

Claims

What is claimed is:

1. — A method of treating muscular dystrophy in a subject in need thereof comprising the step of administering a recombinant adeno-associated virus (rAAV) AAVrh74.tMCK.hSCGA, wherein the rAAV is administered using a systemic route of administration and at a dose of about 1.0×10^{12} vg/kg to about 5.0×10^{15} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard.
2. — The method of claim 1, wherein the rAAV is administered at a dose of about 1.0×10^{12} vg/kg to about 2.0×10^{15} vg/kg, about 5×10^{12} vg/kg to about 1.0×10^{15} vg/kg, about 1.0×10^{13} vg/kg to about 5.0×10^{14} vg/kg, about 2.0×10^{13} vg/kg to about 3.0×10^{14} vg/kg, or about 5×10^{13} vg/kg to about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard.
3. — The method of claim 1, wherein the rAAV is administered at a dose about 5×10^{13} vg/kg to about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard.
4. — The method of claim 1, wherein the rAAV is administered at a dose about 5×10^{13} vg/kg, about 1×10^{14} vg/kg, or about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard.
5. — A method of treating muscular dystrophy in a subject in need thereof comprising the step of administering a recombinant adeno-associated virus (rAAV) AAVrh74.tMCK.hSCGA, wherein the rAAV is administered using a systemic route of administration and is administered at a dose about 1.85×10^{13} vg/kg or 7.41×10^{13} vg/kg based on a linearized DNA or plasmid as the quantitation standard.
6. — The method of any one of claims 1-5, wherein the level of alpha-sarcoglycan gene expression in a cell of the subject is increased after administration of the rAAV as compared to the level of alpha-sarcoglycan gene expression before administration of the rAAV; wherein the serum CK level in the subject is decreased after administration of the rAAV as compared to serum CK level before administration of the rAAV; wherein the locomotor activity and specific force generation are increased; wherein fibrosis is reduced; wherein the resistance to contraction-induced injury in tibialis anterior muscle is increased; and/or wherein the number of alpha-sarcoglycan positive fibers in the muscle tissue of the subject is increased after administration of the rAAV as compared to the number of alpha-sarcoglycan positive fibers before administration of the rAAV.
7. — The method of any one of claims 1-6, wherein the systemic route of administration is an intravenous route.
8. — The method of any one of claims 1-7, wherein the rAAV is administered by injection, infusion or implantation.
9. — The method of any one of claims 1-8, wherein the rAAV is administered by infusion.
10. — The method of any one of claims 1-9, wherein the rAAV is administered by an intravenous route through a peripheral limb vein.

11. ~~The method of any one of claims 1-10, wherein the rAAV comprises a nucleotide sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 1.~~
12. ~~The method of claim 11, wherein the rAAV comprises a nucleotide sequence of SEQ ID NO: 1.~~
13. ~~The method of any one of claims 1-12, wherein the rAAV comprises a nucleotide sequence encoding a polypeptide sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical with SEQ ID NO: 2.~~
14. ~~The method of any one of claims 1-12, wherein the rAAV comprises a nucleotide sequence encoding a polypeptide sequence set forth in SEQ ID NO: 2.~~
15. ~~The method of any one of claims 1-14, wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence with at least at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 4.~~
16. ~~The method of claim 15, wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.~~
17. ~~The method of any one of claims 1-16, wherein the rAAV comprises a tMCK promoter.~~
18. ~~The method of any one of claims 1-16, wherein the tMCK promoter comprises a nucleotide sequence set forth in SEQ ID NO: 3.~~
19. ~~The method of any one of claims 1-18, wherein the rAAV comprises a 5' inverted terminal repeat sequence of SEQ ID NO: 5.~~
20. ~~The method of any one of claims 1-19, wherein the rAAV comprises a 3' inverted terminal repeat sequence of SEQ ID NO: 6.~~
21. ~~The method of any one of claims 1-20, wherein the rAAV comprises a poly-A sequence of SEQ ID NO: 7.~~
22. ~~The method of any one of claims 1-21, wherein the rAAV is of the serotype AAVrh.74.~~
23. ~~The method of any one of claims 1-22, wherein the muscular dystrophy is limb-girdle muscular dystrophy.~~
24. ~~The method of any one of claims 1-23, wherein the muscular dystrophy is limb-girdle muscular dystrophy type 2D (LGMD2D).~~
25. ~~The method of any one of claims 1-24, wherein the subject is suffering from limb-girdle muscular dystrophy, and the rAAV is administered by intravenous infusion at a dose of about 5×10^{13} vg/kg to about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard, and~~

wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.

26. — The method of any one of claims 1-25, wherein the level of alpha-sarcoglycan gene expression in a cell of the subject is increased after administration of the rAAV as compared to the level of alpha-sarcoglycan gene expression before administration of the rAAV.

27. — The method of any one of claims 1-26, wherein fibrosis is reduced in the subject after administration of the rAAV as compared to before administration of the rAAV.

28. — The method of any one of claims 1-26, wherein the fibrosis, the central nucleation, the CK level, and/or collagen deposition in the subject is reduced after administration of the rAAV as compared to before administration of the rAAV.

29. — The method of any one of claims 1-26, wherein the specific force, the fiber diameter size, and/or the eccentric contraction in the muscle of the subject are increased after administration of the rAAV as compared to before administration of the rAAV.

30. — The method of claim 26, wherein the alpha-sarcoglycan gene expression is detected by measuring the alpha-sarcoglycan protein level by Western blot, and/or immunohistochemistry.

31. — A method of expressing alpha-sarcoglycan gene in a cell comprising administering to a subject the scAAVrh74.tMCK.hSGCA construct comprising a nucleotide sequence of SEQ ID NO: 4.

32. — The method of claim 31, wherein expression of the alpha-sarcoglycan gene in the cell of the subject is detected by measuring the alpha-sarcoglycan protein level on a Western blot in muscle biopsies.

33. — The method of claim 31, wherein expression of the alpha-sarcoglycan gene in the cell is detected by measuring the alpha-sarcoglycan protein level by immunohistochemistry in muscle biopsies.

34. — The method of claim 31, wherein expression of the alpha-sarcoglycan gene is measured in the subject by detecting the number of vector genome per microgram of genomic DNA.

35. — A method of decreasing a serum CK level in a subject in need thereof, the method comprising administering to the subject the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.

36. — A method of increasing alpha-sarcoglycan positive fibers in a muscle tissue of a subject comprising administering to the subject the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.

37. — A method of increasing the expression of alpha-sarcoglycan in a subject in need thereof comprising administering to the subject an effective amount of the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.

38. — A composition for treating muscular dystrophy in a subject in need thereof, wherein the composition comprises a recombinant adeno-associated virus (rAAV) AAVrh74.tMCK.hSGCA at a dose of about 1.0×10^{12} vg/kg to about 5.0×10^{15} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard, and wherein the composition is formulated for a systemic route of administration.

39. — The composition for treating muscular dystrophy in a subject in need thereof, wherein the composition comprises a recombinant adeno-associated virus (rAAV) AAVrh74.tMCK.hSGCA at a dose of about 1.85×10^{13} vg/kg or 7.41×10^{13} vg/kg based on a linearized DNA or plasmid as the quantitation standard and wherein the composition is formulated for a systemic route of administration.

40. — A composition comprises a recombinant adeno-associated virus (rAAV), wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 4.

41. — The composition of claim 38 or 40, wherein the rAAV is at a dose about 5×10^{13} vg/kg to about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard.

42. — The composition of claim 38 or 40, wherein the rAAV is at a dose about 5×10^{13} vg/kg, about 1×10^{14} vg/kg, or about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard.

43. — The composition of any one of claims 38-42, wherein the level of alpha-sarcoglycan gene expression in a cell of the subject is increased after administration of the composition as compared to the level of alpha-sarcoglycan gene expression before administration of the composition; or wherein the serum CK level in the subject is decreased after administration of the composition as compared to serum CK level before administration of the composition; or wherein the number of alpha-sarcoglycan positive fibers in the muscle tissue of the subject is increased after administration of the composition as compared to the number of alpha-sarcoglycan positive fibers before administration of the composition.

44. — The composition of any one of claims 38-43, wherein the systemic route of administration is an intravenous route.

45. — The composition of any one of claims 38-44, wherein the composition is formulated for administration by injection, infusion or implantation.

46. — The composition of any one of claims 38-45, wherein the composition is formulated for administration by infusion.

47. ~~The composition of any one of claims 38-46, wherein the composition is formulated for administration by an intravenous route through a peripheral limb vein.~~
48. ~~The composition of any one of claims 38-47, wherein the rAAV comprises a nucleotide sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 1.~~
49. ~~The composition of claim 48, wherein the rAAV comprises a nucleotide sequence of SEQ ID NO: 1.~~
50. ~~The composition of any one of claims 38-49, wherein the rAAV comprises a nucleotide sequence encoding a polypeptide sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical with SEQ ID NO: 2.~~
51. ~~The composition of any one of claims 38-49, wherein the rAAV comprises a nucleotide sequence encoding a polypeptide sequence set forth in SEQ ID NO: 2.~~
52. ~~The composition of any one of claims 38-49, wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence with at least at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 4.~~
53. ~~The composition of claim 52, wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.~~
54. ~~The composition of any one of claims 38-53, wherein the rAAV comprises a tMCK promoter.~~
55. ~~The composition of claim 54, wherein the tMCK promoter comprises a nucleotide sequence set forth in SEQ ID NO: 3.~~
56. ~~The composition of any one of claims 38-55, wherein the rAAV comprises a 5' inverted terminal repeat sequence of SEQ ID NO: 5.~~
57. ~~The composition of any one of claims 38-56, wherein the rAAV comprises a 3' inverted terminal repeat sequence of SEQ ID NO: 6.~~
58. ~~The composition of any one of claims 38-57, wherein the rAAV comprises a poly A sequence of SEQ ID NO: 7.~~
59. ~~The composition of any one of claims 38-58, wherein the rAAV is of the serotype AAVrh.74.~~
60. ~~The composition of any one of claims 38-59, wherein the muscular dystrophy is limb-girdle muscular dystrophy.~~
61. ~~The composition of any one of claims 38-60, wherein the muscular dystrophy is limb-girdle muscular dystrophy type 2D (LGMD2D).~~

62. — The composition of any one of claims 38-61, wherein the subject is suffering from limb-girdle muscular dystrophy, and the composition is formulated for administration by intravenous infusion at a dose of about 5×10^{13} vg/kg to about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard, and wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.

63. — The composition of any one of claims 38-62, wherein the level of alpha-sarcoglycan gene expression in a cell of the subject is increased after administration of the composition as compared to the level of alpha-sarcoglycan gene expression before administration of the composition.

64. — The composition of any one of claims 38-63, wherein fibrosis is reduced in the subject after administration of the composition as compared to before administration of the composition.

65. — The composition of any one of claims 38-63, wherein fibrosis, the central nucleation, the CK level, and/or collagen deposition in the subject is reduced after administration of the composition as compared before administration of the composition.

66. — The composition of any one of claims 38-65, wherein the specific force, the fiber diameter size, and/or the eccentric contraction in the muscle of the subject are increased after administration of the composition as compared to before administration of the composition.

67. — The composition of claim 63, wherein the alpha-sarcoglycan gene expression is detected by measuring the alpha-sarcoglycan protein level by Western blot, and/or immunohistochemistry.

68. — A composition for expressing alpha-sarcoglycan gene in a cell, wherein the composition comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.

69. — The composition of claim 68, wherein expression of the alpha-sarcoglycan gene in the cell of the subject is detected by measuring the alpha-sarcoglycan protein level on a Western blot in muscle biopsies.

70. — The composition of claim 68, wherein expression of the alpha-sarcoglycan gene in the cell is detected by measuring the alpha-sarcoglycan protein level by immunohistochemistry in muscle biopsies.

71. — The composition of claim 68, wherein expression of the alpha-sarcoglycan gene is measured in the subject by detecting the number of vector genome per microgram of genomic DNA.

72. — A composition for decreasing a serum CK level in a subject in need thereof, the composition comprising the scAAVrh74.tMCK.hSGCA construct comprising the nucleotide sequence of SEQ ID NO: 4.

~~73. — A composition for increasing alpha-sarcoglycan positive fibers in a muscle tissue of a subject comprising the scAAVrh74.tMCK.hSGCA construct comprising the nucleotide sequence of SEQ ID NO: 4.~~

~~74. — A composition for increasing the expression of alpha-sarcoglycan in a subject in need thereof comprising the scAAVrh74.tMCK.hSGCA construct comprising the nucleotide sequence of SEQ ID NO: 4.~~

~~75.1. — Use of a recombinant adeno-associated virus (rAAV) AAVrh74.tMCK.hSGCA A for the preparation in the manufacture of a medicament for treating muscular dystrophy in a subject in need thereof, wherein the rAAV is at a dose of about 1.0×10^{12} vg/kg to about 5.0×10^{15} vg/kg 5×10^{13} vg/kg to about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard, and wherein the medicament is formulated for a systemic route of administration.~~

~~76. — The use of claim 75, wherein the rAAV is at a dose of about 1.0×10^{12} vg/kg to about 2.0×10^{15} vg/kg, about 5×10^{12} vg/kg to about 1.0×10^{15} vg/kg, about 1.0×10^{13} vg/kg to about 5.0×10^{14} vg/kg, about 2.0×10^{13} vg/kg to about 3.0×10^{14} vg/kg, or about 5×10^{13} vg/kg to about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard.~~

~~77. — The use of claim 75, wherein the rAAV is at a dose about 5×10^{13} vg/kg to about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard.~~

~~78.2. — The use of claim 75, wherein the rAAV is at a dose about 5×10^{13} vg/kg, about 1×10^{14} vg/kg, or about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard.~~

3. — The use of any one of claims 1 or 2, wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 4.

4. — The use of claim 3, wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.

~~79. — Use of a recombinant adeno-associated virus (rAAV) AAVrh74.tMCK.hSGCA A for the preparation of a medicament for treating muscular dystrophy in a subject in need thereof, wherein the rAAV is at a dose of about 1.85×10^{13} vg/kg or 7.41×10^{13} vg/kg based on a linearized DNA or plasmid as the quantitation standard and wherein the medicament is formulated for a systemic route of administration.~~

~~80.5. — The use of any one of claims ~~75-79~~ 1-4, wherein the level of alpha-sarcoglycan gene expression in a cell of the subject is increased after administration of the medicament as compared to the level of alpha-sarcoglycan gene expression before administration of the medicament; or wherein the serum CK level in the subject is decreased after administration of the medicament as compared to serum CK level before administration of the medicament; or wherein the number of alpha-sarcoglycan positive fibers in the muscle tissue of the subject is increased after administration of the medicament~~

as compared to the number of alpha-sarcoglycan positive fibers before administration of the medicament.

~~81.6.~~ The use of any one of claims ~~75-80~~ 1-5, wherein the systemic route of administration is an intravenous route.

~~82.7.~~ The use of any one of claims ~~75-81~~ 1-6, wherein the medicament is formulated for administration by injection, infusion or implantation.

~~83.8.~~ The use of any one of claims ~~75-82~~ 1-7, wherein the medicament is formulated for administration by infusion.

~~84.9.~~ The use of any one of claims ~~75-83~~ 1-7, wherein the medicament is formulated for administration by an intravenous route through a peripheral limb vein.

~~85.~~ The use of any one of claims ~~75-84~~, wherein the rAAV comprises a nucleotide sequence with at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to SEQ ID NO: 1.

~~86.~~ The use of claim ~~85~~, wherein the rAAV comprises a nucleotide sequence of SEQ ID NO: 1.

~~87.~~ The use of any one of claims ~~75-86~~, wherein the rAAV comprises a nucleotide sequence encoding a polypeptide sequence that is at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identical with SEQ ID NO: 2.

~~88.~~ The use of any one of claims ~~75-86~~, wherein the rAAV comprises a nucleotide sequence encoding a polypeptide sequence set forth in SEQ ID NO: 2.

~~89.~~ The use of any one of claims ~~75-86~~, wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence with at least ~~at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to SEQ ID NO: 4.

~~90.~~ The use of claim ~~89~~, wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.

~~91.~~ The use of any one of claims ~~75-90~~, wherein the rAAV comprises a tMCK promoter.

~~92.~~ The use of claim ~~91~~, wherein the tMCK promoter comprises a nucleotide sequence set forth in SEQ ID NO: 3.

~~93.~~ The use of any one of claims ~~75-92~~, wherein the rAAV comprises a 5' inverted terminal repeat sequence of SEQ ID NO: 5.

~~94.~~ The use of any one of claims ~~75-93~~, wherein the rAAV comprises a 3' inverted terminal repeat sequence of SEQ ID NO: 6.

~~95. The use of any one of claims 73-94, wherein the rAAV comprises a poly A sequence of SEQ ID NO: 7.~~

~~96. The use of any one of claims 73-95, wherein the rAAV is of the serotype AAVrh.74.~~

~~97.10. The use of any one of claims 73-96 1-9, wherein the muscular dystrophy is limb-girdle muscular dystrophy.~~

~~98.11. The use of any one of claims 73-97 1-10, wherein the muscular dystrophy is limb-girdle muscular dystrophy type 2D (LGMD2D).~~

~~99.12. The use of any one of claims 73-98 1-11, wherein the subject is suffering from limb-girdle muscular dystrophy, and the medicament is formulated for intravenous infusion and the rAAV is at a dose of about 5×10^{13} vg/kg to about 2×10^{14} vg/kg based on a supercoiled DNA or plasmid as the quantitation standard, and wherein the rAAV comprises the scAAVrh74.tMCK.hSGCA construct nucleotide sequence of SEQ ID NO: 4.~~

~~100. The use of any one of claims 73-99, wherein the level of alpha-sarcoglycan gene expression in a cell of the subject is increased after administration of the medicament as compared to the level of alpha-sarcoglycan gene expression before administration of the medicament.~~

~~101. The use of any one of claims 73-100, wherein fibrosis is reduced in the subject after administration of the medicament as compared to before administration of the medicament.~~

~~102. The use of one of claims 73-100, wherein fibrosis, central nucleation, CK level, and/or collagen deposition in the subject is reduced after administration of the medicament as compared to the fibrosis before administration of the medicament.~~

~~103. The use of any one of claims 72-102, wherein the specific force, the fiber diameter size, and/or the eccentric contraction in the muscle of the subject are increased after administration of the medicament as compared to before administration of the medicament.~~

~~104. The use of claim 100, wherein the alpha-sarcoglycan gene expression is detected by measuring the alpha-sarcoglycan protein level by Western blot, and/or immunohistochemistry.~~

~~105. A use of scAAVrh74.tMCK.hSGCA construct for the preparation of a medicament for expressing alpha-sarcoglycan gene in a cell, wherein the scAAVrh74.tMCK.hSGCA construct comprises the nucleotide sequence of SEQ ID NO: 4.~~

~~106. The use of claim 105, wherein expression of the alpha-sarcoglycan gene in the cell of the subject is detected by measuring the alpha-sarcoglycan protein level on a Western blot in muscle biopsies.~~

~~107. — The use of claim 105, wherein expression of the alpha-sarcoglycan gene in the cell is detected by measuring the alpha-sarcoglycan protein level by immunohistochemistry in muscle biopsies.~~

~~108. — The use of claim 105, wherein expression of the alpha-sarcoglycan gene is measured in the subject by detecting the number of vector genome per microgram of genomic DNA.~~

~~109-13. Use of a scAAVrh74.tMCK.hSGCA construct for preparation in the manufacture of a medicament for the treatment of muscular dystrophy, wherein the medicament is for decreasing a serum CK level in a subject in need thereof, and wherein the scAAVrh74.tMCK.hSGCA construct comprises the nucleotide sequence of SEQ ID NO: 4.~~

~~110. — Use of a scAAVrh74.tMCK.hSGCA construct for the preparation of a medicament for increasing alpha-sarcoglycan positive fibers in a muscle tissue of a subject, wherein the scAAVrh74.tMCK.hSGCA construct comprises the nucleotide sequence of SEQ ID NO: 4.~~

~~111. — Use of scAAVrh74.tMCK.hSGCA construct for the preparation of a medicament for increasing the expression of alpha-sarcoglycan in a subject in need thereof, the scAAVrh74.tMCK.hSGCA construct comprises the nucleotide sequence of SEQ ID NO: 4.~~

~~112. — The method, composition or use of any one of claims 1-111, wherein the subject is a human subject is 4 to 15 years of age.~~

~~113. — The method, composition or use of any one of claims 1-111, wherein the subject is a pediatric subject, an adolescent subject or a young adult subject.~~

~~114. — The method, composition or use of any one of claims 1-111, wherein the subject is a human subject that is 4-15 years of age, has a confirmed alpha-sarcoglycan (SGCA) mutation in both alleles, was negative for AAVrh74 antibodies and/or had >40% or normal 100 meter walk test.~~

~~115. — The method, composition or use of any one of claims 1-111, wherein the subject is a middle aged adult or elderly subject.~~

~~116. — The method, use or composition of any one of claims 1-111, wherein the subject is a human subject is 25 to 55 years of age.~~

~~117. — The method, composition or use of any one of claims 1-111, wherein the subject is a human subject is over 50 years of age.~~

~~118. — A method of generating the rAAV administered in a method, composition or use of any one of claims 1-117, comprising transferring an AAV vector plasmid to a host cell, wherein the AAV vector plasmid comprises a nucleotide sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 8.~~

~~119. The method of claim 118, wherein the AAV vector plasmid comprises a nucleotide sequence of SEQ ID NO: 8.~~

~~120. The method of claim 118 or 119, wherein the vector plasmid comprises a nucleotide sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1, 4, or 8.~~

~~121. The method of any one of claims 118 or 119, wherein the vector plasmid comprises a nucleotide sequence of SEQ ID NO: 1, 4, or 8.~~

~~122. The method of any one of claims 118-121, further comprising transferring a packaging plasmid and/or a helper virus to the host cell.~~

~~123. The method of any one of claims 118-122, wherein the packaging cell comprises a stably integrated AAV-cap gene.~~

~~124. The method of any one of claims 118-123, wherein the packaging cell comprises a stably integrated AAV-rep gene.~~

~~125. A host cell, comprising an AAV vector plasmid that comprises a nucleotide sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1, 4, or 8.~~

~~126. The host cell of claim 125, wherein the AAV vector plasmid that comprises a nucleotide sequence of SEQ ID NO: 1, 4, or 8.~~