

AAV FORMULATION

TECHNICAL FIELD

[0001] The disclosure relates to a composition comprising recombinant adeno-associated vectors.

INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: file name; "55330A_SeqListing.XML," 175,534 bytes, created on December 27, 2023.

BACKGROUND

[0003] Adeno-associated virus (AAV) is a small, replication-defective, non-enveloped animal virus belonging to the family *Parvoviridae*. The AAV genome consists of a linear single stranded DNA which is ~4.7kb in length. The genome consists of two open reading frames (ORF) flanked by an inverted terminal repeat (ITR) sequence that is about 145 bp in length. The ITR consists of a nucleotide sequence at the 5' end (5' ITR) and a nucleotide sequence located at the 3' end (3' ITR) that contain palindromic sequences. The ITRs function in cis by folding over to form T-shaped hairpin structures by complementary base pairing that function as primers during initiation of DNA replication for second strand synthesis. The two open reading frames encode for rep and cap genes that are involved in replication and packaging of the virion.

[0004] AAVs infect both dividing and quiescent cells. Due to the specificity, efficiency, and safety associated with AAVs, AAV vectors have emerged as an expression vector of choice for gene therapy applications. Production conditions and formulation of AAV vectors must be carefully selected to ensure vector stability, purity, and potency while maintaining patient safety. Delivery to the central nervous system presents unique challenges. The brain and spinal cord are compartmentalized organs, and compositions must have appropriate physicochemical properties tailored for administration to these regions in addition to avoiding inflammation and adverse immunogenic reactions. There is a need in the art for optimized, stable compositions comprising AAV vectors that are suitable for administration to the central nervous system.

SUMMARY

[0005] In one aspect, the present disclosure provides a composition comprising recombinant adeno-associated virus (AAV) vectors comprising a heterologous nucleic acid, sodium chloride, potassium chloride, magnesium chloride, phosphate buffer, and a non-ionic surfactant, at pH of 7.2-7.4. In another aspect, the present disclosure provides the use of the composition as described herein in the manufacture of a medicament for treating a neurological disorder in a subject, wherein the medicament is to be directly administered to the central nervous system of the subject.

[0006] The present disclosure also provides a composition comprising recombinant adeno-associated virus (AAV) vectors comprising a heterologous nucleic acid, sodium chloride, potassium chloride, phosphate buffer, and a non-ionic surfactant, at pH of 7.2-7.4. The present disclosure further provides a composition comprising recombinant adeno-associated virus (AAV) vectors comprising a heterologous

WHAT IS CLAIMED IS:

1. A composition comprising recombinant adeno-associated virus (AAV) vectors comprising a heterologous nucleic acid, sodium chloride, potassium chloride, magnesium chloride, phosphate buffer, and a non-ionic surfactant, at pH of 7.2-7.4.
2. The composition of claim 1, demonstrating a conductivity of 15.0-17.0 mS/cm.
3. The composition of claim 1 or claim 2, wherein the non-ionic surfactant is present at a concentration of about 0.001% to about 0.02% (w/V).
4. The composition of any one of claims 1-3, wherein the non-ionic surfactant is a poloxamer.
5. The composition of claim 4, wherein the non-ionic surfactant is poloxamer 188.
6. The composition of claim 5, wherein the non-ionic surfactant is poloxamer 188 present at a concentration of from about 0.001% (w/V) to about 0.005% (w/V).
7. The composition of claim 6, wherein the non-ionic surfactant is poloxamer 188 present at a concentration of about 0.005% (w/V).
8. The composition of any one of claims 1-7, comprising about 145 mM to about 150 mM sodium chloride.
9. The composition of any one of claims 1-8, comprising about 1.5 mM to about 4.5 mM potassium chloride.
10. The composition of any one of claims 1-9, comprising about 0.05 mM to about 1 mM magnesium chloride.
11. The composition of any one of claims 1-10, comprising about 148 mM of sodium chloride, about 3 mM potassium chloride, and about 0.8 mM magnesium chloride.
12. The composition of any one of claims 1-11, comprising phosphate buffer in an amount sufficient to provide about 0.5 mM to about 2 mM phosphate.
13. The composition of claim 12, comprising phosphate buffer in an amount sufficient to provide about 1 mM phosphate.

14. The composition of any one of claims 1-13, wherein the phosphate buffer is sodium phosphate.
15. The composition of claim 1, wherein the composition comprises 1 mM phosphate, 148 mM NaCl, 3 mM KCl, 0.8 mM magnesium chloride, and 0.005% Poloxamer 188.
16. The composition of claim 1, wherein the composition comprises 1 mM Phosphate, 148 mM NaCl, 3 mM KCl, 0.8 mM magnesium chloride, and 0.01% Poloxamer 188.
17. The composition of claim 15 or 16, wherein the composition further comprises 0.05% Trehalose.
18. The composition of any one of claims 1-17, comprising about 5×10^{13} vg/mL to about 1.5×10^{14} vg/mL AAV vector.
19. The composition of claim 18, comprising about 8×10^{13} vg/mL AAV vector.
20. The composition of any one of claims 1-17, wherein the composition does not comprise calcium chloride.
21. The composition of any one of claims 1-20, wherein the AAV vector comprises a regulatory element active in neural cells.
22. The composition of claim 21, wherein the regulatory element active in neural cells is active in GABAergic neural cells.
23. The composition of claim 19, wherein the AAV vector comprises a sequence of any one of SEQ ID NOs: 81-112.
24. The composition of any one of claims 1-23, wherein the AAV vector comprises a therapeutic transgene.
25. The composition of claim 24, wherein the therapeutic transgene is associated with a neural disease or disorder.
26. The composition of claim 25, wherein the therapeutic transgene is selected from (i): SCN1A, or (ii) a transcription factor which activates SCN1A.
27. The composition of any one of claims 1-26, wherein the AAV vector comprises a sequence of SEQ ID NO: 115.

28. Use of the composition of any one of claims 1-27 in the manufacture of a medicament for treating a neurological disorder in a subject, wherein the medicament is to be directly administered to the central nervous system of the subject.
29. The use of claim 28, wherein the medicament is to be administered to the subject via intracerebroventricular injection.
30. The use of claim 28 or claim 29, wherein the neurological disorder is Dravet syndrome or epilepsy.