 17-20 nucleotides in length.

10. The AAV vector genome of claim 8, wherein the sense strand sequence and the antisense strand sequence are, independently, 20, 21, or 22 nucleotides in length.

11. The AAV vector genome of claim 8, wherein at least one of the sense strand sequence and the antisense strand sequence comprise a 3' overhang of at least 1 or 2 nucleotides.

12. The AAV vector genome of claim 11, which further encodes a modulatory polynucleotide comprising the siRNA duplex.

13. The AAV vector genome of claim 12, wherein the modulatory polynucleotide comprises:
(i) a 5’ flanking region;
(ii) a loop region; and
(iii) a 3’ flanking region.

14. The AAV vector genome of claim 8, further comprising:
(i) a promoter;
(ii) an enhancer
(iii) an intron;
(iv) a polyA sequence,
or a combination thereof.

15. The AAV vector genome of claim 14, wherein the promoter is a ubiquitous promoter or a cell-specific promoter.

16. A recombinant adeno-associated virus (AAV) particle comprising the AAV vector genome of any one of claims 7-15 and an AAV capsid.

17. The recombinant AAV particle of claim 16, comprising an AAV9 capsid or variant thereof, an AAV5 capsid or variant thereof, or an AAVrh10 capsid or variant thereof.

18. A vector encoding the siRNA duplex of any one of claims 1-4.

19. A cell comprising the siRNA duplex of any one of claims 1-4.

20. A pharmaceutical composition comprising the recombinant AAV particle of claim 16, and a pharmaceutically acceptable carrier, for use in treating or ameliorating amyotrophic lateral sclerosis (ALS) in a subject.

21. The pharmaceutical composition of claim 20 for use in inhibiting or suppressing the expression of SOD1 gene in a cell of the subject.

22. The pharmaceutical composition for use of claim 21, wherein the cell is:

(i) a mammalian cell;

(ii) a CNS cell;

(iii) a neuron;

(iv) a motor neuron or a ventral horn motor neuron; or

(v) an astrocyte.

23. The pharmaceutical composition for use of claim 21, wherein the expression of SOD1 mRNA is inhibited or suppressed by 20% to 93%.

24. The pharmaceutical composition for use of claim 20, wherein expression of a SOD1 gene, mRNA, protein, or a combination thereof is inhibited in a CNS cell, a CNS region, or both thereof.

25. The pharmaceutical composition for use of claim 24, wherein:

(i) the CNS cell comprises a motor neuron;

(ii) the CNS region comprises a spinal cord region, a forebrain region, a midbrain region, the hindbrain region, or a combination thereof; or

(iii) the CNS region comprises a spinal cord region.

26. The pharmaceutical composition for use of claim 24, wherein the SOD1 gene, mRNA, or protein is a wild type SOD1 gene, mRNA, or protein; or a SOD1 gene, mRNA, or protein comprising at least one mutation; or a combination thereof.

27. The pharmaceutical composition for use of claim 20, wherein the ALS is:

(i) familial ALS;

(ii) sporadic ALS;

(iii) early stage ALS;

(iv) middle stage ALS; or

(v) late stage ALS.

28. The pharmaceutical composition for use of claim 20, wherein the pharmaceutical composition is administered to the spinal cord.

29. The pharmaceutical composition for use of claim 20, wherein the pharmaceutical composition is formulated for intravenous administration.

30. The pharmaceutical composition for use of claim 20, wherein the pharmaceutical composition is administered to the subject in combination with an additional therapeutic agent suitable for treatment or prevention of ALS.

31. The pharmaceutical composition for use of claim 30, wherein the additional therapeutic agent comprises an antioxidant, an anti-inflammatory agent, an anti-apoptosis agent, a calcium regulator, an antiglutamatergic agent, a structural protein inhibitor, a compound involved in metal ion regulation, Riluzole, Topiramate, Talampanel, Lamotrigine, Dextromethorphan, Gabapentin and AMPA antagonis,Minocycline, Sodium phenylbutyrate, Arimoclomol, ganglioside, Celecoxib, Cyclosporine, Azathioprine, Cyclophosphamide, Plasmaphoresis, Glatiramer acetate, thalidomide, Ceftriaxone, a pyrazolone derivative, a

phenyl carbamate compound, a neuroprotective compound, a hormone, adrenocorticotropic hormone (ACTH), a neurotropic agent, IGF-I, GDNF, BDNF, CTNF, VEGF, Colivelin, Xaliproden, Thyrotrophin-releasing hormone, ADNF, or a combination thereof.