

Claims

WHAT IS CLAIMED IS:

1. ~~A self-complementary recombinant adeno-associated virus 9 (scAAV9) encoding the CLN3 polypeptide, comprising an scAAV9 genome comprising in 5' to 3' order: a P546 promoter comprising the nucleotide sequence of SEQ ID NO: 3, and a polynucleotide encoding the CLN3 polypeptide of SEQ ID NO: 1.~~
2. ~~The scAAV9 of claim 1 wherein the scAAV9 genome comprises in 5' to 3' order: a P546 promoter comprising the nucleotide sequence of SEQ ID NO: 3, an SV40 intron, and a polynucleotide encoding the CLN3 polypeptide of SEQ ID NO: 1~~
3. ~~The scAAV9 of claim 1 wherein the scAAV9 genome comprises in 5' to 3' order: a P546 promoter comprising the sequence of SEQ ID NO: 3, a polynucleotide encoding the CLN3 polypeptide of SEQ ID NO: 1, and a bovine growth hormone polyadenylation poly-A sequence.~~
4. ~~The scAAV9 of any one of claims 1 to 3, further comprising a two AAV inverted terminal repeats.~~
5. ~~. The scAAV9 of any one of claims 1 to 4, wherein the polynucleotide encoding the CLN3 polypeptide comprises a sequence at least 90% identical to SEQ ID NO: 2.~~
6. ~~The scAAV9 of any one of claims 1 to 4, wherein the polynucleotide encoding the CLN3 polypeptide comprises the nucleic acid sequence of SEQ ID NO: 2.~~
7. ~~The scAAV9 of any one of claims 1 to 6 wherein the is scAAV9 genome comprises a nucleic acid sequence at least 90% identical to SEQ ID NO: 4~~
8. ~~. The scAAV9 of any one of claims 1 to 6 wherein the is scAAV9 genome comprises a nucleic acid sequence at least 95% identical to SEQ ID NO: 4.~~
9. ~~The scAAV9 of any one of claims 1 to 6 wherein the is scAAV9 genome comprises the nucleic acid sequence of SEQ ID NO: 4.~~
10. ~~The scAAV9 of any one of claims 1 to 9, wherein the AAV inverted terminal repeats are AAV2 inverted terminal repeats.~~

~~11. The scAAV9 of any one of claims 1 to 10, wherein the rAAV9 genome comprises a single-stranded genome.~~

~~12.1.~~ A nucleic acid molecule comprising a first AAV inverted terminal repeat sequence, a P546 promoter comprising the sequence of SEQ ID NO: 3, a nucleic acid sequence encoding the CLN3 polypeptide of SEQ ID NO: 1 and a second inverted terminal repeat sequence.

~~13.2.~~ The nucleic acid molecule of claim 12 comprising, a first AAV inverted terminal repeat sequence, a P546 promoter comprising the nucleotide sequence of SEQ ID NO: 3, an SV40 intron, a nucleic acid sequence encoding the CLN3 polypeptide of SEQ ID NO: 1 and a second AAV inverted terminal repeat sequence.

~~14.3.~~ The nucleic acid molecule of claim 12 comprising a first AAV inverted terminal repeat sequence, P546 promoter comprising the nucleotide sequence of SEQ ID NO: 3, a nucleic acid encoding the CLN3 polypeptide of SEQ ID NO: 1, a bovine growth hormone polyadenylation poly A sequence and a second AAV inverted terminal repeat sequence.

~~15.4.~~ The nucleic acid molecule of any one of claims 12 to ~~14.3~~, wherein the nucleic acid encoding the CLN3 polypeptide comprises a sequence at least 90% identical to SEQ ID NO: 2.

~~16.5.~~ The nucleic acid molecule of any one of claims 12 to ~~14.3~~, wherein the nucleic acid encoding the CLN3 polypeptide comprises the nucleic acid sequence of SEQ ID NO: 2.

~~17.6.~~ The nucleic acid molecule of any one of claims 12 to ~~16.5~~, comprising a nucleic acid sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 4.

~~18.7.~~ The nucleic acid molecule of any one of claims 12 to ~~16.5~~, comprising a nucleic acid sequence at least 95% identical to the nucleic acid sequence of SEQ ID NO: 4.

~~19.8.~~ The nucleic acid molecule of any one of claims 12 to ~~17.6~~ comprising a nucleic acid sequence of SEQ ID NO: 4.

~~20.9.~~ The nucleic acid molecule of any one of claims ~~15.4~~ to ~~20.8~~, wherein the AAV inverted terminal repeats are AAV2 inverted terminal repeats.

~~21.10.~~ A self-complementary recombinant adeno-associated virus 9 (scAAV9) comprising a nucleic acid molecule of any one of claims 12 to ~~20.9~~.

~~22.11.~~_____The scAAV9 of claim ~~24~~10, wherein the scAAV9 comprising a single-stranded genome.

~~23.12.~~_____A rAAV particle comprising a nucleic acid molecule of any one of claims 12 to ~~20~~9.

~~24.13.~~_____The rAAV particle of claim ~~23~~12 wherein the rAAV particle comprising a single-stranded genome.

~~25.~~ A recombinant adeno-associated virus 9 (rAAV9) viral particle encoding a CLN3 polypeptide, comprising a rAAV9 genome comprising in 5' to 3' order: a P546 promoter and a polynucleotide encoding the CLN3 polypeptide.

~~26.~~ The rAAV9 viral particle of claim 25, wherein the rAAV9 genome comprises a self-complementary genome.

~~27.~~ The rAAV9 viral particle of claim, 25 wherein the rAAV9 genome comprises a single-stranded genome.

~~28.~~ The rAAV9 viral particle of any one of claims 25 to 27, wherein the rAAV9 genome comprises in 5' to 3' order: a first AAV inverted terminal repeat, the P546 promoter, the polynucleotide encoding the CLN3 polypeptide, and a second AAV inverted terminal repeat.

~~29.~~ The rAAV9 viral particle of any one of claims 25 to 28, wherein the P546 promoter comprises a sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 3.

~~30.~~ The rAAV9 viral particle of any one of claims 25 to 29, wherein the CLN3 polypeptide comprises a sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 1.

~~31.~~ The rAAV9 viral particle of any one of claims 25 to 30, wherein the polynucleotide encoding the CLN3 polypeptide comprises a sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 2.

~~32.~~ The rAAV9 viral particle of any one of claims 25 to 31, wherein the rAAV9 genome comprises a sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 4.

~~33.~~ The rAAV9 viral particle of any one of claims 25 to 31, wherein the rAAV9 genome comprises a sequence at least 95% identical to the nucleic acid sequence of SEQ ID NO: 4.

~~34.~~ The rAAV9 viral particle of any one of claims 28 to 33, wherein the AAV inverted terminal repeats are AAV2 inverted terminal repeats.

- ~~35. The rAAV9 viral particle of any one of claims 25 to 34, wherein the rAAV9 genome further comprises an SV40 intron.~~
- ~~36. The rAAV9 viral particle of any one of claims 25 to 35, wherein the rAAV9 genome further comprises a BGH poly A sequence.~~
- ~~37. A nucleic acid molecule comprising a rAAV9 genome comprising in 5' to 3' order: a first AAV inverted terminal repeat, a P546 promoter, a polynucleotide encoding the CLN3 polypeptide, and a second AAV inverted terminal repeat.~~
- ~~38. The nucleic acid molecule of claim 37, wherein the rAAV9 comprises a self complementary genome.~~
- ~~39. The nucleic acid molecule of claim 37, wherein the rAAV9 comprises a single stranded genome.~~
- ~~40. The nucleic acid molecule of any one of claims 37 to 39, wherein the rAAV9 genome comprises in 5' to 3' order: a first AAV inverted terminal repeat, the P546 promoter, the polynucleotide encoding the CLN3 polypeptide, and a second AAV inverted terminal repeat.~~
- ~~41. The nucleic acid molecule of any one of claims 37 to 40, wherein the P546 promoter comprises a sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 3.~~
- ~~42. The nucleic acid molecule of any one of claims 37 and 41, wherein the CLN3 polypeptide comprises a sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 1.~~
- ~~43. The nucleic acid molecule of any one of claims 37 to 42, wherein the polynucleotide encoding the CLN3 polypeptide comprises a sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 2.~~
- ~~44. The nucleic acid molecule of any one of claims 37 to 43, wherein the rAAV9 genome comprises a sequence at least 95% identical to the nucleic acid sequence of SEQ ID NO: 4.~~
- ~~45. The nucleic acid molecule of any one of claims 37 to 44, wherein the AAV inverted terminal repeats are AAV2 inverted terminal repeats.~~
- ~~46. The nucleic acid molecule of any one of claims 37 to 45, wherein the rAAV9 genome comprises a sequence at least 90% identical to the nucleic acid sequence of SEQ ID NO: 4.~~

~~47. The nucleic acid molecule of any one of claims 37 to 46, wherein the rAAV9 genome further comprises an SV40 intron.~~

~~48. The nucleic acid molecule of any one of claims 37 to 47, wherein the rAAV9 genome further comprises a bovine growth hormone (BGH) poly A sequence.~~

~~49.14. A composition comprising the scAAV of any one of claims 1 to 12, 21 or 22 claim 10 or 11, the nucleic acid molecule of any one of claims 12 to 9-20 or 37 to 48, rAAV9 viral particle of any one of claims 23 to 36 claims 12 or 13 and a pharmaceutically acceptable excipient, carrier, or diluent.~~

~~50.15. The composition of claim 4914, wherein the excipient comprises a non-ionic low osmolar compound, a buffer, a polymer, a salt, or a combination thereof.~~

~~51.16. A method of treating CLN3 Batten Disease in a subject comprising administering to the subject a composition comprising Use of a therapeutically effective amount of the scAAV of any one of claims 1 to 12, 21 or 22 claim 10 or 11, the nucleic acid molecule of any one of claims 12 to 9-20 or 37 to 48, rAAV9 viral particle of any one of claims 23 to 36 claim 12 or 13, the nucleic acid of any one of claims 13 to 24, or the composition of claim 4914 or claim 5015 for the preparation of a medicament for the treatment of CLN3 Batten Disease.~~

~~52.17. The method use of claim 5116, wherein the composition medicament is administered formulated for administration via a route selected from the group consisting of intrathecal, intracerebroventricular, intraparenchymal, intravenous, and a combination thereof.~~

~~53.18. The method use of claim 5116, wherein the composition medicament is administered intrathecally formulated for intrathecal administration.~~

~~54.19. The method use of claim 5116, wherein the composition medicament is administered intracerebroventricularly formulated for intracerebroventricular administration.~~

~~55.20. The method use of claim 5116, wherein the composition medicament is administered intravenously formulated for intravenous administration.~~

~~56.21. The method use of any one of claims 51 or 55 16 to 20, wherein the medicament comprises about 1×10^{12} to about 1×10^{15} vg of the rAAV9 viral particle is administered.~~

~~57.22. The method use of any one of claims 51 or 56 16 to 21, wherein the medicament comprises about 6×10^{13} to about 1.2×10^{14} of the rAAV9 viral particle is administered.~~

~~58.23.~~ The method use of any one of claims ~~51 to 57~~ 16 to 22, wherein the treatment administration of the medicament reduces one or more symptoms of CLN3-Batten Disease selected from:

- (a) reduced or slowed lysosomal accumulation of autofluorescent storage material,
- (b) reduced or slowed lysosomal accumulation of ATP Synthase Subunit C,
- (c) reduced or slowed glial activation (astrocytes and/or microglia) activation,
- (d) reduced or slowed astrocytosis,
- (e) reduced or slowed brain volume loss measured by MRI,
- (f) reduced or slowed onset of seizures,
- (g) stabilization, reduced or delayed progression, or improvement in one or more of the UBDRS assessment scales, wherein the reduction, stabilization, or improvement is as compared to the subject prior to ~~administering~~ administration of the composition or to an untreated CLN3-Batten Disease patient.

~~59.24.~~ The method use of any one of claims ~~51 to 58~~ 16 to 23, further comprising placing wherein the subject is placed in the Trendelenberg position after ~~administering~~ administration of the rAAV9 viral particle.

25. A composition suitable for treating of CLN3 Batten Disease, wherein the composition comprises a therapeutically effective amount of the scAAV of claim 10 or 11, the nucleic acid molecule of any one of claims 1 to 9, rAAV9 viral particle of claim 12 or 13, or the composition of claim 14 or claim 15 for the preparation of a medicament for the treatment of CLN3 Batten Disease.

26. The composition of claim 25, wherein the composition is formulated for administration via a route selected from the group consisting of intrathecal, intracerebroventricular, intraparenchymal, intravenous, and a combination thereof.

27. The composition of claim 26, wherein the composition is formulated for intrathecal administration.

28. The composition of claim 26, wherein the composition is formulated for intracerebroventricular administration.

29. The composition of claim 26, wherein the composition is formulated for intravenous administration.

30. The composition of any one of claims 25 to 29, wherein the composition comprises about 1×10^{12} to about 1×10^{15} vg of the rAAV9 viral particles.

31. The composition of any one of claims 25 to 29, wherein the medicament comprises about 6×10^{13} to about 1.2×10^{14} of the rAAV9 viral particles.

32. The composition of any one of claims 25 to 31, wherein administration of the composition reduces one or more symptoms of CLN3-Batten Disease selected from:

(a) reduced or slowed lysosomal accumulation of autofluorescent storage material,

(b) reduced or slowed lysosomal accumulation of ATP Synthase Subunit C,

(c) reduced or slowed glial activation (astrocytes and/or microglia) activation,

(d) reduced or slowed astrogliosis,

(e) reduced or slowed brain volume loss measured by MRI,

(f) reduced or slowed onset of seizures,

(g) stabilization, reduced or delayed progression, or improvement in one or more of the UBDRS assessment scales, wherein the reduction, stabilization, or improvement is as compared to the subject prior to administration of the composition or to an untreated CLN3-Batten Disease patient.

~~60. A method of treating a CLN3 disease in a subject in need thereof comprising, delivering a composition comprising the scAAV of any one of claims 1 to 12, 21 or 22, the nucleic acid molecule of any one of claims 12 to 20 or 37 to 48, rAAV9 viral particle of any one of claims 23 to 36 a brain or spinal cord of a subject in need thereof.~~

~~61. The method of claim 60, wherein the composition is delivered by intrathecal injection, intracerebroventricular injection, intraparenchymal injection, intravenous injection, or a combination thereof.~~

~~62. The method of claim 61, further comprising placing the subject in the Trendelenburg position after intrathecal injection of the composition.~~

~~63. The method of any one of claims 60 to 62, wherein the composition comprises a non-ionic low-osmolar contrast agent.~~

~~64. The method of claim 63, wherein the non-ionic, low-osmolar contrast agent is selected from the group consisting of iobitridol, iohexol, iomeprol, iopamidol, iopentol, iopromide, ioversol, ioxilan, and combinations thereof.~~

- ~~65. The method of any one of claims 60 to 64, wherein delivering to the brain or spinal cord comprises delivery to a brain stem.~~
- ~~66. The method of any one of claims 60 to 64, wherein delivering to the brain or spinal cord comprises delivery to a cerebellum.~~
- ~~67. The method of any one of claims 60 to 64, wherein delivering to the brain or spinal cord comprises delivery to a visual cortex.~~
- ~~68. The method of any one of claims 60 to 64, wherein delivering to the brain or spinal cord comprises delivery to a motor cortex.~~
- ~~69. The method of any one of claims 60 to 64, wherein delivering to the brain or spinal cord comprises delivery to a nerve cell, a glial cell, or both.~~
- ~~70. The method of any one of claims 60 to 69, wherein delivering to the brain or spinal cord comprises delivery to a neuron, a lower motor neuron, a microglial cell, an oligodendrocyte, an astrocyte, a Schwann cell, or a combination thereof.~~
- ~~71. The method of any one of claims 60 to 70, wherein the treatment results in one or more of:~~
- ~~(a) reduced lysosomal accumulation of autofluorescent storage material,~~
 - ~~(b) reduced lysosomal accumulation of ATP Synthase Subunit C,~~
 - ~~(c) reduced glial activation (astrocytes and/or microglia) activation,~~
 - ~~(d) reduced astrogliosis,~~
 - ~~(e) reduced brain volume loss measured by MRI,~~
 - ~~(f) reduced onset of seizures, and~~
 - ~~(g) stabilization, reduced progression, or improvement in one or more of the UBDRS assessment scales, wherein the reduction, stabilization, or improvement is as compared to the subject prior to delivering the composition or to an untreated CLN3-Batten Disease patient.~~