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(54) Titre : COMPOSITIONS ET METHODES POUR LE TRAITEMENT DE LA MALADIE DE PARKINSON
(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE

(57) Abrégé/Abstract:
The present disclosure relates to methods, formulations and devices for the delivery and therapeutic administration of polynucleotides encoding AADC. The present disclosure relates to methods, formulations and devices for the delivery and therapeutic administration of AAV vectors which include polynucleotides encoding AADC. The present disclosure relates to methods, formulations and devices for the delivery7 and therapeutic administration of polynucleotides encoding AADC in the treatment of neurological diseases, disorders and conditions, including Parkinson's Disease.

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DEMANDE OU BREVET VOLUMINEUX

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JUMBO APPLICATIONS/PATENTS

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COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/671,944, filed 05/15/2018, entitled AADC POLYNUCLEOTIDES FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/681,891, filed 06/07/2018, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/684,384, filed 06/13/2018, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/691,748, filed 06/29/2018, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/698,419, filed 07/16/2018, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/703,137, filed 07/25/2018, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/741,021, filed 10/04/2018, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/748,119, filed 10/19/2018, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/756,897, filed 11/07/2018, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/789,909, filed 01/08/2019, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, and U.S. Provisional Patent Application No. 62/831,400, filed 04/09/2019, entitled COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE, the contents of which are each incorporated herein by reference in their entirety.

REFERENCE TO SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing file, entitled 20571025PCT_SEQLST, was created on May 15, 2019, and is 6,442,762 bytes in size. The information in electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The present disclosure relates to methods, formulations and devices for the delivery and therapeutic administration of polynucleotides encoding AADC. The present disclosure relates to methods, formulations and devices for the delivery and therapeutic administration of AAV vectors which include polynucleotides encoding AADC. The present disclosure relates to methods, formulations and devices for the delivery and therapeutic administration of polynucleotides encoding AADC in the treatment of neurological diseases, disorders and conditions, including Parkinson's Disease.

BACKGROUND

[0004] Aromatic L-amino acid decarboxylase (AADC) is a homodimeric pyridoxal phosphate-dependent enzyme responsible for the synthesis of dopamine and serotonin. The encoded protein catalyzes the decarboxylation of L-3,4-dihydroxyphenylalanine (L-DOPA or levodopa) to dopamine; L-5-hydroxytryptophan to serotonin; and L-tryptophan to tryptamine. Defects in this gene are the cause of aromatic L-amino-acid decarboxylase deficiency (AADCD), which is an inborn error in neurotransmitter metabolism leading to combined serotonin and catecholamine deficiency that results in severe motor and autonomic dysfunctions.

[0005] Parkinson's Disease (PD) is a progressive neurodegenerative disease of the central nervous system (CNS) producing sensory and motor symptoms. Dopamine replacement (i.e., levodopa) has been the standard pharmacotherapy for motor impairment in PD. However, the benefit of dopamine therapy becomes less marked over time, due, in part, to the progressive death of dopamine-generating cells and corresponding loss of AADC activity. Furthermore, systemic administration of high-dose dopamine is complicated by side effects, such as fluctuations in motor performance, dyskinesias, and hallucinations, resulting from dopaminergic stimulation of the mesolimbic system. One strategy to restore dopaminergic function and minimize side effects is the use of gene therapy to deliver AADC directly to a targeted region of the CNS.

[0006] The adeno-associated virus (AAV) has emerged as an attractive vector for gene therapy due to its long-term gene expression, the inability to autonomously replicate without a helper virus, the ability to transduce dividing and non-dividing cells, and the lack of pathogenicity from wild-type infections (See e.g., Hadaczek et al. Mol. Ther. 18(8), 1458-1461, Aug. 2010). AAV is a helper-dependent DNA parvovirus which belongs to the genus *Dependovirus*.

[0007] The present disclosure provides methods, formulations and devices for the delivery and therapeutic administration of such improved nucleic acid constructs, e.g., polynucleotides,

for use with AAV-derived vectors comprising dopa carboxylase ("DDC") gene sequence which encodes a full-length AADC protein for the purpose of gene therapy in the treatment of Parkinson's Disease.

[0008] The nucleic acid constructs described herein comprise at least a 5'-ITR and a 3'-ITR, each or both of which may be derived from an AAV, positioned about a *DDC gene* sequence, as well as additional components required for gene expression and clone selection.

SUMMARY

[0009] The present disclosure presents a method of administering a pharmaceutical composition to a subject. In certain embodiments, the method includes administering to the subject a pharmaceutical composition which includes an adeno-associated virus (AAV) particle which includes an AAV2 capsid and a vector genome, wherein the vector genome includes a nucleotide sequence which has at least 97% identity to SEQ ID NO: 979. In certain embodiments, the vector genome includes a nucleotide sequence which has at least 99% identity to SEQ ID NO: 979. In certain embodiments, the vector genome includes SEQ ID NO: 979.

[0010] In certain embodiments, the pharmaceutical composition is administered to the subject by posterior surgical infusion into at least one putamen of the subject; wherein the average total putaminal coverage from the posterior administration is at least 50%. In certain embodiments, the average total putaminal coverage from the posterior administration is 50-65%. In certain embodiments, the average total putaminal coverage from the posterior administration is 50-60%. In certain embodiments, the average total putaminal coverage from the posterior administration is 55-65%. In certain embodiments, the posterior administration of the pharmaceutical composition is bilateral to both the right putamen and the left putamen of the subject during a single procedure. In certain embodiments, the surgical time is 7-10 hours or 7-9 hours. In certain embodiments, the infusion time is 2.5-4.5 hours, 2.5-5.0 hours, 3.0-4.5 hours, 3.0-5.0 hours, 3.5-4.5 hours or 3.5-5.0 hours.

[0011] In certain embodiments, the pharmaceutical composition is administered to the subject by transfrontal surgical infusion into at least one putamen of the subject; and wherein the average total putaminal coverage from the posterior administration is 30-50%. In certain embodiments, the average total putaminal coverage from the transfrontal administration is 35-50%. In certain embodiments, the average total putaminal coverage from the transfrontal administration is 40-50%. In certain embodiments, the transfrontal administration of the pharmaceutical composition is bilateral to both the right putamen and the left putamen of the subject during a single procedure.

[0012] In certain embodiments, the pharmaceutical composition includes an AAV concentration of between 2.0×10^{12} vg/ml and 3.0×10^{12} vg/ml. In certain embodiments, the pharmaceutical composition includes an AAV concentration of between 2.4×10^{12} vg/ml and 2.8×10^{12} vg/ml. In certain embodiments, the pharmaceutical composition includes an AAV concentration of about 2.6×10^{12} vg/ml. In certain embodiments, the pharmaceutical composition includes an AAV concentration of 2.6×10^{12} vg/ml.

[0013] In certain embodiments, the pharmaceutical composition is administered at a volume of up to 1800 µL per putamen. In certain embodiments, the pharmaceutical composition is administered at a volume of up to 1500 µL per putamen. In certain embodiments, the pharmaceutical composition is administered at a volume of up to 1200 µL per putamen. In certain embodiments, the pharmaceutical composition is administered at a volume of up to 900 µL per putamen. In certain embodiments, the pharmaceutical composition is administered at a volume of up to 450 µL per putamen.

[0014] In certain embodiments, the total viral dosage from the administration is between 2.0×10^{12} vg/ml and 9.4×10^{12} vg/ml. In certain embodiments, the total viral dosage from the administration is between 3.5×10^{12} vg/ml and 8.0×10^{12} vg/ml.

[0015] In certain embodiments, the pharmaceutical composition is a formulation which includes sodium chloride, sodium phosphate and pluronic acid F-68, and wherein the formulation has a pH between 7.0-7.5. In certain embodiments, the formulation includes 150-200 mM sodium chloride, 8-12 mM sodium phosphate and 0.001-0.01% w/v pluronic acid F-68, at a pH between 7.2-7.4. In certain embodiments, the formulation includes 180mM sodium chloride, 10mM sodium phosphate and 0.001% w/v pluronic acid F-68, at a pH of 7.3.

[0016] The present disclosure presents a method of treating a neurological disease in a subject. In certain embodiments, the method includes administering to the subject a pharmaceutical composition according to the administration methods of the present disclosure. In certain embodiments, the method includes administering to the subject a pharmaceutical composition which includes an adeno-associated virus (AAV) particle which includes an AAV2 capsid and a vector genome, wherein the vector genome includes a nucleotide sequence which has at least 97% identity to SEQ ID NO: 979. In certain embodiments, the vector genome includes a nucleotide sequence which has at least 99% identity to SEQ ID NO: 979. In certain embodiments, the vector genome includes SEQ ID NO: 979. In certain embodiments, the neurological disease is Parkinson's Disease.

[0017] In certain embodiments, the administration of the pharmaceutical composition produces a therapeutically effective outcome.

[0018] In certain embodiments, the therapeutically effective outcome includes an increase in AADC enzyme activity relative to baseline of more than 50%, as measured by PET ^{18}F-Dopa analysis 2-7 months after administration. In certain embodiments, the increase in AADC enzyme activity relative to baseline is between 50%-85%. In certain embodiments, the increase in AADC enzyme activity relative to baseline is between 60%-85%. In certain embodiments, the increase in AADC enzyme activity relative to baseline is between 70%-85%.

[0019] In certain embodiments, the therapeutically effective outcome includes a reduced UPDRS III score in the "ON" medication state relative to baseline of up to 20%, as measured 6 months after administration. In certain embodiments, the reduction in UPDRS III score in the "ON" medication state relative to baseline is between 15%-20% at 6 months. In certain embodiments, the therapeutically effective outcome includes a reduced UPDRS III score in the "ON" medication state relative to baseline of up to 30%, as measured 12 months after administration. In certain embodiments, the reduction in UPDRS III score in the "ON" medication state relative to baseline is between 20%-30% at 12 months. In certain embodiments, the patient has a baseline UPDRS III "ON" score greater than 10. In certain embodiments, the patient has a baseline UPDRS III "ON" score between 10 and 14. In certain embodiments, the therapeutically effective outcome includes a reduced UPDRS III score in the "OFF" medication state relative to baseline of up to 26%, as measured 6 months after administration. In certain embodiments, the reduction in UPDRS III score in the "OFF" medication state relative to baseline is between 20%-26% at 6 months. In certain embodiments, the therapeutically effective outcome includes a reduced UPDRS III score in the "OFF" medication state relative to baseline of up to 33%, as measured 12 months after administration. In certain embodiments, the reduction in UPDRS III score in the "OFF" medication state relative to baseline is between 25%-33% at 12 months. In certain embodiments, the patient has a baseline UPDRS III "OFF" score greater than 30. In certain embodiments, the patient has a baseline UPDRS III "OFF" score between 30 and 36.5.

[0020] In certain embodiments, the therapeutically effective outcome includes an increase in diary ON-time without troublesome dyskinesia of at least 3.0 hours relative to baseline, as measured by Hauser motor diary at 6 months. In certain embodiments, the increase in diary ON-time without troublesome dyskinesia relative to baseline is between 3.0 hours to 3.9 hours at 6 months. In certain embodiments, the therapeutically effective outcome includes an increase in diary ON -time without troublesome dyskinesia of at least 2.5 hours relative to baseline, as measured by Hauser motor diary at 12 months. In certain embodiments, the increase in diary ON-time without troublesome dyskinesia relative to baseline is between 2.5 hours to 3.0 hours at

12 months. In certain embodiments, the therapeutically effective outcome includes a decrease in diary OFF-time of at least 3.0 hours relative to baseline, as measured by Hauser motor diary at 6 months. In certain embodiments, the decrease in diary OFF -time relative to baseline is between 3.0 hours to 3.9 hours at 6 months. In certain embodiments, the therapeutically effective outcome includes a decrease in diary OFF -time of at least 2.5 hours relative to baseline, as measured by Hauser motor diary at 12 months. In certain embodiments, the decrease in diary OFF -time relative to baseline is between 2.5 hours to 3.0 hours at 12 months.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the disclosure, as illustrated in the accompanying drawings. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the disclosure.

[0022] FIG. 1 is a schematic of one embodiment a viral genome of the present disclosure.

[0023] FIG. 2 shows the percent coverage of the putamen corresponding with certain embodiments of the present disclosure, which is represented by average coverage of left and right putamen by volume (total and posterior). Error bars are standard errors.

[0024] FIG. 3 shows ^{18}F-DOPA uptake ratios corresponding with certain embodiments of the present disclosure for subjects at 2-7 months post-infusion in comparison to moderate PD control subjects and healthy non-PD subjects. Standardized uptake value ratio (SOR) values are calculated using bilaterally averaged occipital time-activity curve (kBq/mL) region-of-interest values in each subject.

[0025] FIG. 4 shows AADC expression and activity in the putamen (top) and levodopa equivalent doses (LEDs) at 6 months as a percentage compared to baseline (bottom), corresponding with certain embodiments of the present disclosure. Error bars are standard errors.

[0026] FIG. 5 shows the percentage change in levodopa-equivalent dose as compared to baseline, corresponding with certain embodiments of the present disclosure. Error bars are standard errors.

[0027] FIG. 6 shows the change in diary reported ON-time without troublesome dyskinesia corresponding with certain embodiments of the present disclosure. Error bars are standard errors.

[0028] FIG. 7 shows the improvement (reduction) of patient scores on a Unified Parkinson's Disease Rating Scale (UPDRS) Part III, in the patients "ON" medicated state, corresponding with certain embodiments of the present disclosure. Error bars are standard errors.

[0029] FIG. 8 shows the improvement (reduction) of patient scores on a Unified Parkinson's Disease Rating Scale (UPDRS) Part III, in the patients "OFF" medicated state, corresponding with certain embodiments of the present disclosure. Error bars are standard errors.

[0030] FIG. 9 shows the improvement (reduction) of patient stages under the Modified Hoehn and Yahr (mH&Y) scale from baseline, corresponding with certain embodiments of the present disclosure.

[0031] FIG. 10 shows the improvement (reduction) of patients' score on a quality of life assessment (Parkinson's Disease Questionnaire (PDQ-39)), corresponding with certain embodiments of the present disclosure. Error bars are standard errors.

[0032] FIG. 11a shows the improvement in patient quality of life, as assessed by the Clinical Global Impression of Change (CGI-C) scale, corresponding with certain embodiments of the present disclosure.

[0033] FIG. 11b shows the improvement in patient quality of life, as assessed by the Patient Global Impression of Change (PGI-C) scale, corresponding with certain embodiments of the present disclosure.

[0034] FIG. 12a shows UPDRS III AUC scores after IV Levodopa administration up to 7.5 x 10^{11} vg, corresponding with certain embodiments of the present disclosure.

[0035] FIG. 12b shows UPDRS III AUC scores after IV Levodopa administration up to 1.5 x 10^{12} vg, corresponding with certain embodiments of the present disclosure.

[0036] FIG. 12c shows UPDRS III AUC scores after IV Levodopa administration up to 4.7 x 10^{12} vg, corresponding with certain embodiments of the present disclosure.

[0037] FIG. 13 shows the time (min) to UPDRS III response (≥30% change from pre-dose levels) after IV Levodopa administration, corresponding with certain embodiments of the present disclosure.

[0038] FIG. 14 shows the duration (min) of UPDRS III response (≥30% change from pre-dose levels) after IV Levodopa administration, corresponding with certain embodiments of the present disclosure.

[0039] FIG. 15 shows timelines for the delivery of AAV2-hAADC corresponding with certain embodiments of the present disclosure.

[0040] FIG. 16 shows the correlation between ^{18}F-DOPA uptake and corresponding vector coverage of the putamen of patients, corresponding with certain embodiments of the present disclosure.

DETAILED DESCRIPTION

I. COMPOSITIONS OF THE DISCLOSURE

Adeno-associated viruses (AAVs) and AAV particles

[0041] Viruses of the Parvoviridae family are small non-enveloped icosahedral capsid viruses characterized by a single stranded DNA genome. Parvoviridae family viruses consist of two subfamilies: Parvovirinae, which infect vertebrates, and Densovirinae, which infect invertebrates. Due to its relatively simple structure, easily manipulated using standard molecular biology techniques, this virus family is useful as a biological tool. The genome of the virus may be modified to contain a minimum of components for the assembly of a functional recombinant virus, or viral particle, which is loaded with or engineered to express or deliver a desired payload, which may be delivered to a target cell, tissue, organ, or organism.

[0042] The parvoviruses and other members of the Parvoviridae family are generally described in Kenneth I. Berns, "Parvoviridae: The Viruses and Their Replication," Chapter 69 in FIELDS VIROLOGY (3d Ed. 1996), the contents of which are incorporated by reference in their entirety.

[0043] The Parvoviridae family comprises the Dependovirus genus which includes adeno-associated viruses (AAV) capable of replication in vertebrate hosts including, but not limited to, human, primate, bovine, canine, equine, and ovine species.

[0044] The vector genome is a linear, single-stranded DNA (ssDNA) molecule approximately 5,000 nucleotides (nt) in length. The AAV viral genome can comprise a payload region and at least one inverted terminal repeat (ITR) or ITR region. ITRs traditionally flank the coding nucleotide sequences for the non-structural proteins (encoded by Rep genes) and the structural proteins (encoded by capsid genes or Cap genes). While not wishing to be bound by theory, an AAV viral genome typically comprises two ITR sequences. The vector genome comprises a characteristic T-shaped hairpin structure defined by the self-complementary terminal 145 nt of the 5' and 3' ends of the ssDNA which form an energetically stable double stranded region. The double stranded hairpin structures comprise multiple functions including, but not limited to, acting as an origin for DNA replication by functioning as primers for the endogenous DNA polymerase complex of the host viral replication cell.

[0045] In addition to the encoded heterologous payload, AAV particles may comprise the viral genome, in whole or in part, of any naturally occurring and/or recombinant AAV serotype nucleotide sequence or variant. AAV variants may have sequences of significant homology at the nucleic acid (genome or capsid) and amino acid levels (capsids), to produce constructs which are generally physical and functional equivalents, replicate by similar mechanisms, and assemble

by similar mechanisms. Chiorini et al.,J. Vir.71: 6823-33(1997); Srivastava et al.,J. Vir.45:555-64 (1983); Chiorini et al.,J. Vir.73:1309-1319 (1999); Rutledge et al.,J. Vir.72:309-319 (1998); and Wu et al.,J. Vir.74: 8635-47 (2000), the contents of each of which are incorporated herein by reference in their entirety.

[0046] In certain embodiments, AAV particles of the present disclosure are recombinant AAV particles which are replication defective, lacking sequences encoding functional Rep and Cap proteins within their viral genome. These defective AAV particles may lack most or all parental coding sequences and essentially carry only one or two AAV ITR sequences and the nucleic acid of interest for delivery to a cell, a tissue, an organ or an organism.

[0047] In certain embodiments, the viral genome of the AAV particles of the present disclosure comprise at least one control element which provides for the replication, transcription and translation of a coding sequence encoded therein. Not all of the control elements need always be present as long as the coding sequence is capable of being replicated, transcribed and/or translated in an appropriate host cell. Non-limiting examples of expression control elements include sequences for transcription initiation and/or termination, promoter and/or enhancer sequences, efficient RNA processing signals such as splicing and polyadenylation signals, sequences that stabilize cytoplasmic mRNA, sequences that enhance translation efficacy (e.g., Kozak consensus sequence), sequences that enhance protein stability, and/or sequences that enhance protein processing and/or secretion.

[0048] According to the present disclosure, AAV particles for use in therapeutics and/or diagnostics comprise a virus that has been distilled or reduced to the minimum components necessary for transduction of a nucleic acid payload or cargo of interest. In this manner, AAV particles are engineered as vehicles for specific delivery while lacking the deleterious replication and/or integration features found in wild-type viruses.

[0049] AAV particles of the present disclosure may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. As used herein, a "vector" is any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule such as the nucleic acids described herein.

[0050] In addition to single stranded AAV particles (e.g., ssAAVs), the present disclosure also provides for self-complementary AAV (scAAVs) particles. scAAV particles contain DNA strands which anneal together to form double stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the cell.

[0051] In certain embodiments, the AAV particle of the present disclosure is an scAAV.

[0052] In certain embodiments, the AAV particle of the present disclosure is an ssAAV.

[0053] Methods for producing and/or modifying AAV particles are disclosed in the art such as pseudotyped AAV particles (PCT Patent Publication Nos. WO200028004; WO200123001; WO2004112727; WO 2005005610 and WO 2005072364, the content of each of which is incorporated herein by reference in its entirety).

[0054] AAV particles may be modified to enhance the efficiency of delivery. Such modified AAV particles can be packaged efficiently and be used to successfully infect the target cells at high frequency and with minimal toxicity. In some embodiments the capsids of the AAV particles are engineered according to the methods described in US Publication Number US 20130195801, the contents of which are incorporated herein by reference in their entirety.

[0055] In certain embodiments, the AAV particles comprising a payload region encoding the polypeptides of the disclosure may be introduced into mammalian cells.

AAV serotypes

[0056] AAV particles of the present disclosure may comprise or be derived from any natural or recombinant AAV serotype. According to the present disclosure, the AAV particles may utilize or be based on a serotype selected from any of the following PHP.B, PHP.A, AAV1, AAV2, AAV2G9, AAV3, AAV3a, AAV3b, AAV3-3, AAV4, AAV4-4, AAV5, AAV6, AAV6.1, AAV6.2, AAV6.1.2, AAV7, AAV7.2, AAV8, AAV9, AAV9.11, AAV9.13, AAV9.16, AAV9.24, AAV9.45, AAV9.47, AAV9.61, AAV9.68, AAV9.84, AAV9.9, AAV10, AAV11, AAV12, AAV16.3, AAV24.1, AAV27.3, AAV42.12, AAV42-1b, AAV42-2, AAV42-3a, AAV42-3b, AAV42-4, AAV42-5a, AAV42-5b, AAV42-6b, AAV42-8, AAV42-10, AAV42-11, AAV42-12, AAV42-13, AAV42-15, AAV42-aa, AAV43-1, AAV43-12, AAV43-20, AAV43-21, AAV43-23, AAV43-25, AAV43-5, AAV44.1, AAV44.2, AAV44.5, AAV223.1, AAV223.2, AAV223.4, AAV223.5, AAV223.6, AAV223.7, AAV1-7/rh.48, AAV1-8/rh.49, AAV2-15/rh.62, AAV2-3/rh.61, AAV2-4/rh.50, AAV2-5/rh.51, AAV3.1/hu.6, AAV3.1/hu.9, AAV3-9/rh.52, AAV3-11/rh.53, AAV4-8/r11.64, AAV4-9/rh.54, AAV4-19/rh.55, AAV5-3/rh.57, AAV5-22/rh.58, AAV7.3/hu.7, AAV16.8/hu.10, AAV16.12/hu.11, AAV29.3/bb.1, AAV29.5/bb.2, AAV106.1/hu.37, AAV114.3/hu.40, AAV127.2/hu.41, AAV127.5/hu.42, AAV128.3/hu.44, AAV130.4/hu.48, AAV145.1/hu.53, AAV145.5/hu.54, AAV145.6/hu.55, AAV161.10/hu.60, AAV161.6/hu.61, AAV33.12/hu.17, AAV33.4/hu.15, AAV33.8/hu.16, AAV52/hu.19, AAV52.1/hu.20, AAV58.2/hu.25, AAVA3.3, AAVA3.4, AAVA3.5, AAVA3.7, AAVC1, AAVC2, AAVC5, AAV-DJ, AAV-DJ8, AAVF3, AAVF5, AAVH2, AAVrh.72, AAVhu.8, AAVrh.68, AAVrh.70, AAVpi.1, AAVpi.3, AAVpi.2, AAVrh.60, AAVrh.44, AAVrh.65, AAVrh.55, AAVrh.47, AAVrh.69, AAVrh.45, AAVrh.59, AAVhu.12, AAVH6, AAVLK03, AAVH-1/hu.1, AAVH-5/hu.3, AAVLG-10/rh.40, AAVLG-4/rh.38, AAVLG-

9/hu.39, AAVN721-8/rh.43, AAVCh.5, AAVCh.5R1, AAVcy.2, AAVcy.3, AAVcy.4, AAVcy.5, AAVCy.5R1, AAVCy.5R2, AAVCy.5R3, AAVCy.5R4, AAVcy.6, AAVhu.1, AAVhu.2, AAVhu.3, AAVhu.4, AAVhu.5, AAVhu.6, AAVhu.7, AAVhu.9, AAVhu.10, AAVhu.11, AAVhu.13, AAVhu.15, AAVhu.16, AAVhu.17, AAVhu.18, AAVhu.20, AAVhu.21, AAVhu.22, AAVhu.23.2, AAVhu.24, AAVhu.25, AAVhu.27, AAVhu.28, AAVhu.29, AAVhu.29R, AAVhu.31, AAVhu.32, AAVhu.34, AAVhu.35, AAVhu.37, AAVhu.39, AAVhu.40, AAVhu.41, AAVhu.42, AAVhu.43, AAVhu.44, AAVhu.44R1, AAVhu.44R2, AAVhu.44R3, AAVhu.45, AAVhu.46, AAVhu.47, AAVhu.48, AAVhu.48R1, AAVhu.48R2, AAVhu.48R3, AAVhu.49, AAVhu.51, AAVhu.52, AAVhu.54, AAVhu.55, AAVhu.56, AAVhu.57, AAVhu.58, AAVhu.60, AAVhu.61, AAVhu.63, AAVhu.64, AAVhu.66, AAVhu.67, AAVhu.14/9, AAVhu.t 19, AAVrh.2, AAVrh.2R, AAVrh.8, AAVrh.8R, AAVrh.10, AAVrh.12, AAVrh.13, AAVrh.13R, AAVrh.14, AAVrh.17, AAVrh.18, AAVrh.19, AAVrh.20, AAVrh.21, AAVrh.22, AAVrh.23, AAVrh.24, AAVrh.25, AAVrh.31, AAVrh.32, AAVrh.33, AAVrh.34, AAVrh.35, AAVrh.36, AAVrh.37, AAVrh.37R2, AAVrh.38, AAVrh.39, AAVrh.40, AAVrh.46, AAVrh.48, AAVrh.48.1, AAVrh.48.1.2, AAVrh.48.2, AAVrh.49, AAVrh.51, AAVrh.52, AAVrh.53, AAVrh.54, AAVrh.56, AAVrh.57, AAVrh.58, AAVrh.61, AAVrh.64, AAVrh.64R1, AAVrh.64R2, AAVrh.67, AAVrh.73, AAVrh.74, AAVrh8R, AAVrh8R A586R mutant, AAVrh8R R533A mutant, AAAV, BAAV, caprine AAV, bovine AAV, ovine AAV, AAVhE1.1, AAVhEr1.5, AAVhER1.14, AAVhEr1.8, AAVhEr1.16, AAVhEr1.18, AAVhEr1.35, AAVhEr1.7, AAVhEr1.36, AAVhEr2.29, AAVhEr2.4, AAVhEr2.16, AAVhEr2.30, AAVhEr2.31, AAVhEr2.36, AAVhER1.23, AAVhEr3.1, AAV2.5T , AAV-PAEC, AAV-LK01, AAV-LK02, AAV-LK03, AAV-LK04, AAV-LK05, AAV-LK06, AAV-LK07, AAV-LK08, AAV-LK09, AAV-LK10, AAV-LK11, AAV-LK12, AAV-LK13, AAV-LK14, AAV-LK15, AAV-LK16, AAV-LK17, AAV-LK18, AAV-LK19, AAV-PAEC2, AAV-PAEC4, AAV-PAEC6, AAV-PAEC7, AAV-PAEC8, AAV-PAEC11, AAV-PAEC12, AAV-2-pre-miRNA-101 , AAV-8h, AAV-8b, AAV-h, AAV-b, AAV SM 10-2 , AAV Shuffle 100-1 , AAV Shuffle 100-3, AAV Shuffle 100-7, AAV Shuffle 10-2, AAV Shuffle 10-6, AAV Shuffle 10-8, AAV Shuffle 100-2, AAV SM 10-1, AAV SM 10-8 , AAV SM 100-3, AAV SM 100-10, BNP61 AAV, BNP62 AAV, BNP63 AAV, AAVrh.50, AAVrh.43, AAVrh.62, AAVrh.48, AAVhu.19, AAVhu.11, AAVhu.53, AAV4-8/rh.64, AAVLG-9/hu.39, AAV54.5/hu.23, AAV54.2/hu.22, AAV54.7/hu.24, AAV54.1/hu.21, AAV54.4R/hu.27, AAV46.2/hu.28, AAV46.6/hu.29, AAV128.1/hu.43, true type AAV (ttAAV), UPENN AAV 10, Japanese AAV 10 serotypes, AAV CBr-7.1, AAV CBr-7.10, AAV CBr-7.2, AAV CBr-7.3, AAV CBr-7.4, AAV CBr-7.5, AAV CBr-7.7, AAV CBr-7.8, AAV CBr-B7.3, AAV CBr-B7.4,

AAV CBr-E1, AAV CBr-E2, AAV CBr-E3, AAV CBr-E4, AAV CBr-E5, AAV CBr-e5, AAV CBr-E6, AAV CBr-E7, AAV CBr-E8, AAV CHt-1, AAV CHt-2, AAV CHt-3, AAV CHt-6.1, AAV CHt-6.10, AAV CHt-6.5, AAV CHt-6.6, AAV CHt-6.7, AAV CHt-6.8, AAV CHt-P1, AAV CHt-P2, AAV CHt-P5, AAV CHt-P6, AAV CHt-P8, AAV CHt-P9, AAV CKd-1, AAV CKd-10, AAV CKd-2, AAV CKd-3, AAV CKd-4, AAV CKd-6, AAV CKd-7, AAV CKd-8, AAV CKd-B1, AAV CKd-B2, AAV CKd-B3, AAV CKd-B4, AAV CKd-B5, AAV CKd-B6, AAV CKd-B7, AAV CKd-B8, AAV CKd-H1, AAV CKd-H2, AAV CKd-H3, AAV CKd-H4, AAV CKd-H5, AAV CKd-H6, AAV CKd-N3, AAV CKd-N4, AAV CKd-N9, AAV CLg-F1, AAV CLg-F2, AAV CLg-F3, AAV CLg-F4, AAV CLg-F5, AAV CLg-F6, AAV CLg-F7, AAV CLg-F8, AAV CLv-1, AAV CLv1-1, AAV Clv1-10, AAV CLv1-2, AAV CLv-12, AAV CLv1-3, AAV CLv-13, AAV CLv1-4, AAV Clv1-7, AAV Clv1-8, AAV Clv1-9, AAV CLv-2, AAV CLv-3, AAV CLv-4, AAV CLv-6, AAV CLv-8, AAV CLv-D1, AAV CLv-D2, AAV CLv-D3, AAV CLv-D4, AAV CLv-D5, AAV CLv-D6, AAV CLv-D7, AAV CLv-D8, AAV CLv-E1, AAV CLv-K1, AAV CLv-K3, AAV CLv-K6, AAV CLv-L4, AAV CLv-L5, AAV CLv-L6, AAV CLv-M1, AAV CLv-M11, AAV CLv-M2, AAV CLv-M5, AAV CLv-M6, AAV CLv-M7, AAV CLv-M8, AAV CLv-M9, AAV CLv-R1, AAV CLv-R2, AAV CLv-R3, AAV CLv-R4, AAV CLv-R5, AAV CLv-R6, AAV CLv-R7, AAV CLv-R8, AAV CLv-R9, AAV CSp-1, AAV CSp-10, AAV CSp-11, AAV CSp-2, AAV CSp-3, AAV CSp-4, AAV CSp-6, AAV CSp-7, AAV CSp-8, AAV CSp-8.10, AAV CSp-8.2, AAV CSp-8.4, AAV CSp-8.5, AAV CSp-8.6, AAV CSp-8.7, AAV CSp-8.8, AAV CSp-8.9, AAV CSp-9, AAV.hu.48R3, AAV.VR-355, AAV3B, AAV4, AAV5, AAVF1/HSC1, AAVF11/HSC11, AAVF12/HSC12, AAVF13/HSC13, AAVF14/HSC14, AAVF15/HSC15, AAVF16/HSC16, AAVF17/HSC17, AAVF2/HSC2, AAVF3/HSC3, AAVF4/HSC4, AAVF5/HSC5, AAVF6/HSC6, AAVF7/HSC7, AAVF8/HSC8, AAVF9/HSC9, PHP.B (AAV-PHP.B), PHP.A (AAV.PHP.A), G2B-26, G2B-13, TH1.1-32, TH1.1-35, AAVPHP.B2, AAVPHP.B3, AAVPHP.N/PHP.B-DGT, AAVPHP.B-EST, AAVPHP.B-GGT, AAVPHP.B-ATP, AAVPHP.B-ATT-T, AAVPHP.B-DGT-T, AAVPHP.B-GGT-T, AAVPHP.B-SGS, AAVPHP.B-AQP, AAVPHP.B-QQP, AAVPHP.B-SNP(3), AAVPHP.B-SNP, AAVPHP.B-QGT, AAVPHP.B-NQT, AAVPHP.B-EGS, AAVPHP.B-SGN, AAVPHP.B-EGT, AAVPHP.B-DST, AAVPHP.B-DST, AAVPHP.B-STP, AAVPHP.B-PQP, AAVPHP.B-SQP, AAVPHP.B-QLP, AAVPHP.B-TMP, AAVPHP.B-TTP, AAVPHP.S/G2A12, AAVG2A15/G2A3, AAVG2B4, and/or AAVG2B5, and variants thereof.

[0057] In some embodiments, the AAV serotype may be, or have, a modification as described in United States Publication No. US 20160361439, the contents of which are herein incorporated by reference in their entirety, such as but not limited to, Y252F, Y272F, Y444F, Y500F, Y700F,

Y704F, Y730F, Y275F, Y281F, Y508F, Y576F, Y612G, Y673F, and Y720F of the wild-type AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, and hybrids thereof.

[0058] In some embodiments, the AAV serotype may be, or have, a mutation as described in United States Patent No. US 9546112, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, at least two, but not all the F129L, D418E, K531E, L584F, V598A and H642N mutations in the sequence of AAV6 (SEQ ID NO:4 of US 9546112), AAV1 (SEQ ID NO:6 of US 9546112), AAV2, AAV3, AAV4, AAV5, AAV7, AAV9, AAV10 or AAV11 or derivatives thereof. In yet another embodiment, the AAV serotype may be, or have, an AAV6 sequence comprising the K531E mutation (SEQ ID NO:5 of US 9546112).

[0059] In some embodiments, the AAV serotype may be, or have, a mutation in the AAV1 sequence, as described in in United States Publication No. US 20130224836, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, at least one of the surface-exposed tyrosine residues, preferably, at positions 252, 273, 445, 701, 705 and 731 of AAV1 (SEQ ID NO: 2 of US 20130224836) substituted with another amino acid, preferably with a phenylalanine residue. In certain embodiments, the AAV serotype may be, or have, a mutation in the AAV9 sequence, such as, but not limited to, at least one of the surface-exposed tyrosine residues, preferably, at positions 252, 272, 444, 500, 700, 704 and 730 of AAV2 (SEQ ID NO: 4 of US 20130224836) substituted with another amino acid, preferably with a phenylalanine residue. In certain embodiments, the tyrosine residue at position 446 of AAV9 (SEQ ID NO: 6 US 20130224836) is substituted with a phenylalanine residue.

[0060] In some embodiments, the serotype may be AAV2 or a variant thereof, as described in International Publication No. WO2016130589, herein incorporated by reference in its entirety. The amino acid sequence of AAV2 may comprise N587A, E548A, or N708A mutations. In certain embodiments, the amino acid sequence of any AAV may comprise a V708K mutation.

[0061] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Publication No. US20030138772, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV1 (SEQ ID NO: 6 and 64 of US20030138772), AAV2 (SEQ ID NO: 7 and 70 of US20030138772), AAV3 (SEQ ID NO: 8 and 71 of US20030138772), AAV4 (SEQ ID NO: 63 of US20030138772), AAV5 (SEQ ID NO: 114 of US20030138772), AAV6 (SEQ ID NO: 65 of US20030138772), AAV7 (SEQ ID NO: 1-3 of US20030138772), AAV8 (SEQ ID NO: 4 and 95 of US20030138772), AAV9 (SEQ ID NO: 5 and 100 of US20030138772), AAV10 (SEQ ID NO: 117 of US20030138772), AAV11 (SEQ ID NO: 118 of US20030138772), AAV12 (SEQ ID NO: 119 of US20030138772), AAVrh10

(amino acids 1 to 738 of SEQ ID NO: 81 of US20030138772), AAV16.3 (US20030138772 SEQ ID NO: 10), AAV29.3/bb.1 (US20030138772 SEQ ID NO: 11), AAV29.4 (US20030138772 SEQ ID NO: 12), AAV29.5/bb.2 (US20030138772 SEQ ID NO: 13), AAV1.3 (US20030138772 SEQ ID NO: 14), AAV13.3 (US20030138772 SEQ ID NO: 15), AAV24.1 (US20030138772 SEQ ID NO: 16), AAV27.3 (US20030138772 SEQ ID NO: 17), AAV7.2 (US20030138772 SEQ ID NO: 18), AAVC1 (US20030138772 SEQ ID NO: 19), AAVC3 (US20030138772 SEQ ID NO: 20), AAVC5 (US20030138772 SEQ ID NO: 21), AAVF1 (US20030138772 SEQ ID NO: 22), AAVF3 (US20030138772 SEQ ID NO: 23), AAVF5 (US20030138772 SEQ ID NO: 24), AAVH6 (US20030138772 SEQ ID NO: 25), AAVH2 (US20030138772 SEQ ID NO: 26), AAV42-8 (US20030138772 SEQ ID NO: 27), AAV42-15 (US20030138772 SEQ ID NO: 28), AAV42-5b (US20030138772 SEQ ID NO: 29), AAV42-1b (US20030138772 SEQ ID NO: 30), AAV42-13 (US20030138772 SEQ ID NO: 31), AAV42-3a (US20030138772 SEQ ID NO: 32), AAV42-4 (US20030138772 SEQ ID NO: 33), AAV42-5a (US20030138772 SEQ ID NO: 34), AAV42-10 (US20030138772 SEQ ID NO: 35), AAV42-3b (US20030138772 SEQ ID NO: 36), AAV42-11 (US20030138772 SEQ ID NO: 37), AAV42-6b (US20030138772 SEQ ID NO: 38), AAV43-1 (US20030138772 SEQ ID NO: 39), AAV43-5 (US20030138772 SEQ ID NO: 40), AAV43-12 (US20030138772 SEQ ID NO: 41), AAV43-20 (US20030138772 SEQ ID NO: 42), AAV43-21 (US20030138772 SEQ ID NO: 43), AAV43-23 (US20030138772 SEQ ID NO: 44), AAV43-25 (US20030138772 SEQ ID NO: 45), AAV44.1 (US20030138772 SEQ ID NO: 46), AAV44.5 (US20030138772 SEQ ID NO: 47), AAV223.1 (US20030138772 SEQ ID NO: 48), AAV223.2 (US20030138772 SEQ ID NO: 49), AAV223.4 (US20030138772 SEQ ID NO: 50), AAV223.5 (US20030138772 SEQ ID NO: 51), AAV223.6 (US20030138772 SEQ ID NO: 52), AAV223.7 (US20030138772 SEQ ID NO: 53), AAVA3.4 (US20030138772 SEQ ID NO: 54), AAVA3.5 (US20030138772 SEQ ID NO: 55), AAVA3.7 (US20030138772 SEQ ID NO: 56), AAVA3.3 (US20030138772 SEQ ID NO: 57), AAV42.12 (US20030138772 SEQ ID NO: 58), AAV44.2 (US20030138772 SEQ ID NO: 59), AAV42-2 (US20030138772 SEQ ID NO: 9), or variants thereof.

[0062] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Publication No. US20150159173, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV2 (SEQ ID NO: 7 and 23 of US20150159173), rh20 (SEQ ID NO: 1 of US20150159173), rh32/33 (SEQ ID NO: 2 of US20150159173), rh39 (SEQ ID NO: 3, 20 and 36 of US20150159173), rh46 (SEQ ID NO: 4 and 22 of US20150159173), rh73 (SEQ ID NO: 5 of US20150159173), rh74 (SEQ ID NO: 6 of US20150159173), AAV6.1 (SEQ ID NO: 29 of US20150159173), rh.8 (SEQ ID NO: 41 of

US20150159173), rh.48.1 (SEQ ID NO: 44 of US20150159173), hu.44 (SEQ ID NO: 45 of US20150159173), hu.29 (SEQ ID NO: 42 of US20150159173), hu.48 (SEQ ID NO: 38 of US20150159173), rh54 (SEQ ID NO: 49 of US20150159173), AAV2 (SEQ ID NO: 7 of US20150159173), cy.5 (SEQ ID NO: 8 and 24 of US20150159173), rh.10 (SEQ ID NO: 9 and 25 of US20150159173), rh.13 (SEQ ID NO: 10 and 26 of US20150159173), AAV1 (SEQ ID NO: 11 and 27 of US20150159173), AAV3 (SEQ ID NO: 12 and 28 of US20150159173), AAV6 (SEQ ID NO: 13 and 29 of US20150159173), AAV7 (SEQ ID NO: 14 and 30 of US20150159173), AAV8 (SEQ ID NO: 15 and 31 of US20150159173), hu.13 (SEQ ID NO: 16 and 32 of US20150159173), hu.26 (SEQ ID NO: 17 and 33 of US20150159173), hu.37 (SEQ ID NO: 18 and 34 of US20150159173), hu.53 (SEQ ID NO: 19 and 35 of US20150159173), rh.43 (SEQ ID NO: 21 and 37 of US20150159173), rh2 (SEQ ID NO: 39 of US20150159173), rh.37 (SEQ ID NO: 40 of US20150159173), rh.64 (SEQ ID NO: 43 of US20150159173), rh.48 (SEQ ID NO: 44 of US20150159173), ch.5 (SEQ ID NO 46 of US20150159173), rh.67 (SEQ ID NO: 47 of US20150159173), rh.58 (SEQ ID NO: 48 of US20150159173), or variants thereof including, but not limited to Cy5R1, Cy5R2, Cy5R3, Cy5R4, rh.13R, rh.37R2, rh.2R, rh.8R, rh.48.1, rh.48.2, rh.48.1.2, hu.44R1, hu.44R2, hu.44R3, hu.29R, ch.5R1, rh64R1, rh64R2, AAV6.2, AAV6.1, AAV6.12, hu.48R1, hu.48R2, and hu.48R3.

[0063] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US 7198951, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV9 (SEQ ID NO: 1-3 of US 7198951), AAV2 (SEQ ID NO: 4 of US 7198951), AAV1 (SEQ ID NO: 5 of US 7198951), AAV3 (SEQ ID NO: 6 of US 7198951), and AAV8 (SEQ ID NO: 7 of US7198951).

[0064] In some embodiments, the AAV serotype may be, or have, a mutation in the AAV9 sequence as described by N Pulicherla et al. (Molecular Therapy 19(6):1070-1078 (2011), herein incorporated by reference in its entirety), such as but not limited to, AAV9.9, AAV9.11, AAV9.13, AAV9.16, AAV9.24, AAV9.45, AAV9.47, AAV9.61, AAV9.68, AAV9.84.

[0065] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US 6156303, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV3B (SEQ ID NO: 1 and 10 of US 6156303), AAV6 (SEQ ID NO: 2, 7 and 11 of US 6156303), AAV2 (SEQ ID NO: 3 and 8 of US 6156303), AAV3A (SEQ ID NO: 4 and 9, of US 6156303), or derivatives thereof.

[0066] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Publication No. US20140359799, the contents of which are herein incorporated by

reference in their entirety, such as, but not limited to, AAV8 (SEQ ID NO: 1 of US20140359799), AAVDJ (SEQ ID NO: 2 and 3 of US20140359799), or variants thereof.

[0067] In some embodiments, the serotype may be AAVDJ or a variant thereof, such as AAVDJ8 (or AAV-DJ8), as described by Grimm et al. (Journal of Virology 82(12): 5887-5911 (2008), herein incorporated by reference in its entirety). The amino acid sequence of AAVDJ8 may comprise two or more mutations in order to remove the heparin binding domain (HBD). In certain embodiments, the AAV-DJ sequence described as SEQ ID NO: 1 in US Patent No. 7,588,772, the contents of which are herein incorporated by reference in their entirety, may comprise two mutations: (1) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (2) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr). In certain embodiments, may comprise three mutations: (1) K406R where lysine (K; Lys) at amino acid 406 is changed to arginine (R; Arg), (2) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (3) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr).

[0068] In some embodiments, the AAV serotype may be, or have, a sequence of AAV4 as described in International Publication No. WO1998011244, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV4 (SEQ ID NO: 1-20 of WO1998011244).

[0069] In some embodiments, the AAV serotype may be, or have, a mutation in the AAV2 sequence to generate AAV2G9 as described in International Publication No. WO2014144229 and herein incorporated by reference in its entirety.

[0070] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2005033321, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV3-3 (SEQ ID NO: 217 of WO2005033321), AAV1 (SEQ ID NO: 219 and 202 of WO2005033321), AAV106.1/hu.37 (SEQ ID No: 10 of WO2005033321), AAV114.3/hu.40 (SEQ ID No: 11 of WO2005033321), AAV127.2/hu.41 (SEQ ID NO:6 and 8 of WO2005033321), AAV128.3/hu.44 (SEQ ID No: 81 of WO2005033321), AAV130.4/hu.48 (SEQ ID NO: 78 of WO2005033321), AAV145.1/hu.53 (SEQ ID No: 176 and 177 of WO2005033321), AAV145.6/hu.56 (SEQ ID NO: 168 and 192 of WO2005033321), AAV16.12/hu.11 (SEQ ID NO:: 153 and 57 of WO2005033321), AAV16.8/hu.10 (SEQ ID NO:: 156 and 56 of WO2005033321), AAV161.10/hu.60 (SEQ ID No: 170 of WO2005033321), AAV161.6/hu.61 (SEQ ID No: 174 of WO2005033321), AAV1-7/rh.48 (SEQ ID NO: 32 of WO2005033321), AAV1-8/rh.49 (SEQ ID NOs: 103 and 25 of WO2005033321), AAV2 (SEQ ID NO: 211 and 221 of WO2005033321), AAV2-15/rh.62 (SEQ

ID No: 33 and 114 of WO2005033321), AAV2-3/rh.61 (SEQ ID NO: 21 of WO2005033321), AAV2-4/rh.50 (SEQ ID No: 23 and 108 of WO2005033321), AAV2-5/rh.51 (SEQ ID NO: 104 and 22 of WO2005033321), AAV3.1/hu.6 (SEQ ID NO: 5 and 84 of WO2005033321), AAV3.1/hu.9 (SEQ ID NO: 155 and 58 of WO2005033321), AAV3-11/rh.53 (SEQ ID NO: 186 and 176 of WO2005033321), AAV3-3 (SEQ ID NO: 200 of WO2005033321), AAV33.12/hu.17 (SEQ ID NO:4 of WO2005033321), AAV33.4/hu.15 (SEQ ID No: 50 of WO2005033321), AAV33.8/hu.16 (SEQ ID No: 51 of WO2005033321), AAV3-9/rh.52 (SEQ ID NO: 96 and 18 of WO2005033321), AAV4-19/rh.55 (SEQ ID NO: 117 of WO2005033321), AAV4-4 (SEQ ID NO: 201 and 218 of WO2005033321), AAV4-9/rh.54 (SEQ ID NO: 116 of WO2005033321), AAV5 (SEQ ID NO: 199 and 216 of WO2005033321), AAV52.1/hu.20 (SEQ ID NO: 63 of WO2005033321), AAV52/hu.19 (SEQ ID NO: 133 of WO2005033321), AAV5-22/rh.58 (SEQ ID No: 27 of WO2005033321), AAV5-3/rh.57 (SEQ ID NO: 105 of WO2005033321), AAV5-3/rh.57 (SEQ ID No: 26 of WO2005033321), AAV58.2/hu.25 (SEQ ID No: 49 of WO2005033321), AAV6 (SEQ ID NO: 203 and 220 of WO2005033321), AAV7 (SEQ ID NO: 222 and 213 of WO2005033321), AAV7.3/hu.7 (SEQ ID No: 55 of WO2005033321), AAV8 (SEQ ID NO: 223 and 214 of WO2005033321), AAVH-1/hu.1 (SEQ ID No: 46 of WO2005033321), AAVH-5/hu.3 (SEQ ID No: 44 of WO2005033321), AAVhu.1 (SEQ ID NO: 144 of WO2005033321), AAVhu.10 (SEQ ID NO: 156 of WO2005033321), AAVhu.11 (SEQ ID NO: 153 of WO2005033321), AAVhu.12 (WO2005033321 SEQ ID NO: 59), AAVhu.13 (SEQ ID NO: 129 of WO2005033321), AAVhu.14/AAV9 (SEQ ID NO: 123 and 3 of WO2005033321), AAVhu.15 (SEQ ID NO: 147 of WO2005033321), AAVhu.16 (SEQ ID NO: 148 of WO2005033321), AAVhu.17 (SEQ ID NO: 83 of WO2005033321), AAVhu.18 (SEQ ID NO: 149 of WO2005033321), AAVhu.19 (SEQ ID NO: 133 of WO2005033321), AAVhu.2 (SEQ ID NO: 143 of WO2005033321), AAVhu.20 (SEQ ID NO: 134 of WO2005033321), AAVhu.21 (SEQ ID NO: 135 of WO2005033321), AAVhu.22 (SEQ ID NO: 138 of WO2005033321), AAVhu.23.2 (SEQ ID NO: 137 of WO2005033321), AAVhu.24 (SEQ ID NO: 136 of WO2005033321), AAVhu.25 (SEQ ID NO: 146 of WO2005033321), AAVhu.27 (SEQ ID NO: 140 of WO2005033321), AAVhu.29 (SEQ ID NO: 132 of WO2005033321), AAVhu.3 (SEQ ID NO: 145 of WO2005033321), AAVhu.31 (SEQ ID NO: 121 of WO2005033321), AAVhu.32 (SEQ ID NO: 122 of WO2005033321), AAVhu.34 (SEQ ID NO: 125 of WO2005033321), AAVhu.35 (SEQ ID NO: 164 of WO2005033321), AAVhu.37 (SEQ ID NO: 88 of WO2005033321), AAVhu.39 (SEQ ID NO: 102 of WO2005033321), AAVhu.4 (SEQ ID NO: 141 of WO2005033321), AAVhu.40 (SEQ ID NO: 87 of WO2005033321), AAVhu.41 (SEQ ID NO: 91 of WO2005033321), AAVhu.42 (SEQ ID NO: 85 of

WO2005033321), AAVhu.43 (SEQ ID NO: 160 of WO2005033321), AAVhu.44 (SEQ ID NO: 144 of WO2005033321), AAVhu.45 (SEQ ID NO: 127 of WO2005033321), AAVhu.46 (SEQ ID NO: 159 of WO2005033321), AAVhu.47 (SEQ ID NO: 128 of WO2005033321), AAVhu.48 (SEQ ID NO: 157 of WO2005033321), AAVhu.49 (SEQ ID NO: 189 of WO2005033321), AAVhu.51 (SEQ ID NO: 190 of WO2005033321), AAVhu.52 (SEQ ID NO: 191 of WO2005033321), AAVhu.53 (SEQ ID NO: 186 of WO2005033321), AAVhu.54 (SEQ ID NO: 188 of WO2005033321), AAVhu.55 (SEQ ID NO: 187 of WO2005033321), AAVhu.56 (SEQ ID NO: 192 of WO2005033321), AAVhu.57 (SEQ ID NO: 193 of WO2005033321), AAVhu.58 (SEQ ID NO: 194 of WO2005033321), AAVhu.6 (SEQ ID NO: 84 of WO2005033321), AAVhu.60 (SEQ ID NO: 184 of WO2005033321), AAVhu.61 (SEQ ID NO: 185 of WO2005033321), AAVhu.63 (SEQ ID NO: 195 of WO2005033321), AAVhu.64 (SEQ ID NO: 196 of WO2005033321), AAVhu.66 (SEQ ID NO: 197 of WO2005033321), AAVhu.67 (SEQ ID NO: 198 of WO2005033321), AAVhu.7 (SEQ ID NO: 150 of WO2005033321), AAVhu.8 (WO2005033321 SEQ ID NO: 12), AAVhu.9 (SEQ ID NO: 155 of WO2005033321), AAVLG-10/rh.40 (SEQ ID No: 14 of WO2005033321), AAVLG-4/rh.38 (SEQ ID NO: 86 of WO2005033321), AAVLG-4/rh.38 (SEQ ID No: 7 of WO2005033321), AAVN721-8/rh.43 (SEQ ID NO: 163 of WO2005033321), AAVN721-8/rh.43 (SEQ ID No: 43 of WO2005033321), AAVpi.1 (WO2005033321 SEQ ID NO: 28), AAVpi.2 (WO2005033321 SEQ ID NO: 30), AAVpi.3 (WO2005033321 SEQ ID NO: 29), AAVrh.38 (SEQ ID NO: 86 of WO2005033321), AAVrh.40 (SEQ ID NO: 92 of WO2005033321), AAVrh.43 (SEQ ID NO: 163 of WO2005033321), AAVrh.44 (WO2005033321 SEQ ID NO: 34), AAVrh.45 (WO2005033321 SEQ ID NO: 41), AAVrh.47 (WO2005033321 SEQ ID NO: 38), AAVrh.48 (SEQ ID NO: 115 of WO2005033321), AAVrh.49 (SEQ ID NO: 103 of WO2005033321), AAVrh.50 (SEQ ID NO: 108 of WO2005033321), AAVrh.51 (SEQ ID NO: 104 of WO2005033321), AAVrh.52 (SEQ ID NO: 96 of WO2005033321), AAVrh.53 (SEQ ID NO: 97 of WO2005033321), AAVrh.55 (WO2005033321 SEQ ID NO: 37), AAVrh.56 (SEQ ID NO: 152 of WO2005033321), AAVrh.57 (SEQ ID NO: 105 of WO2005033321), AAVrh.58 (SEQ ID NO: 106 of WO2005033321), AAVrh.59 (WO2005033321 SEQ ID NO: 42), AAVrh.60 (WO2005033321 SEQ ID NO: 31), AAVrh.61 (SEQ ID NO: 107 of WO2005033321), AAVrh.62 (SEQ ID NO: 114 of WO2005033321), AAVrh.64 (SEQ ID NO: 99 of WO2005033321), AAVrh.65 (WO2005033321 SEQ ID NO: 35), AAVrh.68 (WO2005033321 SEQ ID NO: 16), AAVrh.69 (WO2005033321 SEQ ID NO: 39), AAVrh.70 (WO2005033321 SEQ ID NO: 20), AAVrh.72 (WO2005033321 SEQ ID NO: 9), or variants thereof including, but not limited to, AAVcy.2, AAVcy.3, AAVcy.4, AAVcy.5, AAVcy.6, AAVrh.12, AAVrh.17,

AAVrh.18, AAVrh.19, AAVrh.21, AAVrh.22, AAVrh.23, AAVrh.24, AAVrh.25, AAVrh.25/42 15, AAVrh.31, AAVrh.32, AAVrh.33, AAVrh.34, AAVrh.35, AAVrh.36, AAVrh.37, AAVrh14. Non limiting examples of variants include SEQ ID NO: 13, 15, 17, 19, 24, 36, 40, 45, 47, 48, 51-54, 60-62, 64-77, 79, 80, 82, 89, 90, 93-95, 98, 100, 101, , 109-113, 118-120, 124, 126, 131, 139, 142, 151,154, 158, 161, 162, 165-183, 202, 204-212, 215, 219, 224-236, of WO2005033321, the contents of which are herein incorporated by reference in their entirety.

[0071] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2015168666, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVrh8R (SEQ ID NO: 9 of WO2015168666), AAVrh8R A586R mutant (SEQ ID NO: 10 of WO2015168666), AAVrh8R R533A mutant (SEQ ID NO: 11 of WO2015168666), or variants thereof.

[0072] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US9233131, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVhE1.1 (SEQ ID NO:44 of US9233131), AAVhEr1.5 (SEQ ID NO:45 of US9233131), AAVhER1.14 (SEQ ID NO:46 of US9233131), AAVhEr1.8 (SEQ ID NO:47 of US9233131), AAVhEr1.16 (SEQ ID NO:48 of US9233131), AAVhEr1.18 (SEQ ID NO:49 of US9233131), AAVhEr1.35 (SEQ ID NO:50 of US9233131), AAVhEr1.7 (SEQ ID NO:51 of US9233131), AAVhEr1.36 (SEQ ID NO:52 of US9233131), AAVhEr2.29 (SEQ ID NO:53 of US9233131), AAVhEr2.4 (SEQ ID NO:54 of US9233131), AAVhEr2.16 (SEQ ID NO:55 of US9233131), AAVhEr2.30 (SEQ ID NO:56 of US9233131), AAVhEr2.31 (SEQ ID NO:58 of US9233131), AAVhEr2.36 (SEQ ID NO:57 of US9233131), AAVhER1.23 (SEQ ID NO:53 of US9233131), AAVhEr3.1 (SEQ ID NO:59 of US9233131), AAV2.5T (SEQ ID NO:42 of US9233131), or variants thereof.

[0073] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20150376607, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-PAEC (SEQ ID NO:1 of US20150376607), AAV-LK01 (SEQ ID NO:2 of US20150376607), AAV-LK02 (SEQ ID NO:3 of US20150376607), AAV-LK03 (SEQ ID NO:4 of US20150376607), AAV-LK04 (SEQ ID NO:5 of US20150376607), AAV-LK05 (SEQ ID NO:6 of US20150376607), AAV-LK06 (SEQ ID NO:7 of US20150376607), AAV-LK07 (SEQ ID NO:8 of US20150376607), AAV-LK08 (SEQ ID NO:9 of US20150376607), AAV-LK09 (SEQ ID NO:10 of US20150376607), AAV-LK10 (SEQ ID NO:11 of US20150376607), AAV-LK11 (SEQ ID NO:12 of US20150376607), AAV-LK12 (SEQ ID NO:13 of US20150376607), AAV-LK13 (SEQ ID NO:14 of US20150376607), AAV-LK14 (SEQ ID NO:15 of US20150376607), AAV-

LK15 (SEQ ID NO:16 of US20150376607), AAV-LK16 (SEQ ID NO:17 of US20150376607), AAV-LK17 (SEQ ID NO:18 of US20150376607), AAV-LK18 (SEQ ID NO:19 of US20150376607), AAV-LK19 (SEQ ID NO:20 of US20150376607), AAV-PAEC2 (SEQ ID NO:21 of US20150376607), AAV-PAEC4 (SEQ ID NO:22 of US20150376607), AAV-PAEC6 (SEQ ID NO:23 of US20150376607), AAV-PAEC7 (SEQ ID NO:24 of US20150376607), AAV-PAEC8 (SEQ ID NO:25 of US20150376607), AAV-PAEC11 (SEQ ID NO:26 of US20150376607), AAV-PAEC12 (SEQ ID NO:27, of US20150376607), or variants thereof.

[0074] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US9163261, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-2-pre-miRNA-101 (SEQ ID NO: 1 US9163261), or variants thereof.

[0075] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20150376240, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-8h (SEQ ID NO: 6 of US20150376240), AAV-8b (SEQ ID NO: 5 of US20150376240), AAV-h (SEQ ID NO: 2 of US20150376240), AAV-b (SEQ ID NO: 1 of US20150376240), or variants thereof.

[0076] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20160017295, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV SM 10-2 (SEQ ID NO: 22 of US20160017295), AAV Shuffle 100-1 (SEQ ID NO: 23 of US20160017295), AAV Shuffle 100-3 (SEQ ID NO: 24 of US20160017295), AAV Shuffle 100-7 (SEQ ID NO: 25 of US20160017295), AAV Shuffle 10-2 (SEQ ID NO: 34 of US20160017295), AAV Shuffle 10-6 (SEQ ID NO: 35 of US20160017295), AAV Shuffle 10-8 (SEQ ID NO: 36 of US20160017295), AAV Shuffle 100-2 (SEQ ID NO: 37 of US20160017295), AAV SM 10-1 (SEQ ID NO: 38 of US20160017295), AAV SM 10-8 (SEQ ID NO: 39 of US20160017295), AAV SM 100-3 (SEQ ID NO: 40 of US20160017295), AAV SM 100-10 (SEQ ID NO: 41 of US20160017295), or variants thereof.

[0077] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20150238550, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BNP61 AAV (SEQ ID NO: 1 of US20150238550), BNP62 AAV (SEQ ID NO: 3 of US20150238550), BNP63 AAV (SEQ ID NO: 4 of US20150238550), or variants thereof.

[0078] In some embodiments, the AAV serotype may be or may have a sequence as described in United States Patent Publication No. US20150315612, the contents of which are herein

incorporated by reference in their entirety, such as, but not limited to, AAVrh.50 (SEQ ID NO: 108 of US20150315612), AAVrh.43 (SEQ ID NO: 163 of US20150315612), AAVrh.62 (SEQ ID NO: 114 of US20150315612), AAVrh.48 (SEQ ID NO: 115 of US20150315612), AAVhu.19 (SEQ ID NO: 133 of US20150315612), AAVhu.11 (SEQ ID NO: 153 of US20150315612), AAVhu.53 (SEQ ID NO: 186 of US20150315612), AAV4-8/rh.64 (SEQ ID No: 15 of US20150315612), AAVLG-9/hu.39 (SEQ ID No: 24 of US20150315612), AAV54.5/hu.23 (SEQ ID No: 60 of US20150315612), AAV54.2/hu.22 (SEQ ID No: 67 of US20150315612), AAV54.7/hu.24 (SEQ ID No: 66 of US20150315612), AAV54.1/hu.21 (SEQ ID No: 65 of US20150315612), AAV54.4R/hu.27 (SEQ ID No: 64 of US20150315612), AAV46.2/hu.28 (SEQ ID No: 68 of US20150315612), AAV46.6/hu.29 (SEQ ID No: 69 of US20150315612), AAV128.1/hu.43 (SEQ ID No: 80 of US20150315612), or variants thereof.

[0079] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2015121501, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, true type AAV (ttAAV) (SEQ ID NO: 2 of WO2015121501), "UPenn AAV10" (SEQ ID NO: 8 of WO2015121501), "Japanese AAV10" (SEQ ID NO: 9 of WO2015121501), or variants thereof.

[0080] According to the present disclosure, AAV capsid serotype selection or use may be from a variety of species. In certain embodiments, the AAV may be an avian AAV (AAAV). The AAAV serotype may be, or have, a sequence as described in United States Patent No. US 9238800, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAAV (SEQ ID NO: 1, 2, 4, 6, 8, 10, 12, and 14 of US 9,238,800), or variants thereof.

[0081] In certain embodiments, the AAV may be a bovine AAV (BAAV). The BAAV serotype may be, or have, a sequence as described in United States Patent No. US 9,193,769, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BAAV (SEQ ID NO: 1 and 6 of US 9193769), or variants thereof. The BAAV serotype may be or have a sequence as described in United States Patent No. US7427396, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BAAV (SEQ ID NO: 5 and 6 of US7427396), or variants thereof.

[0082] In certain embodiments, the AAV may be a caprine AAV. The caprine AAV serotype may be, or have, a sequence as described in United States Patent No. US7427396, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, caprine AAV (SEQ ID NO: 3 of US7427396), or variants thereof.

[0083] In other embodiments the AAV may be engineered as a hybrid AAV from two or more parental serotypes. In certain embodiments, the AAV may be AAV2G9 which comprises sequences from AAV2 and AAV9. The AAV2G9 AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20160017005, the contents of which are herein incorporated by reference in its entirety.

[0084] In certain embodiments, the AAV may be a serotype generated by the AAV9 capsid library with mutations in amino acids 390-627 (VP1 numbering) as described by Pulicherla et al. (Molecular Therapy 19(6):1070-1078 (2011), the contents of which are herein incorporated by reference in their entirety. The serotype and corresponding nucleotide and amino acid substitutions may be, but is not limited to, AAV9.1 (G1594C; D532H), AAV6.2 (T1418A and T1436X; V473D and I479K), AAV9.3 (T1238A; F413Y), AAV9.4 (T1250C and A1617T; F417S), AAV9.5 (A1235G, A1314T, A1642G, C1760T; Q412R, T548A, A587V), AAV9.6 (T1231A; F411I), AAV9.9 (G1203A, G1785T; W595C), AAV9.10 (A1500G, T1676C; M559T), AAV9.11 (A1425T, A1702C, A1769T; T568P, Q590L), AAV9.13 (A1369C, A1720T; N457H, T574S), AAV9.14 (T1340A, T1362C, T1560C, G1713A; L447H), AAV9.16 (A1775T; Q592L), AAV9.24 (T1507C, T1521G; W503R), AAV9.26 (A1337G, A1769C; Y446C, Q590P), AAV9.33 (A1667C; D556A), AAV9.34 (A1534G, C1794T; N512D), AAV9.35 (A1289T, T1450A, C1494T, A1515T, C1794A, G1816A; Q430L, Y484N, N98K, V606I), AAV9.40 (A1694T, E565V), AAV9.41 (A1348T, T1362C; T450S), AAV9.44 (A1684C, A1701T, A1737G; N562H, K567N), AAV9.45 (A1492T, C1804T; N498Y, L602F), AAV9.46 (G1441C, T1525C, T1549G; G481R, W509R, L517V), 9.47 (G1241A, G1358A, A1669G, C1745T; S414N, G453D, K557E, T582I), AAV9.48 (C1445T, A1736T; P482L, Q579L), AAV9.50 (A1638T, C1683T, T1805A; Q546H, L602H), AAV9.53 (G1301A, A1405C, C1664T, G1811T; R134Q, S469R, A555V, G604V), AAV9.54 (C1531A, T1609A; L511I, L537M), AAV9.55 (T1605A; F535L), AAV9.58 (C1475T, C1579A; T492I, H527N), AAV.59 (T1336C; Y446H), AAV9.61 (A1493T; N498I), AAV9.64 (C1531A, A1617T; L511I), AAV9.65 (C1335T, T1530C, C1568A; A523D), AAV9.68 (C1510A; P504T), AAV9.80 (G1441A,;G481R), AAV9.83 (C1402A, A1500T; P468T, E500D), AAV9.87 (T1464C, T1468C; S490P), AAV9.90 (A1196T; Y399F), AAV9.91 (T1316G, A1583T, C1782G, T1806C; L439R, K528I), AAV9.93 (A1273G, A1421G, A1638C, C1712T, G1732A, A1744T, A1832T; S425G, Q474R, Q546H, P571L, G578R, T582S, D611V), AAV9.94 (A1675T; M559L) and AAV9.95 (T1605A; F535L).

[0085] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2016049230, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAVF1/HSC1 (SEQ ID NO: 2 and 20 of

WO2016049230), AAVF2/HSC2 (SEQ ID NO: 3 and 21 of WO2016049230), AAVF3/HSC3 (SEQ ID NO: 5 and 22 of WO2016049230), AAVF4/HSC4 (SEQ ID NO: 6 and 23 of WO2016049230), AAVF5/HSC5 (SEQ ID NO: 11 and 25 of WO2016049230), AAVF6/HSC6 (SEQ ID NO: 7 and 24 of WO2016049230), AAVF7/HSC7 (SEQ ID NO: 8 and 27 of WO2016049230), AAVF8/HSC8 (SEQ ID NO: 9 and 28 of WO2016049230), AAVF9/HSC9 (SEQ ID NO: 10 and 29 of WO2016049230), AAVF11/HSC11 (SEQ ID NO: 4 and 26 of WO2016049230), AAVF12/HSC12 (SEQ ID NO: 12 and 30 of WO2016049230), AAVF13/HSC13 (SEQ ID NO: 14 and 31 of WO2016049230), AAVF14/HSC14 (SEQ ID NO: 15 and 32 of WO2016049230), AAVF15/HSC15 (SEQ ID NO: 16 and 33 of WO2016049230), AAVF16/HSC16 (SEQ ID NO: 17 and 34 of WO2016049230), AAVF17/HSC17 (SEQ ID NO: 13 and 35 of WO2016049230), or variants or derivatives thereof.

[0086] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US 8734809, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV CBr-E1 (SEQ ID NO: 13 and 87 of US8734809), AAV CBr-E2 (SEQ ID NO: 14 and 88 of US8734809), AAV CBr-E3 (SEQ ID NO: 15 and 89 of US8734809), AAV CBr-E4 (SEQ ID NO: 16 and 90 of US8734809), AAV CBr-E5 (SEQ ID NO: 17 and 91 of US8734809), AAV CBr-e5 (SEQ ID NO: 18 and 92 of US8734809), AAV CBr-E6 (SEQ ID NO: 19 and 93 of US8734809), AAV CBr-E7 (SEQ ID NO: 20 and 94 of US8734809), AAV CBr-E8 (SEQ ID NO: 21 and 95 of US8734809), AAV CLv-D1 (SEQ ID NO: 22 and 96 of US8734809), AAV CLv-D2 (SEQ ID NO: 23 and 97 of US8734809), AAV CLv-D3 (SEQ ID NO: 24 and 98 of US8734809), AAV CLv-D4 (SEQ ID NO: 25 and 99 of US8734809), AAV CLv-D5 (SEQ ID NO: 26 and 100 of US8734809), AAV CLv-D6 (SEQ ID NO: 27 and 101 of US8734809), AAV CLv-D7 (SEQ ID NO: 28 and 102 of US8734809), AAV CLv-D8 (SEQ ID NO: 29 and 103 of US8734809), AAV CLv-E1 (SEQ ID NO: 13 and 87 of US8734809), AAV CLv-R1 (SEQ ID NO: 30 and 104 of US8734809), AAV CLv-R2 (SEQ ID NO: 31 and 105 of US8734809), AAV CLv-R3 (SEQ ID NO: 32 and 106 of US8734809), AAV CLv-R4 (SEQ ID NO: 33 and 107 of US8734809), AAV CLv-R5 (SEQ ID NO: 34 and 108 of US8734809), AAV CLv-R6 (SEQ ID NO: 35 and 109 of US8734809), AAV CLv-R7 (SEQ ID NO: 36 and 110 of US8734809), AAV CLv-R8 (SEQ ID NO: X and X of US8734809), AAV CLv-R9 (SEQ ID NO: X and X of US8734809), AAV CLg-F1 (SEQ ID NO: 39 and 113 of US8734809), AAV CLg-F2 (SEQ ID NO: 40 and 114 of US8734809), AAV CLg-F3 (SEQ ID NO: 41 and 115 of US8734809), AAV CLg-F4 (SEQ ID NO: 42 and 116 of US8734809), AAV CLg-F5 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F6 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F7 (SEQ ID NO: 44 and 118 of US8734809), AAV

CLg-F8 (SEQ ID NO: 43 and 117 of US8734809), AAV CSp-1 (SEQ ID NO: 45 and 119 of US8734809), AAV CSp-10 (SEQ ID NO: 46 and 120 of US8734809), AAV CSp-11 (SEQ ID NO: 47 and 121 of US8734809), AAV CSp-2 (SEQ ID NO: 48 and 122 of US8734809), AAV CSp-3 (SEQ ID NO: 49 and 123 of US8734809), AAV CSp-4 (SEQ ID NO: 50 and 124 of US8734809), AAV CSp-6 (SEQ ID NO: 51 and 125 of US8734809), AAV CSp-7 (SEQ ID NO: 52 and 126 of US8734809), AAV CSp-8 (SEQ ID NO: 53 and 127 of US8734809), AAV CSp-9 (SEQ ID NO: 54 and 128 of US8734809), AAV CHt-2 (SEQ ID NO: 55 and 129 of US8734809), AAV CHt-3 (SEQ ID NO: 56 and 130 of US8734809), AAV CKd-1 (SEQ ID NO: 57 and 131 of US8734809), AAV CKd-10 (SEQ ID NO: 58 and 132 of US8734809), AAV CKd-2 (SEQ ID NO: 59 and 133 of US8734809), AAV CKd-3 (SEQ ID NO: 60 and 134 of US8734809), AAV CKd-4 (SEQ ID NO: 61 and 135 of US8734809), AAV CKd-6 (SEQ ID NO: 62 and 136 of US8734809), AAV CKd-7 (SEQ ID NO: 63 and 137 of US8734809), AAV CKd-8 (SEQ ID NO: 64 and 138 of US8734809), AAV CLv-1 (SEQ ID NO: 35 and 139 of US8734809), AAV CLv-12 (SEQ ID NO: 66 and 140 of US8734809), AAV CLv-13 (SEQ ID NO: 67 and 141 of US8734809), AAV CLv-2 (SEQ ID NO: 68 and 142 of US8734809), AAV CLv-3 (SEQ ID NO: 69 and 143 of US8734809), AAV CLv-4 (SEQ ID NO: 70 and 144 of US8734809), AAV CLv-6 (SEQ ID NO: 71 and 145 of US8734809), AAV CLv-8 (SEQ ID NO: 72 and 146 of US8734809), AAV CKd-B1 (SEQ ID NO: 73 and 147 of US8734809), AAV CKd-B2 (SEQ ID NO: 74 and 148 of US8734809), AAV CKd-B3 (SEQ ID NO: 75 and 149 of US8734809), AAV CKd-B4 (SEQ ID NO: 76 and 150 of US8734809), AAV CKd-B5 (SEQ ID NO: 77 and 151 of US8734809), AAV CKd-B6 (SEQ ID NO: 78 and 152 of US8734809), AAV CKd-B7 (SEQ ID NO: 79 and 153 of US8734809), AAV CKd-B8 (SEQ ID NO: 80 and 154 of US8734809), AAV CKd-H1 (SEQ ID NO: 81 and 155 of US8734809), AAV CKd-H2 (SEQ ID NO: 82 and 156 of US8734809), AAV CKd-H3 (SEQ ID NO: 83 and 157 of US8734809), AAV CKd-H4 (SEQ ID NO: 84 and 158 of US8734809), AAV CKd-H5 (SEQ ID NO: 85 and 159 of US8734809), AAV CKd-H6 (SEQ ID NO: 77 and 151 of US8734809), AAV CHt-1 (SEQ ID NO: 86 and 160 of US8734809), AAV CLv1-1 (SEQ ID NO: 171 of US8734809), AAV CLv1-2 (SEQ ID NO: 172 of US8734809), AAV CLv1-3 (SEQ ID NO: 173 of US8734809), AAV CLv1-4 (SEQ ID NO: 174 of US8734809), AAV Clv1-7 (SEQ ID NO: 175 of US8734809), AAV Clv1-8 (SEQ ID NO: 176 of US8734809), AAV Clv1-9 (SEQ ID NO: 177 of US8734809), AAV Clv1-10 (SEQ ID NO: 178 of US8734809), AAV.VR-355 (SEQ ID NO: 181 of US8734809), AAV.hu.48R3 (SEQ ID NO: 183 of US8734809), or variants or derivatives thereof.

[0087] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2016065001, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV CHt-P2 (SEQ ID NO: 1 and 51 of WO2016065001), AAV CHt-P5 (SEQ ID NO: 2 and 52 of WO2016065001), AAV CHt-P9 (SEQ ID NO: 3 and 53 of WO2016065001), AAV CBr-7.1 (SEQ ID NO: 4 and 54 of WO2016065001), AAV CBr-7.2 (SEQ ID NO: 5 and 55 of WO2016065001), AAV CBr-7.3 (SEQ ID NO: 6 and 56 of WO2016065001), AAV CBr-7.4 (SEQ ID NO: 7 and 57 of WO2016065001), AAV CBr-7.5 (SEQ ID NO: 8 and 58 of WO2016065001), AAV CBr-7.7 (SEQ ID NO: 9 and 59 of WO2016065001), AAV CBr-7.8 (SEQ ID NO: 10 and 60 of WO2016065001), AAV CBr-7.10 (SEQ ID NO: 11 and 61 of WO2016065001), AAV CKd-N3 (SEQ ID NO: 12 and 62 of WO2016065001), AAV CKd-N4 (SEQ ID NO: 13 and 63 of WO2016065001), AAV CKd-N9 (SEQ ID NO: 14 and 64 of WO2016065001), AAV CLv-L4 (SEQ ID NO: 15 and 65 of WO2016065001), AAV CLv-L5 (SEQ ID NO: 16 and 66 of WO2016065001), AAV CLv-L6 (SEQ ID NO: 17 and 67 of WO2016065001), AAV CLv-K1 (SEQ ID NO: 18 and 68 of WO2016065001), AAV CLv-K3 (SEQ ID NO: 19 and 69 of WO2016065001), AAV CLv-K6 (SEQ ID NO: 20 and 70 of WO2016065001), AAV CLv-M1 (SEQ ID NO: 21 and 71 of WO2016065001), AAV CLv-M11 (SEQ ID NO: 22 and 72 of WO2016065001), AAV CLv-M2 (SEQ ID NO: 23 and 73 of WO2016065001), AAV CLv-M5 (SEQ ID NO: 24 and 74 of WO2016065001), AAV CLv-M6 (SEQ ID NO: 25 and 75 of WO2016065001), AAV CLv-M7 (SEQ ID NO: 26 and 76 of WO2016065001), AAV CLv-M8 (SEQ ID NO: 27 and 77 of WO2016065001), AAV CLv-M9 (SEQ ID NO: 28 and 78 of WO2016065001), AAV CHt-P1 (SEQ ID NO: 29 and 79 of WO2016065001), AAV CHt-P6 (SEQ ID NO: 30 and 80 of WO2016065001), AAV CHt-P8 (SEQ ID NO: 31 and 81 of WO2016065001), AAV CHt-6.1 (SEQ ID NO: 32 and 82 of WO2016065001), AAV CHt-6.10 (SEQ ID NO: 33 and 83 of WO2016065001), AAV CHt-6.5 (SEQ ID NO: 34 and 84 of WO2016065001), AAV CHt-6.6 (SEQ ID NO: 35 and 85 of WO2016065001), AAV CHt-6.7 (SEQ ID NO: 36 and 86 of WO2016065001), AAV CHt-6.8 (SEQ ID NO: 37 and 87 of WO2016065001), AAV CSp-8.10 (SEQ ID NO: 38 and 88 of WO2016065001), AAV CSp-8.2 (SEQ ID NO: 39 and 89 of WO2016065001), AAV CSp-8.4 (SEQ ID NO: 40 and 90 of WO2016065001), AAV CSp-8.5 (SEQ ID NO: 41 and 91 of WO2016065001), AAV CSp-8.6 (SEQ ID NO: 42 and 92 of WO2016065001), AAV CSp-8.7 (SEQ ID NO: 43 and 93 of WO2016065001), AAV CSp-8.8 (SEQ ID NO: 44 and 94 of WO2016065001), AAV CSp-8.9 (SEQ ID NO: 45 and 95 of WO2016065001), AAV CBr-B7.3 (SEQ ID NO: 46 and 96 of WO2016065001), AAV CBr-B7.4 (SEQ ID NO: 47 and 97 of WO2016065001), AAV3B (SEQ

ID NO: 48 and 98 of WO2016065001), AAV4 (SEQ ID NO: 49 and 99 of WO2016065001), AAV5 (SEQ ID NO: 50 and 100 of WO2016065001), or variants or derivatives thereof.

[0088] In some embodiments, the AAV serotype may be, or have, a modification as described in United States Publication No. US 20160361439, the contents of which are herein incorporated by reference in their entirety, such as but not limited to, Y252F, Y272F, Y444F, Y500F, Y700F, Y704F, Y730F, Y275F, Y281F, Y508F, Y576F, Y612G, Y673F, and Y720F of the wild-type AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, and hybrids thereof.

[0089] In some embodiments, the AAV serotype may be, or have, a mutation as described in United States Patent No. US 9546112, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, at least two, but not all the F129L, D418E, K531E, L584F, V598A and H642N mutations in the sequence of AAV6 (SEQ ID NO:4 of US 9546112), AAV1 (SEQ ID NO:6 of US 9546112), AAV2, AAV3, AAV4, AAV5, AAV7, AAV9, AAV10 or AAV11 or derivatives thereof. In yet another embodiment, the AAV serotype may be, or have, an AAV6 sequence comprising the K531E mutation (SEQ ID NO:5 of US 9546112).

[0090] In some embodiments, the AAV serotype may be, or have, a mutation in the AAV1 sequence, as described in in United States Publication No. US 20130224836, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, at least one of the surface-exposed tyrosine residues, preferably, at positions 252, 273, 445, 701, 705 and 731 of AAV1 (SEQ ID NO: 2 of US 20130224836) substituted with another amino acid, preferably with a phenylalanine residue. In certain embodiments, the AAV serotype may be, or have, a mutation in the AAV9 sequence, such as, but not limited to, at least one of the surface-exposed tyrosine residues, preferably, at positions 252, 272, 444, 500, 700, 704 and 730 of AAV2 (SEQ ID NO: 4 of US 20130224836) substituted with another amino acid, preferably with a phenylalanine residue. In certain embodiments, the tyrosine residue at position 446 of AAV9 (SEQ ID NO: 6 US 20130224836) is substituted with a phenylalanine residue.

[0091] In some embodiments, the serotype may be AAV2 or a variant thereof, as described in International Publication No. WO2016130589, herein incorporated by reference in its entirety. The amino acid sequence of AAV2 may comprise N587A, E548A, or N708A mutations. In certain embodiments, the amino acid sequence of any AAV may comprise a V708K mutation.

[0092] In certain embodiments, the AAV may be a serotype selected from any of those found in Table 1.

[0093] In certain embodiments, the AAV may comprise a sequence, fragment or variant thereof, of the sequences in Table 1.

[0094] In certain embodiments, the AAV may be encoded by a sequence, fragment or variant as described in Table 1.

Table 1. AAV Serotypes

Serotype	SEQ ID NO	Reference Information
AAVPHP.B or G2B-26	1	WO2015038958 SEQ ID NO: 8 and 13
AAVPHP.B	2	WO2015038958 SEQ ID NO: 9
AAVG2B-13	3	WO2015038958 SEQ ID NO: 12
AAVTH1.1-32	4	WO2015038958 SEQ ID NO: 14
AAVTH1.1-35	5	WO2015038958 SEQ ID NO: 15
AAV1	6	US20150159173 SEQ ID NO: 11, US20150315612 SEQ ID NO: 202
AAV1	7	US20160017295 SEQ ID NO: 1US20030138772 SEQ ID NO: 64, US20150159173 SEQ ID NO: 27, US20150315612 SEQ ID NO: 219, US7198951 SEQ ID NO: 5
AAV1	8	US20030138772 SEQ ID NO: 6
AAV1.3	9	US20030138772 SEQ ID NO: 14
AAV10	10	US20030138772 SEQ ID NO: 117
AAV10	11	WO2015121501 SEQ ID NO: 9
AAV10	12	WO2015121501 SEQ ID NO: 8
AAV11	13	US20030138772 SEQ ID NO: 118
AAV12	14	US20030138772 SEQ ID NO: 119
AAV2	15	US20150159173 SEQ ID NO: 7, US20150315612 SEQ ID NO: 211
AAV2	16	US20030138772 SEQ ID NO: 70, US20150159173 SEQ ID NO: 23, US20150315612 SEQ ID NO: 221, US20160017295 SEQ ID NO: 2, US6156303 SEQ ID NO: 4, US7198951 SEQ ID NO: 4, WO2015121501 SEQ ID NO: 1
AAV2	17	US6156303 SEQ ID NO: 8
AAV2	18	US20030138772 SEQ ID NO: 7
AAV2	19	US6156303 SEQ ID NO: 3
AAV2.5T	20	US9233131 SEQ ID NO: 42
AAV223.10	21	US20030138772 SEQ ID NO: 75
AAV223.2	22	US20030138772 SEQ ID NO: 49
AAV223.2	23	US20030138772 SEQ ID NO: 76
AAV223.4	24	US20030138772 SEQ ID NO: 50
AAV223.4	25	US20030138772 SEQ ID NO: 73
AAV223.5	26	US20030138772 SEQ ID NO: 51
AAV223.5	27	US20030138772 SEQ ID NO: 74
AAV223.6	28	US20030138772 SEQ ID NO: 52
AAV223.6	29	US20030138772 SEQ ID NO: 78
AAV223.7	30	US20030138772 SEQ ID NO: 53
AAV223.7	31	US20030138772 SEQ ID NO: 77
AAV29.3	32	US20030138772 SEQ ID NO: 82
AAV29.4	33	US20030138772 SEQ ID NO: 12
AAV29.5	34	US20030138772 SEQ ID NO: 83
AAV29.5 (AAVbb.2)	35	US20030138772 SEQ ID NO: 13
AAV3	36	US20150159173 SEQ ID NO: 12

AAV3	37	US20030138772 SEQ ID NO: 71, US20150159173 SEQ ID NO: 28, US20160017295 SEQ ID NO: 3, US7198951 SEQ ID NO: 6
AAV3	38	US20030138772 SEQ ID NO: 8
AAV3.3b	39	US20030138772 SEQ ID NO: 72
AAV3-3	40	US20150315612 SEQ ID NO: 200
AAV3-3	41	US20150315612 SEQ ID NO: 217
AAV3a	42	US6156303 SEQ ID NO: 5
AAV3a	43	US6156303 SEQ ID NO: 9
AAV3b	44	US6156303 SEQ ID NO: 6
AAV3b	45	US6156303 SEQ ID NO: 10
AAV3b	46	US6156303 SEQ ID NO: 1
AAV4	47	US20140348794 SEQ ID NO: 17
AAV4	48	US20140348794 SEQ ID NO: 5
AAV4	49	US20140348794 SEQ ID NO: 3
AAV4	50	US20140348794 SEQ ID NO: 14
AAV4	51	US20140348794 SEQ ID NO: 15
AAV4	52	US20140348794 SEQ ID NO: 19
AAV4	53	US20140348794 SEQ ID NO: 12
AAV4	54	US20140348794 SEQ ID NO: 13
AAV4	55	US20140348794 SEQ ID NO: 7
AAV4	56	US20140348794 SEQ ID NO: 8
AAV4	57	US20140348794 SEQ ID NO: 9
AAV4	58	US20140348794 SEQ ID NO: 2
AAV4	59	US20140348794 SEQ ID NO: 10
AAV4	60	US20140348794 SEQ ID NO: 11
AAV4	61	US20140348794 SEQ ID NO: 18
AAV4	62	US20030138772 SEQ ID NO: 63, US20160017295 SEQ ID NO: 4, US20140348794 SEQ ID NO: 4
AAV4	63	US20140348794 SEQ ID NO: 16
AAV4	64	US20140348794 SEQ ID NO: 20
AAV4	65	US20140348794 SEQ ID NO: 6
AAV4	66	US20140348794 SEQ ID NO: 1
AAV42.2	67	US20030138772 SEQ ID NO: 9
AAV42.2	68	US20030138772 SEQ ID NO: 102
AAV42.3b	69	US20030138772 SEQ ID NO: 36
AAV42.3B	70	US20030138772 SEQ ID NO: 107
AAV42.4	71	US20030138772 SEQ ID NO: 33
AAV42.4	72	US20030138772 SEQ ID NO: 88
AAV42.8	73	US20030138772 SEQ ID NO: 27
AAV42.8	74	US20030138772 SEQ ID NO: 85
AAV43.1	75	US20030138772 SEQ ID NO: 39
AAV43.1	76	US20030138772 SEQ ID NO: 92
AAV43.12	77	US20030138772 SEQ ID NO: 41
AAV43.12	78	US20030138772 SEQ ID NO: 93
AAV43.20	79	US20030138772 SEQ ID NO: 42
AAV43.20	80	US20030138772 SEQ ID NO: 99

AAV43.21	81	US20030138772 SEQ ID NO: 43
AAV43.21	82	US20030138772 SEQ ID NO: 96
AAV43.23	83	US20030138772 SEQ ID NO: 44
AAV43.23	84	US20030138772 SEQ ID NO: 98
AAV43.25	85	US20030138772 SEQ ID NO: 45
AAV43.25	86	US20030138772 SEQ ID NO: 97
AAV43.5	87	US20030138772 SEQ ID NO: 40
AAV43.5	88	US20030138772 SEQ ID NO: 94
AAV4-4	89	US20150315612 SEQ ID NO: 201
AAV4-4	90	US20150315612 SEQ ID NO: 218
AAV44.1	91	US20030138772 SEQ ID NO: 46
AAV44.1	92	US20030138772 SEQ ID NO: 79
AAV44.5	93	US20030138772 SEQ ID NO: 47
AAV44.5	94	US20030138772 SEQ ID NO: 80
AAV4407	95	US20150315612 SEQ ID NO: 90
AAV5	96	US7427396 SEQ ID NO: 1
AAV5	97	US20030138772 SEQ ID NO: 114
AAV5	98	US20160017295 SEQ ID NO: 5, US7427396 SEQ ID NO: 2, US20150315612 SEQ ID NO: 216
AAV5	99	US20150315612 SEQ ID NO: 199
AAV6	100	US20150159173 SEQ ID NO: 13
AAV6	101	US20030138772 SEQ ID NO: 65, US20150159173 SEQ ID NO: 29, US20160017295 SEQ ID NO: 6, US6156303 SEQ ID NO: 7
AAV6	102	US6156303 SEQ ID NO: 11
AAV6	103	US6156303 SEQ ID NO: 2
AAV6	104	US20150315612 SEQ ID NO: 203
AAV6	105	US20150315612 SEQ ID NO: 220
AAV6.1	106	US20150159173
AAV6.12	107	US20150159173
AAV6.2	108	US20150159173
AAV7	109	US20150159173 SEQ ID NO: 14
AAV7	110	US20150315612 SEQ ID NO: 183
AAV7	111	US20030138772 SEQ ID NO: 2, US20150159173 SEQ ID NO: 30, US20150315612 SEQ ID NO: 181, US20160017295 SEQ ID NO: 7
AAV7	112	US20030138772 SEQ ID NO: 3
AAV7	113	US20030138772 SEQ ID NO: 1, US20150315612 SEQ ID NO: 180
AAV7	114	US20150315612 SEQ ID NO: 213
AAV7	115	US20150315612 SEQ ID NO: 222
AAV8	116	US20150159173 SEQ ID NO: 15
AAV8	117	US20150376240 SEQ ID NO: 7
AAV8	118	US20030138772 SEQ ID NO: 4, US20150315612 SEQ ID NO: 182
AAV8	119	US20030138772 SEQ ID NO: 95, US20140359799 SEQ ID NO: 1, US20150159173 SEQ ID NO: 31, US20160017295 SEQ ID NO: 8, US7198951 SEQ ID NO: 7, US20150315612 SEQ ID NO: 223
AAV8	120	US20150376240 SEQ ID NO: 8

AAV8	121	US20150315612 SEQ ID NO: 214
AAV-8b	122	US20150376240 SEQ ID NO: 5
AAV-8b	123	US20150376240 SEQ ID NO: 3
AAV-8h	124	US20150376240 SEQ ID NO: 6
AAV-8h	125	US20150376240 SEQ ID NO: 4
AAV9	126	US20030138772 SEQ ID NO: 5
AAV9	127	US7198951 SEQ ID NO: 1
AAV9	128	US20160017295 SEQ ID NO: 9
AAV9	129	US20030138772 SEQ ID NO: 100, US7198951 SEQ ID NO: 2
AAV9	130	US7198951 SEQ ID NO: 3
AAV9 (AAVhu.14)	131	US7906111 SEQ ID NO: 3; WO2015038958 SEQ ID NO: 11
AAV9 (AAVhu.14)	132	US7906111 SEQ ID NO: 123; WO2015038958 SEQ ID NO: 2
AAVA3.1	133	US20030138772 SEQ ID NO: 120
AAVA3.3	134	US20030138772 SEQ ID NO: 57
AAVA3.3	135	US20030138772 SEQ ID NO: 66
AAVA3.4	136	US20030138772 SEQ ID NO: 54
AAVA3.4	137	US20030138772 SEQ ID NO: 68
AAVA3.5	138	US20030138772 SEQ ID NO: 55
AAVA3.5	139	US20030138772 SEQ ID NO: 69
AAVA3.7	140	US20030138772 SEQ ID NO: 56
AAVA3.7	141	US20030138772 SEQ ID NO: 67
AAV29.3 (AAVbb.1)	142	US20030138772 SEQ ID NO: 11
AAVC2	143	US20030138772 SEQ ID NO: 61
AAVCh.5	144	US20150159173 SEQ ID NO: 46, US20150315612 SEQ ID NO: 234
AAVcy.2 (AAV13.3)	145	US20030138772 SEQ ID NO: 15
AAV24.1	146	US20030138772 SEQ ID NO: 101
AAVcy.3 (AAV24.1)	147	US20030138772 SEQ ID NO: 16
AAV27.3	148	US20030138772 SEQ ID NO: 104
AAVcy.4 (AAV27.3)	149	US20030138772 SEQ ID NO: 17
AAVcy.5	150	US20150315612 SEQ ID NO: 227
AAV7.2	151	US20030138772 SEQ ID NO: 103
AAVcy.5 (AAV7.2)	152	US20030138772 SEQ ID NO: 18
AAV16.3	153	US20030138772 SEQ ID NO: 105
AAVcy.6 (AAV16.3)	154	US20030138772 SEQ ID NO: 10
AAVcy.5	155	US20150159173 SEQ ID NO: 8
AAVcy.5	156	US20150159173 SEQ ID NO: 24
AAVCy.5R1	157	US20150159173
AAVCy.5R2	158	US20150159173
AAVCy.5R3	159	US20150159173
AAVCy.5R4	160	US20150159173
AAVDJ	161	US20140359799 SEQ ID NO: 3, US7588772 SEQ ID NO: 2
AAVDJ	162	US20140359799 SEQ ID NO: 2, US7588772 SEQ ID NO: 1

AAVDJ-8	163	US7588772; Grimm et al 2008
AAVDJ-8	164	US7588772; Grimm et al 2008
AAVF5	165	US20030138772 SEQ ID NO: 110
AAVH2	166	US20030138772 SEQ ID NO: 26
AAVH6	167	US20030138772 SEQ ID NO: 25
AAVhE1.1	168	US9233131 SEQ ID NO: 44
AAVhEr1.14	169	US9233131 SEQ ID NO: 46
AAVhEr1.16	170	US9233131 SEQ ID NO: 48
AAVhEr1.18	171	US9233131 SEQ ID NO: 49
AAVhEr1.23 (AAVhEr2.29)	172	US9233131 SEQ ID NO: 53
AAVhEr1.35	173	US9233131 SEQ ID NO: 50
AAVhEr1.36	174	US9233131 SEQ ID NO: 52
AAVhEr1.5	175	US9233131 SEQ ID NO: 45
AAVhEr1.7	176	US9233131 SEQ ID NO: 51
AAVhEr1.8	177	US9233131 SEQ ID NO: 47
AAVhEr2.16	178	US9233131 SEQ ID NO: 55
AAVhEr2.30	179	US9233131 SEQ ID NO: 56
AAVhEr2.31	180	US9233131 SEQ ID NO: 58
AAVhEr2.36	181	US9233131 SEQ ID NO: 57
AAVhEr2.4	182	US9233131 SEQ ID NO: 54
AAVhEr3.1	183	US9233131 SEQ ID NO: 59
AAVhu.1	184	US20150315612 SEQ ID NO: 46
AAVhu.1	185	US20150315612 SEQ ID NO: 144
AAVhu.10 (AAV16.8)	186	US20150315612 SEQ ID NO: 56
AAVhu.10 (AAV16.8)	187	US20150315612 SEQ ID NO: 156
AAVhu.11 (AAV16.12)	188	US20150315612 SEQ ID NO: 57
AAVhu.11 (AAV16.12)	189	US20150315612 SEQ ID NO: 153
AAVhu.12	190	US20150315612 SEQ ID NO: 59
AAVhu.12	191	US20150315612 SEQ ID NO: 154
AAVhu.13	192	US20150159173 SEQ ID NO: 16, US20150315612 SEQ ID NO: 71
AAVhu.13	193	US20150159173 SEQ ID NO: 32, US20150315612 SEQ ID NO: 129
AAVhu.136.1	194	US20150315612 SEQ ID NO: 165
AAVhu.140.1	195	US20150315612 SEQ ID NO: 166
AAVhu.140.2	196	US20150315612 SEQ ID NO: 167
AAVhu.145.6	197	US20150315612 SEQ ID No: 178
AAVhu.15	198	US20150315612 SEQ ID NO: 147
AAVhu.15 (AAV33.4)	199	US20150315612 SEQ ID NO: 50
AAVhu.156.1	200	US20150315612 SEQ ID No: 179
AAVhu.16	201	US20150315612 SEQ ID NO: 148
AAVhu.16 (AAV33.8)	202	US20150315612 SEQ ID NO: 51
AAVhu.17	203	US20150315612 SEQ ID NO: 83
AAVhu.17 (AAV33.12)	204	US20150315612 SEQ ID NO: 4
AAVhu.172.1	205	US20150315612 SEQ ID NO: 171
AAVhu.172.2	206	US20150315612 SEQ ID NO: 172
AAVhu.173.4	207	US20150315612 SEQ ID NO: 173

AAVhu.173.8	208	US20150315612 SEQ ID NO: 175
AAVhu.18	209	US20150315612 SEQ ID NO: 52
AAVhu.18	210	US20150315612 SEQ ID NO: 149
AAVhu.19	211	US20150315612 SEQ ID NO: 62
AAVhu.19	212	US20150315612 SEQ ID NO: 133
AAVhu.2	213	US20150315612 SEQ ID NO: 48
AAVhu.2	214	US20150315612 SEQ ID NO: 143
AAVhu.20	215	US20150315612 SEQ ID NO: 63
AAVhu.20	216	US20150315612 SEQ ID NO: 134
AAVhu.21	217	US20150315612 SEQ ID NO: 65
AAVhu.21	218	US20150315612 SEQ ID NO: 135
AAVhu.22	219	US20150315612 SEQ ID NO: 67
AAVhu.22	220	US20150315612 SEQ ID NO: 138
AAVhu.23	221	US20150315612 SEQ ID NO: 60
AAVhu.23.2	222	US20150315612 SEQ ID NO: 137
AAVhu.24	223	US20150315612 SEQ ID NO: 66
AAVhu.24	224	US20150315612 SEQ ID NO: 136
AAVhu.25	225	US20150315612 SEQ ID NO: 49
AAVhu.25	226	US20150315612 SEQ ID NO: 146
AAVhu.26	227	US20150159173 SEQ ID NO: 17, US20150315612 SEQ ID NO: 61
AAVhu.26	228	US20150159173 SEQ ID NO: 33, US20150315612 SEQ ID NO: 139
AAVhu.27	229	US20150315612 SEQ ID NO: 64
AAVhu.27	230	US20150315612 SEQ ID NO: 140
AAVhu.28	231	US20150315612 SEQ ID NO: 68
AAVhu.28	232	US20150315612 SEQ ID NO: 130
AAVhu.29	233	US20150315612 SEQ ID NO: 69
AAVhu.29	234	US20150159173 SEQ ID NO: 42, US20150315612 SEQ ID NO: 132
AAVhu.29	235	US20150315612 SEQ ID NO: 225
AAVhu.29R	236	US20150159173
AAVhu.3	237	US20150315612 SEQ ID NO: 44
AAVhu.3	238	US20150315612 SEQ ID NO: 145
AAVhu.30	239	US20150315612 SEQ ID NO: 70
AAVhu.30	240	US20150315612 SEQ ID NO: 131
AAVhu.31	241	US20150315612 SEQ ID NO: 1
AAVhu.31	242	US20150315612 SEQ ID NO: 121
AAVhu.32	243	US20150315612 SEQ ID NO: 2
AAVhu.32	244	US20150315612 SEQ ID NO: 122
AAVhu.33	245	US20150315612 SEQ ID NO: 75
AAVhu.33	246	US20150315612 SEQ ID NO: 124
AAVhu.34	247	US20150315612 SEQ ID NO: 72
AAVhu.34	248	US20150315612 SEQ ID NO: 125
AAVhu.35	249	US20150315612 SEQ ID NO: 73
AAVhu.35	250	US20150315612 SEQ ID NO: 164
AAVhu.36	251	US20150315612 SEQ ID NO: 74

AAVhu.36	252	US20150315612 SEQ ID NO: 126
AAVhu.37	253	US20150159173 SEQ ID NO: 34, US20150315612 SEQ ID NO: 88
AAVhu.37 (AAV106.1)	254	US20150315612 SEQ ID NO: 10, US20150159173 SEQ ID NO: 18
AAVhu.38	255	US20150315612 SEQ ID NO: 161
AAVhu.39	256	US20150315612 SEQ ID NO: 102
AAVhu.39 (AAVLG-9)	257	US20150315612 SEQ ID NO: 24
AAVhu.4	258	US20150315612 SEQ ID NO: 47
AAVhu.4	259	US20150315612 SEQ ID NO: 141
AAVhu.40	260	US20150315612 SEQ ID NO: 87
AAVhu.40 (AAV114.3)	261	US20150315612 SEQ ID No: 11
AAVhu.41	262	US20150315612 SEQ ID NO: 91
AAVhu.41 (AAV127.2)	263	US20150315612 SEQ ID NO: 6
AAVhu.42	264	US20150315612 SEQ ID NO: 85
AAVhu.42 (AAV127.5)	265	US20150315612 SEQ ID NO: 8
AAVhu.43	266	US20150315612 SEQ ID NO: 160
AAVhu.43	267	US20150315612 SEQ ID NO: 236
AAVhu.43 (AAV128.1)	268	US20150315612 SEQ ID NO: 80
AAVhu.44	269	US20150159173 SEQ ID NO: 45, US20150315612 SEQ ID NO: 158
AAVhu.44 (AAV128.3)	270	US20150315612 SEQ ID NO: 81
AAVhu.44R1	271	US20150159173
AAVhu.44R2	272	US20150159173
AAVhu.44R3	273	US20150159173
AAVhu.45	274	US20150315612 SEQ ID NO: 76
AAVhu.45	275	US20150315612 SEQ ID NO: 127
AAVhu.46	276	US20150315612 SEQ ID NO: 82
AAVhu.46	277	US20150315612 SEQ ID NO: 159
AAVhu.46	278	US20150315612 SEQ ID NO: 224
AAVhu.47	279	US20150315612 SEQ ID NO: 77
AAVhu.47	280	US20150315612 SEQ ID NO: 128
AAVhu.48	281	US20150159173 SEQ ID NO: 38
AAVhu.48	282	US20150315612 SEQ ID NO: 157
AAVhu.48 (AAV130.4)	283	US20150315612 SEQ ID NO: 78
AAVhu.48R1	284	US20150159173
AAVhu.48R2	285	US20150159173
AAVhu.48R3	286	US20150159173
AAVhu.49	287	US20150315612 SEQ ID NO: 209
AAVhu.49	288	US20150315612 SEQ ID NO: 189
AAVhu.5	289	US20150315612 SEQ ID NO: 45
AAVhu.5	290	US20150315612 SEQ ID NO: 142
AAVhu.51	291	US20150315612 SEQ ID NO: 208
AAVhu.51	292	US20150315612 SEQ ID NO: 190
AAVhu.52	293	US20150315612 SEQ ID NO: 210
AAVhu.52	294	US20150315612 SEQ ID NO: 191
AAVhu.53	295	US20150159173 SEQ ID NO: 19

AAVhu.53	296	US20150159173 SEQ ID NO: 35
AAVhu.53 (AAV145.1)	297	US20150315612 SEQ ID NO: 176
AAVhu.54	298	US20150315612 SEQ ID NO: 188
AAVhu.54 (AAV145.5)	299	US20150315612 SEQ ID No: 177
AAVhu.55	300	US20150315612 SEQ ID NO: 187
AAVhu.56	301	US20150315612 SEQ ID NO: 205
AAVhu.56 (AAV145.6)	302	US20150315612 SEQ ID NO: 168
AAVhu.56 (AAV145.6)	303	US20150315612 SEQ ID NO: 192
AAVhu.57	304	US20150315612 SEQ ID NO: 206
AAVhu.57	305	US20150315612 SEQ ID NO: 169
AAVhu.57	306	US20150315612 SEQ ID NO: 193
AAVhu.58	307	US20150315612 SEQ ID NO: 207
AAVhu.58	308	US20150315612 SEQ ID NO: 194
AAVhu.6 (AAV3.1)	309	US20150315612 SEQ ID NO: 5
AAVhu.6 (AAV3.1)	310	US20150315612 SEQ ID NO: 84
AAVhu.60	311	US20150315612 SEQ ID NO: 184
AAVhu.60 (AAV161.10)	312	US20150315612 SEQ ID NO: 170
AAVhu.61	313	US20150315612 SEQ ID NO: 185
AAVhu.61 (AAV161.6)	314	US20150315612 SEQ ID NO: 174
AAVhu.63	315	US20150315612 SEQ ID NO: 204
AAVhu.63	316	US20150315612 SEQ ID NO: 195
AAVhu.64	317	US20150315612 SEQ ID NO: 212
AAVhu.64	318	US20150315612 SEQ ID NO: 196
AAVhu.66	319	US20150315612 SEQ ID NO: 197
AAVhu.67	320	US20150315612 SEQ ID NO: 215
AAVhu.67	321	US20150315612 SEQ ID NO: 198
AAVhu.7	322	US20150315612 SEQ ID NO: 226
AAVhu.7	323	US20150315612 SEQ ID NO: 150
AAVhu.7 (AAV7.3)	324	US20150315612 SEQ ID NO: 55
AAVhu.71	325	US20150315612 SEQ ID NO: 79
AAVhu.8	326	US20150315612 SEQ ID NO: 53
AAVhu.8	327	US20150315612 SEQ ID NO: 12
AAVhu.8	328	US20150315612 SEQ ID NO: 151
AAVhu.9 (AAV3.1)	329	US20150315612 SEQ ID NO: 58
AAVhu.9 (AAV3.1)	330	US20150315612 SEQ ID NO: 155
AAV-LK01	331	US20150376607 SEQ ID NO: 2
AAV-LK01	332	US20150376607 SEQ ID NO: 29
AAV-LK02	333	US20150376607 SEQ ID NO: 3
AAV-LK02	334	US20150376607 SEQ ID NO: 30
AAV-LK03	335	US20150376607 SEQ ID NO: 4
AAV-LK03	336	WO2015121501 SEQ ID NO: 12, US20150376607 SEQ ID NO: 31
AAV-LK04	337	US20150376607 SEQ ID NO: 5
AAV-LK04	338	US20150376607 SEQ ID NO: 32
AAV-LK05	339	US20150376607 SEQ ID NO: 6
AAV-LK05	340	US20150376607 SEQ ID NO: 33

AAV-LK06	341	US20150376607 SEQ ID NO: 7
AAV-LK06	342	US20150376607 SEQ ID NO: 34
AAV-LK07	343	US20150376607 SEQ ID NO: 8
AAV-LK07	344	US20150376607 SEQ ID NO: 35
AAV-LK08	345	US20150376607 SEQ ID NO: 9
AAV-LK08	346	US20150376607 SEQ ID NO: 36
AAV-LK09	347	US20150376607 SEQ ID NO: 10
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AAV-LK11	351	US20150376607 SEQ ID NO: 12
AAV-LK11	352	US20150376607 SEQ ID NO: 39
AAV-LK12	353	US20150376607 SEQ ID NO: 13
AAV-LK12	354	US20150376607 SEQ ID NO: 40
AAV-LK13	355	US20150376607 SEQ ID NO: 14
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AAV-LK15	359	US20150376607 SEQ ID NO: 16
AAV-LK15	360	US20150376607 SEQ ID NO: 43
AAV-LK16	361	US20150376607 SEQ ID NO: 17
AAV-LK16	362	US20150376607 SEQ ID NO: 44
AAV-LK17	363	US20150376607 SEQ ID NO: 18
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AAV-PAEC11	371	US20150376607 SEQ ID NO: 26
AAV-PAEC11	372	US20150376607 SEQ ID NO: 54
AAV-PAEC12	373	US20150376607 SEQ ID NO: 27
AAV-PAEC12	374	US20150376607 SEQ ID NO: 51
AAV-PAEC13	375	US20150376607 SEQ ID NO: 28
AAV-PAEC13	376	US20150376607 SEQ ID NO: 49
AAV-PAEC2	377	US20150376607 SEQ ID NO: 21
AAV-PAEC2	378	US20150376607 SEQ ID NO: 56
AAV-PAEC4	379	US20150376607 SEQ ID NO: 22
AAV-PAEC4	380	US20150376607 SEQ ID NO: 55
AAV-PAEC6	381	US20150376607 SEQ ID NO: 23
AAV-PAEC6	382	US20150376607 SEQ ID NO: 52
AAV-PAEC7	383	US20150376607 SEQ ID NO: 24
AAV-PAEC7	384	US20150376607 SEQ ID NO: 53
AAV-PAEC8	385	US20150376607 SEQ ID NO: 25
AAV-PAEC8	386	US20150376607 SEQ ID NO: 50

AAVpi.1	387	US20150315612 SEQ ID NO: 28
AAVpi.1	388	US20150315612 SEQ ID NO: 93
AAVpi.2	389	US20150315612 SEQ ID NO: 30
AAVpi.2	390	US20150315612 SEQ ID NO: 95
AAVpi.3	391	US20150315612 SEQ ID NO: 29
AAVpi.3	392	US20150315612 SEQ ID NO: 94
AAVrh.10	393	US20150159173 SEQ ID NO: 9
AAVrh.10	394	US20150159173 SEQ ID NO: 25
AAV44.2	395	US20030138772 SEQ ID NO: 59
AAVrh.10 (AAV44.2)	396	US20030138772 SEQ ID NO: 81
AAV42.1B	397	US20030138772 SEQ ID NO: 90
AAVrh.12 (AAV42.1b)	398	US20030138772 SEQ ID NO: 30
AAVrh.13	399	US20150159173 SEQ ID NO: 10
AAVrh.13	400	US20150159173 SEQ ID NO: 26
AAVrh.13	401	US20150315612 SEQ ID NO: 228
AAVrh.13R	402	US20150159173
AAV42.3A	403	US20030138772 SEQ ID NO: 87
AAVrh.14 (AAV42.3a)	404	US20030138772 SEQ ID NO: 32
AAV42.5A	405	US20030138772 SEQ ID NO: 89
AAVrh.17 (AAV42.5a)	406	US20030138772 SEQ ID NO: 34
AAV42.5B	407	US20030138772 SEQ ID NO: 91
AAVrh.18 (AAV42.5b)	408	US20030138772 SEQ ID NO: 29
AAV42.6B	409	US20030138772 SEQ ID NO: 112
AAVrh.19 (AAV42.6b)	410	US20030138772 SEQ ID NO: 38
AAVrh.2	411	US20150159173 SEQ ID NO: 39
AAVrh.2	412	US20150315612 SEQ ID NO: 231
AAVrh.20	413	US20150159173 SEQ ID NO: 1
AAV42.10	414	US20030138772 SEQ ID NO: 106
AAVrh.21 (AAV42.10)	415	US20030138772 SEQ ID NO: 35
AAV42.11	416	US20030138772 SEQ ID NO: 108
AAVrh.22 (AAV42.11)	417	US20030138772 SEQ ID NO: 37
AAV42.12	418	US20030138772 SEQ ID NO: 113
AAVrh.23 (AAV42.12)	419	US20030138772 SEQ ID NO: 58
AAV42.13	420	US20030138772 SEQ ID NO: 86
AAVrh.24 (AAV42.13)	421	US20030138772 SEQ ID NO: 31
AAV42.15	422	US20030138772 SEQ ID NO: 84
AAVrh.25 (AAV42.15)	423	US20030138772 SEQ ID NO: 28
AAVrh.2R	424	US20150159173
AAVrh.31 (AAV223.1)	425	US20030138772 SEQ ID NO: 48
AAVC1	426	US20030138772 SEQ ID NO: 60
AAVrh.32 (AAVC1)	427	US20030138772 SEQ ID NO: 19
AAVrh.32/33	428	US20150159173 SEQ ID NO: 2
AAVrh.33 (AAVC3)	429	US20030138772 SEQ ID NO: 20
AAVC5	430	US20030138772 SEQ ID NO: 62
AAVrh.34 (AAVC5)	431	US20030138772 SEQ ID NO: 21
AAVF1	432	US20030138772 SEQ ID NO: 109

AAVrh.35 (AAVF1)	433	US20030138772 SEQ ID NO: 22
AAVF3	434	US20030138772 SEQ ID NO: 111
AAVrh.36 (AAVF3)	435	US20030138772 SEQ ID NO: 23
AAVrh.37	436	US20030138772 SEQ ID NO: 24
AAVrh.37	437	US20150159173 SEQ ID NO: 40
AAVrh.37	438	US20150315612 SEQ ID NO: 229
AAVrh.37R2	439	US20150159173
AAVrh.38 (AAVLG-4)	440	US20150315612 SEQ ID NO: 7
AAVrh.38 (AAVLG-4)	441	US20150315612 SEQ ID NO: 86
AAVrh.39	442	US20150159173 SEQ ID NO: 20, US20150315612 SEQ ID NO: 13
AAVrh.39	443	US20150159173 SEQ ID NO: 3, US20150159173 SEQ ID NO: 36, US20150315612 SEQ ID NO: 89
AAVrh.40	444	US20150315612 SEQ ID NO: 92
AAVrh.40 (AAVLG-10)	445	US20150315612 SEQ ID No: 14
AAVrh.43 (AAVN721-8)	446	US20150315612 SEQ ID NO: 43, US20150159173 SEQ ID NO: 21
AAVrh.43 (AAVN721-8)	447	US20150315612 SEQ ID NO: 163, US20150159173 SEQ ID NO: 37
AAVrh.44	448	US20150315612 SEQ ID NO: 34
AAVrh.44	449	US20150315612 SEQ ID NO: 111
AAVrh.45	450	US20150315612 SEQ ID NO: 41
AAVrh.45	451	US20150315612 SEQ ID NO: 109
AAVrh.46	452	US20150159173 SEQ ID NO: 22, US20150315612 SEQ ID NO: 19
AAVrh.46	453	US20150159173 SEQ ID NO: 4, US20150315612 SEQ ID NO: 101
AAVrh.47	454	US20150315612 SEQ ID NO: 38
AAVrh.47	455	US20150315612 SEQ ID NO: 118
AAVrh.48	456	US20150159173 SEQ ID NO: 44, US20150315612 SEQ ID NO: 115
AAVrh.48.1	457	US20150159173
AAVrh.48.1.2	458	US20150159173
AAVrh.48.2	459	US20150159173
AAVrh.48 (AAV1-7)	460	US20150315612 SEQ ID NO: 32
AAVrh.49 (AAV1-8)	461	US20150315612 SEQ ID NO: 25
AAVrh.49 (AAV1-8)	462	US20150315612 SEQ ID NO: 103
AAVrh.50 (AAV2-4)	463	US20150315612 SEQ ID NO: 23
AAVrh.50 (AAV2-4)	464	US20150315612 SEQ ID NO: 108
AAVrh.51 (AAV2-5)	465	US20150315612 SEQ ID No: 22
AAVrh.51 (AAV2-5)	466	US20150315612 SEQ ID NO: 104
AAVrh.52 (AAV3-9)	467	US20150315612 SEQ ID NO: 18
AAVrh.52 (AAV3-9)	468	US20150315612 SEQ ID NO: 96
AAVrh.53	469	US20150315612 SEQ ID NO: 97
AAVrh.53 (AAV3-11)	470	US20150315612 SEQ ID NO: 17
AAVrh.53 (AAV3-11)	471	US20150315612 SEQ ID NO: 186
AAVrh.54	472	US20150315612 SEQ ID NO: 40
AAVrh.54	473	US20150159173 SEQ ID NO: 49, US20150315612 SEQ ID NO: 116

AAVrh.55	474	US20150315612 SEQ ID NO: 37
AAVrh.55 (AAV4-19)	475	US20150315612 SEQ ID NO: 117
AAVrh.56	476	US20150315612 SEQ ID NO: 54
AAVrh.56	477	US20150315612 SEQ ID NO: 152
AAVrh.57	478	US20150315612 SEQ ID NO: 26
AAVrh.57	479	US20150315612 SEQ ID NO: 105
AAVrh.58	480	US20150315612 SEQ ID NO: 27
AAVrh.58	481	US20150159173 SEQ ID NO: 48, US20150315612 SEQ ID NO: 106
AAVrh.58	482	US20150315612 SEQ ID NO: 232
AAVrh.59	483	US20150315612 SEQ ID NO: 42
AAVrh.59	484	US20150315612 SEQ ID NO: 110
AAVrh.60	485	US20150315612 SEQ ID NO: 31
AAVrh.60	486	US20150315612 SEQ ID NO: 120
AAVrh.61	487	US20150315612 SEQ ID NO: 107
AAVrh.61 (AAV2-3)	488	US20150315612 SEQ ID NO: 21
AAVrh.62 (AAV2-15)	489	US20150315612 SEQ ID No: 33
AAVrh.62 (AAV2-15)	490	US20150315612 SEQ ID NO: 114
AAVrh.64	491	US20150315612 SEQ ID No: 15
AAVrh.64	492	US20150159173 SEQ ID NO: 43, US20150315612 SEQ ID NO: 99
AAVrh.64	493	US20150315612 SEQ ID NO: 233
AAVRh.64R1	494	US20150159173
AAVRh.64R2	495	US20150159173
AAVrh.65	496	US20150315612 SEQ ID NO: 35
AAVrh.65	497	US20150315612 SEQ ID NO: 112
AAVrh.67	498	US20150315612 SEQ ID NO: 36
AAVrh.67	499	US20150315612 SEQ ID NO: 230
AAVrh.67	500	US20150159173 SEQ ID NO: 47, US20150315612 SEQ ID NO: 113
AAVrh.68	501	US20150315612 SEQ ID NO: 16
AAVrh.68	502	US20150315612 SEQ ID NO: 100
AAVrh.69	503	US20150315612 SEQ ID NO: 39
AAVrh.69	504	US20150315612 SEQ ID NO: 119
AAVrh.70	505	US20150315612 SEQ ID NO: 20
AAVrh.70	506	US20150315612 SEQ ID NO: 98
AAVrh.71	507	US20150315612 SEQ ID NO: 162
AAVrh.72	508	US20150315612 SEQ ID NO: 9
AAVrh.73	509	US20150159173 SEQ ID NO: 5
AAVrh.74	510	US20150159173 SEQ ID NO: 6
AAVrh.8	511	US20150159173 SEQ ID NO: 41
AAVrh.8	512	US20150315612 SEQ ID NO: 235
AAVrh.8R	513	US20150159173, WO2015168666 SEQ ID NO: 9
AAVrh.8R A586R mutant	514	WO2015168666 SEQ ID NO: 10
AAVrh.8R R533A mutant	515	WO2015168666 SEQ ID NO: 11
BAAV (bovine AAV)	516	US9193769 SEQ ID NO: 8
BAAV (bovine AAV)	517	US9193769 SEQ ID NO: 10

BAAV (bovine AAV)	518	US9193769 SEQ ID NO: 4
BAAV (bovine AAV)	519	US9193769 SEQ ID NO: 2
BAAV (bovine AAV)	520	US9193769 SEQ ID NO: 6
BAAV (bovine AAV)	521	US9193769 SEQ ID NO: 1
BAAV (bovine AAV)	522	US9193769 SEQ ID NO: 5
BAAV (bovine AAV)	523	US9193769 SEQ ID NO: 3
BAAV (bovine AAV)	524	US9193769 SEQ ID NO: 11
BAAV (bovine AAV)	525	US7427396 SEQ ID NO: 5
BAAV (bovine AAV)	526	US7427396 SEQ ID NO: 6
BAAV (bovine AAV)	527	US9193769 SEQ ID NO: 7
BAAV (bovine AAV)	528	US9193769 SEQ ID NO: 9
BNP61 AAV	529	US20150238550 SEQ ID NO: 1
BNP61 AAV	530	US20150238550 SEQ ID NO: 2
BNP62 AAV	531	US20150238550 SEQ ID NO: 3
BNP63 AAV	532	US20150238550 SEQ ID NO: 4
caprine AAV	533	US7427396 SEQ ID NO: 3
caprine AAV	534	US7427396 SEQ ID NO: 4
true type AAV (ttAAV)	535	WO2015121501 SEQ ID NO: 2
AAAV (Avian AAV)	536	US9238800 SEQ ID NO: 12
AAAV (Avian AAV)	537	US9238800 SEQ ID NO: 2
AAAV (Avian AAV)	538	US9238800 SEQ ID NO: 6
AAAV (Avian AAV)	539	US9238800 SEQ ID NO: 4
AAAV (Avian AAV)	540	US9238800 SEQ ID NO: 8
AAAV (Avian AAV)	541	US9238800 SEQ ID NO: 14
AAAV (Avian AAV)	542	US9238800 SEQ ID NO: 10
AAAV (Avian AAV)	543	US9238800 SEQ ID NO: 15
AAAV (Avian AAV)	544	US9238800 SEQ ID NO: 5
AAAV (Avian AAV)	545	US9238800 SEQ ID NO: 9
AAAV (Avian AAV)	546	US9238800 SEQ ID NO: 3
AAAV (Avian AAV)	547	US9238800 SEQ ID NO: 7
AAAV (Avian AAV)	548	US9238800 SEQ ID NO: 11
AAAV (Avian AAV)	549	US9238800 SEQ ID NO: 13
AAAV (Avian AAV)	550	US9238800 SEQ ID NO: 1
AAV Shuffle 100-1	551	US20160017295 SEQ ID NO: 23
AAV Shuffle 100-1	552	US20160017295 SEQ ID NO: 11
AAV Shuffle 100-2	553	US20160017295 SEQ ID NO: 37
AAV Shuffle 100-2	554	US20160017295 SEQ ID NO: 29
AAV Shuffle 100-3	555	US20160017295 SEQ ID NO: 24
AAV Shuffle 100-3	556	US20160017295 SEQ ID NO: 12
AAV Shuffle 100-7	557	US20160017295 SEQ ID NO: 25
AAV Shuffle 100-7	558	US20160017295 SEQ ID NO: 13
AAV Shuffle 10-2	559	US20160017295 SEQ ID NO: 34
AAV Shuffle 10-2	560	US20160017295 SEQ ID NO: 26
AAV Shuffle 10-6	561	US20160017295 SEQ ID NO: 35
AAV Shuffle 10-6	562	US20160017295 SEQ ID NO: 27
AAV Shuffle 10-8	563	US20160017295 SEQ ID NO: 36
AAV Shuffle 10-8	564	US20160017295 SEQ ID NO: 28

AAV SM 100-10	565	US20160017295 SEQ ID NO: 41
AAV SM 100-10	566	US20160017295 SEQ ID NO: 33
AAV SM 100-3	567	US20160017295 SEQ ID NO: 40
AAV SM 100-3	568	US20160017295 SEQ ID NO: 32
AAV SM 10-1	569	US20160017295 SEQ ID NO: 38
AAV SM 10-1	570	US20160017295 SEQ ID NO: 30
AAV SM 10-2	571	US20160017295 SEQ ID NO: 10
AAV SM 10-2	572	US20160017295 SEQ ID NO: 22
AAV SM 10-8	573	US20160017295 SEQ ID NO: 39
AAV SM 10-8	574	US20160017295 SEQ ID NO: 31
AAVF1/HSC1	575	WO2016049230 SEQ ID NO: 20
AAVF2/HSC2	576	WO2016049230 SEQ ID NO: 21
AAVF3/HSC3	577	WO2016049230 SEQ ID NO: 22
AAVF4/HSC4	578	WO2016049230 SEQ ID NO: 23
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AAVF6/HSC6	580	WO2016049230 SEQ ID NO: 24
AAVF7/HSC7	581	WO2016049230 SEQ ID NO: 27
AAVF8/HSC8	582	WO2016049230 SEQ ID NO: 28
AAVF9/HSC9	583	WO2016049230 SEQ ID NO: 29
AAVF11/HSC11	584	WO2016049230 SEQ ID NO: 26
AAVF12/HSC12	585	WO2016049230 SEQ ID NO: 30
AAVF13/HSC13	586	WO2016049230 SEQ ID NO: 31
AAVF14/HSC14	587	WO2016049230 SEQ ID NO: 32
AAVF15/HSC15	588	WO2016049230 SEQ ID NO: 33
AAVF16/HSC16	589	WO2016049230 SEQ ID NO: 34
AAVF17/HSC17	590	WO2016049230 SEQ ID NO: 35
AAVF1/HSC1	591	WO2016049230 SEQ ID NO: 2
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AAVF17/HSC17	606	WO2016049230 SEQ ID NO: 13
AAV CBr-E1	607	US8734809 SEQ ID NO: 13
AAV CBr-E2	608	US8734809 SEQ ID NO: 14
AAV CBr-E3	609	US8734809 SEQ ID NO: 15
AAV CBr-E4	610	US8734809 SEQ ID NO: 16

AAV CBr-E5	611	US8734809 SEQ ID NO: 17
AAV CBr-e5	612	US8734809 SEQ ID NO: 18
AAV CBr-E6	613	US8734809 SEQ ID NO: 19
AAV CBr-E7	614	US8734809 SEQ ID NO: 20
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AAV CLv-D1	616	US8734809 SEQ ID NO: 22
AAV CLv-D2	617	US8734809 SEQ ID NO: 23
AAV CLv-D3	618	US8734809 SEQ ID NO: 24
AAV CLv-D4	619	US8734809 SEQ ID NO: 25
AAV CLv-D5	620	US8734809 SEQ ID NO: 26
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AAV CLv-D7	622	US8734809 SEQ ID NO: 28
AAV CLv-D8	623	US8734809 SEQ ID NO: 29
AAV CLv-E1	624	US8734809 SEQ ID NO: 13
AAV CLv-R1	625	US8734809 SEQ ID NO: 30
AAV CLv-R2	626	US8734809 SEQ ID NO: 31
AAV CLv-R3	627	US8734809 SEQ ID NO: 32
AAV CLv-R4	628	US8734809 SEQ ID NO: 33
AAV CLv-R5	629	US8734809 SEQ ID NO: 34
AAV CLv-R6	630	US8734809 SEQ ID NO: 35
AAV CLv-R7	631	US8734809 SEQ ID NO: 36
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AAV CLv-R9	633	US8734809 SEQ ID NO: 38
AAV CLg-F1	634	US8734809 SEQ ID NO: 39
AAV CLg-F2	635	US8734809 SEQ ID NO: 40
AAV CLg-F3	636	US8734809 SEQ ID NO: 41
AAV CLg-F4	637	US8734809 SEQ ID NO: 42
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AAV CLg-F8	641	US8734809 SEQ ID NO: 43
AAV CSp-1	642	US8734809 SEQ ID NO: 45
AAV CSp-10	643	US8734809 SEQ ID NO: 46
AAV CSp-11	644	US8734809 SEQ ID NO: 47
AAV CSp-2	645	US8734809 SEQ ID NO: 48
AAV CSp-3	646	US8734809 SEQ ID NO: 49
AAV CSp-4	647	US8734809 SEQ ID NO: 50
AAV CSp-6	648	US8734809 SEQ ID NO: 51
AAV CSp-7	649	US8734809 SEQ ID NO: 52
AAV CSp-8	650	US8734809 SEQ ID NO: 53
AAV CSp-9	651	US8734809 SEQ ID NO: 54
AAV CHt-2	652	US8734809 SEQ ID NO: 55
AAV CHt-3	653	US8734809 SEQ ID NO: 56
AAV CKd-1	654	US8734809 SEQ ID NO: 57
AAV CKd-10	655	US8734809 SEQ ID NO: 58
AAV CKd-2	656	US8734809 SEQ ID NO: 59

AAV CKd-3	657	US8734809 SEQ ID NO: 60
AAV CKd-4	658	US8734809 SEQ ID NO: 61
AAV CKd-6	659	US8734809 SEQ ID NO: 62
AAV CKd-7	660	US8734809 SEQ ID NO: 63
AAV CKd-8	661	US8734809 SEQ ID NO: 64
AAV CLv-1	662	US8734809 SEQ ID NO: 65
AAV CLv-12	663	US8734809 SEQ ID NO: 66
AAV CLv-13	664	US8734809 SEQ ID NO: 67
AAV CLv-2	665	US8734809 SEQ ID NO: 68
AAV CLv-3	666	US8734809 SEQ ID NO: 69
AAV CLv-4	667	US8734809 SEQ ID NO: 70
AAV CLv-6	668	US8734809 SEQ ID NO: 71
AAV CLv-8	669	US8734809 SEQ ID NO: 72
AAV CKd-B1	670	US8734809 SEQ ID NO: 73
AAV CKd-B2	671	US8734809 SEQ ID NO: 74
AAV CKd-B3	672	US8734809 SEQ ID NO: 75
AAV CKd-B4	673	US8734809 SEQ ID NO: 76
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AAV CKd-H5	682	US8734809 SEQ ID NO: 85
AAV CKd-H6	683	US8734809 SEQ ID NO: 77
AAV CHt-1	684	US8734809 SEQ ID NO: 86
AAV CLv1-1	685	US8734809 SEQ ID NO: 171
AAV CLv1-2	686	US8734809 SEQ ID NO: 172
AAV CLv1-3	687	US8734809 SEQ ID NO: 173
AAV CLv1-4	688	US8734809 SEQ ID NO: 174
AAV Clv1-7	689	US8734809 SEQ ID NO: 175
AAV Clv1-8	690	US8734809 SEQ ID NO: 176
AAV Clv1-9	691	US8734809 SEQ ID NO: 177
AAV Clv1-10	692	US8734809 SEQ ID NO: 178
AAV.VR-355	693	US8734809 SEQ ID NO: 181
AAV.hu.48R3	694	US8734809 SEQ ID NO: 183
AAV CBr-E1	695	US8734809 SEQ ID NO: 87
AAV CBr-E2	696	US8734809 SEQ ID NO: 88
AAV CBr-E3	697	US8734809 SEQ ID NO: 89
AAV CBr-E4	698	US8734809 SEQ ID NO: 90
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AAV CBr-e5	700	US8734809 SEQ ID NO: 92
AAV CBr-E6	701	US8734809 SEQ ID NO: 93
AAV CBr-E7	702	US8734809 SEQ ID NO: 94

AAV CBr-E8	703	US8734809 SEQ ID NO: 95
AAV CLv-D1	704	US8734809 SEQ ID NO: 96
AAV CLv-D2	705	US8734809 SEQ ID NO: 97
AAV CLv-D3	706	US8734809 SEQ ID NO: 98
AAV CLv-D4	707	US8734809 SEQ ID NO: 99
AAV CLv-D5	708	US8734809 SEQ ID NO: 100
AAV CLv-D6	709	US8734809 SEQ ID NO: 101
AAV CLv-D7	710	US8734809 SEQ ID NO: 102
AAV CLv-D8	711	US8734809 SEQ ID NO: 103
AAV CLv-E1	712	US8734809 SEQ ID NO: 87
AAV CLv-R1	713	US8734809 SEQ ID NO: 104
AAV CLv-R2	714	US8734809 SEQ ID NO: 105
AAV CLv-R3	715	US8734809 SEQ ID NO: 106
AAV CLv-R4	716	US8734809 SEQ ID NO: 107
AAV CLv-R5	717	US8734809 SEQ ID NO: 108
AAV CLv-R6	718	US8734809 SEQ ID NO: 109
AAV CLv-R7	719	US8734809 SEQ ID NO: 110
AAV CLv-R8	720	US8734809 SEQ ID NO: 111
AAV CLv-R9	721	US8734809 SEQ ID NO: 112
AAV CLg-F1	722	US8734809 SEQ ID NO: 113
AAV CLg-F2	723	US8734809 SEQ ID NO: 114
AAV CLg-F3	724	US8734809 SEQ ID NO: 115
AAV CLg-F4	725	US8734809 SEQ ID NO: 116
AAV CLg-F5	726	US8734809 SEQ ID NO: 117
AAV CLg-F6	727	US8734809 SEQ ID NO: 117
AAV CLg-F7	728	US8734809 SEQ ID NO: 118
AAV CLg-F8	729	US8734809 SEQ ID NO: 117
AAV CSp-1	730	US8734809 SEQ ID NO: 119
AAV CSp-10	731	US8734809 SEQ ID NO: 120
AAV CSp-11	732	US8734809 SEQ ID NO: 121
AAV CSp-2	733	US8734809 SEQ ID NO: 122
AAV CSp-3	734	US8734809 SEQ ID NO: 123
AAV CSp-4	735	US8734809 SEQ ID NO: 124
AAV CSp-6	736	US8734809 SEQ ID NO: 125
AAV CSp-7	737	US8734809 SEQ ID NO: 126
AAV CSp-8	738	US8734809 SEQ ID NO: 127
AAV CSp-9	739	US8734809 SEQ ID NO: 128
AAV CHt-2	740	US8734809 SEQ ID NO: 129
AAV CHt-3	741	US8734809 SEQ ID NO: 130
AAV CKd-1	742	US8734809 SEQ ID NO: 131
AAV CKd-10	743	US8734809 SEQ ID NO: 132
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AAV CKd-3	745	US8734809 SEQ ID NO: 134
AAV CKd-4	746	US8734809 SEQ ID NO: 135
AAV CKd-6	747	US8734809 SEQ ID NO: 136
AAV CKd-7	748	US8734809 SEQ ID NO: 137

AAV CKd-8	749	US8734809 SEQ ID NO: 138
AAV CLv-1	750	US8734809 SEQ ID NO: 139
AAV CLv-12	751	US8734809 SEQ ID NO: 140
AAV CLv-13	752	US8734809 SEQ ID NO: 141
AAV CLv-2	753	US8734809 SEQ ID NO: 142
AAV CLv-3	754	US8734809 SEQ ID NO: 143
AAV CLv-4	755	US8734809 SEQ ID NO: 144
AAV CLv-6	756	US8734809 SEQ ID NO: 145
AAV CLv-8	757	US8734809 SEQ ID NO: 146
AAV CKd-B1	758	US8734809 SEQ ID NO: 147
AAV CKd-B2	759	US8734809 SEQ ID NO: 148
AAV CKd-B3	760	US8734809 SEQ ID NO: 149
AAV CKd-B4	761	US8734809 SEQ ID NO: 150
AAV CKd-B5	762	US8734809 SEQ ID NO: 151
AAV CKd-B6	763	US8734809 SEQ ID NO: 152
AAV CKd-B7	764	US8734809 SEQ ID NO: 153
AAV CKd-B8	765	US8734809 SEQ ID NO: 154
AAV CKd-H1	766	US8734809 SEQ ID NO: 155
AAV CKd-H2	767	US8734809 SEQ ID NO: 156
AAV CKd-H3	768	US8734809 SEQ ID NO: 157
AAV CKd-H4	769	US8734809 SEQ ID NO: 158
AAV CKd-H5	770	US8734809 SEQ ID NO: 159
AAV CKd-H6	771	US8734809 SEQ ID NO: 151
AAV CHt-1	772	US8734809 SEQ ID NO: 160
AAV CHt-P2	773	WO2016065001 SEQ ID NO: 1
AAV CHt-P5	774	WO2016065001 SEQ ID NO: 2
AAV CHt-P9	775	WO2016065001 SEQ ID NO: 3
AAV CBr-7.1	776	WO2016065001 SEQ ID NO: 4
AAV CBr-7.2	777	WO2016065001 SEQ ID NO: 5
AAV CBr-7.3	778	WO2016065001 SEQ ID NO: 6
AAV CBr-7.4	779	WO2016065001 SEQ ID NO: 7
AAV CBr-7.5	780	WO2016065001 SEQ ID NO: 8
AAV CBr-7.7	781	WO2016065001 SEQ ID NO: 9
AAV CBr-7.8	782	WO2016065001 SEQ ID NO: 10
AAV CBr-7.10	783	WO2016065001 SEQ ID NO: 11
AAV CKd-N3	784	WO2016065001 SEQ ID NO: 12
AAV CKd-N4	785	WO2016065001 SEQ ID NO: 13
AAV CKd-N9	786	WO2016065001 SEQ ID NO: 14
AAV CLv-L4	787	WO2016065001 SEQ ID NO: 15
AAV CLv-L5	788	WO2016065001 SEQ ID NO: 16
AAV CLv-L6	789	WO2016065001 SEQ ID NO: 17
AAV CLv-K1	790	WO2016065001 SEQ ID NO: 18
AAV CLv-K3	791	WO2016065001 SEQ ID NO: 19
AAV CLv-K6	792	WO2016065001 SEQ ID NO: 20
AAV CLv-M1	793	WO2016065001 SEQ ID NO: 21
AAV CLv-M11	794	WO2016065001 SEQ ID NO: 22

AAV CLv-M2	795	WO2016065001 SEQ ID NO: 23
AAV CLv-M5	796	WO2016065001 SEQ ID NO: 24
AAV CLv-M6	797	WO2016065001 SEQ ID NO: 25
AAV CLv-M7	798	WO2016065001 SEQ ID NO: 26
AAV CLv-M8	799	WO2016065001 SEQ ID NO: 27
AAV CLv-M9	800	WO2016065001 SEQ ID NO: 28
AAV CHt-P1	801	WO2016065001 SEQ ID NO: 29
AAV CHt-P6	802	WO2016065001 SEQ ID NO: 30
AAV CHt-P8	803	WO2016065001 SEQ ID NO: 31
AAV CHt-6.1	804	WO2016065001 SEQ ID NO: 32
AAV CHt-6.10	805	WO2016065001 SEQ ID NO: 33
AAV CHt-6.5	806	WO2016065001 SEQ ID NO: 34
AAV CHt-6.6	807	WO2016065001 SEQ ID NO: 35
AAV CHt-6.7	808	WO2016065001 SEQ ID NO: 36
AAV CHt-6.8	809	WO2016065001 SEQ ID NO: 37
AAV CSp-8.10	810	WO2016065001 SEQ ID NO: 38
AAV CSp-8.2	811	WO2016065001 SEQ ID NO: 39
AAV CSp-8.4	812	WO2016065001 SEQ ID NO: 40
AAV CSp-8.5	813	WO2016065001 SEQ ID NO: 41
AAV CSp-8.6	814	WO2016065001 SEQ ID NO: 42
AAV CSp-8.7	815	WO2016065001 SEQ ID NO: 43
AAV CSp-8.8	816	WO2016065001 SEQ ID NO: 44
AAV CSp-8.9	817	WO2016065001 SEQ ID NO: 45
AAV CBr-B7.3	818	WO2016065001 SEQ ID NO: 46
AAV CBr-B7.4	819	WO2016065001 SEQ ID NO: 47
AAV3B	820	WO2016065001 SEQ ID NO: 48
AAV4	821	WO2016065001 SEQ ID NO: 49
AAV5	822	WO2016065001 SEQ ID NO: 50
AAV CHt-P2	823	WO2016065001 SEQ ID NO: 51
AAV CHt-P5	824	WO2016065001 SEQ ID NO: 52
AAV CHt-P9	825	WO2016065001 SEQ ID NO: 53
AAV CBr-7.1	826	WO2016065001 SEQ ID NO: 54
AAV CBr-7.2	827	WO2016065001 SEQ ID NO: 55
AAV CBr-7.3	828	WO2016065001 SEQ ID NO: 56
AAV CBr-7.4	829	WO2016065001 SEQ ID NO: 57
AAV CBr-7.5	830	WO2016065001 SEQ ID NO: 58
AAV CBr-7.7	831	WO2016065001 SEQ ID NO: 59
AAV CBr-7.8	832	WO2016065001 SEQ ID NO: 60
AAV CBr-7.10	833	WO2016065001 SEQ ID NO: 61
AAV CKd-N3	834	WO2016065001 SEQ ID NO: 62
AAV CKd-N4	835	WO2016065001 SEQ ID NO: 63
AAV CKd-N9	836	WO2016065001 SEQ ID NO: 64
AAV CLv-L4	837	WO2016065001 SEQ ID NO: 65
AAV CLv-L5	838	WO2016065001 SEQ ID NO: 66
AAV CLv-L6	839	WO2016065001 SEQ ID NO: 67
AAV CLv-K1	840	WO2016065001 SEQ ID NO: 68

AAV CLv-K3	841	WO2016065001 SEQ ID NO: 69
AAV CLv-K6	842	WO2016065001 SEQ ID NO: 70
AAV CLv-M1	843	WO2016065001 SEQ ID NO: 71
AAV CLv-M11	844	WO2016065001 SEQ ID NO: 72
AAV CLv-M2	845	WO2016065001 SEQ ID NO: 73
AAV CLv-M5	846	WO2016065001 SEQ ID NO: 74
AAV CLv-M6	847	WO2016065001 SEQ ID NO: 75
AAV CLv-M7	848	WO2016065001 SEQ ID NO: 76
AAV CLv-M8	849	WO2016065001 SEQ ID NO: 77
AAV CLv-M9	850	WO2016065001 SEQ ID NO: 78
AAV CHt-P1	851	WO2016065001 SEQ ID NO: 79
AAV CHt-P6	852	WO2016065001 SEQ ID NO: 80
AAV CHt-P8	853	WO2016065001 SEQ ID NO: 81
AAV CHt-6.1	854	WO2016065001 SEQ ID NO: 82
AAV CHt-6.10	855	WO2016065001 SEQ ID NO: 83
AAV CHt-6.5	856	WO2016065001 SEQ ID NO: 84
AAV CHt-6.6	857	WO2016065001 SEQ ID NO: 85
AAV CHt-6.7	858	WO2016065001 SEQ ID NO: 86
AAV CHt-6.8	859	WO2016065001 SEQ ID NO: 87
AAV CSp-8.10	860	WO2016065001 SEQ ID NO: 88
AAV CSp-8.2	861	WO2016065001 SEQ ID NO: 89
AAV CSp-8.4	862	WO2016065001 SEQ ID NO: 90
AAV CSp-8.5	863	WO2016065001 SEQ ID NO: 91
AAV CSp-8.6	864	WO2016065001 SEQ ID NO: 92
AAV CSp-8.7	865	WO2016065001 SEQ ID NO: 93
AAV CSp-8.8	866	WO2016065001 SEQ ID NO: 94
AAV CSp-8.9	867	WO2016065001 SEQ ID NO: 95
AAV CBr-B7.3	868	WO2016065001 SEQ ID NO: 96
AAV CBr-B7.4	869	WO2016065001 SEQ ID NO: 97
AAV3B	870	WO2016065001 SEQ ID NO: 98
AAV4	871	WO2016065001 SEQ ID NO: 99
AAV5	872	WO2016065001 SEQ ID NO: 100
PHP.N/PHP.B-DGT	873	WO2017100671 SEQ ID NO: 46
PHP.S/G2A12	874	WO2017100671 SEQ ID NO: 47
AAV9/hu.14 K449R	875	WO2017100671 SEQ ID NO: 45
GPV	992	US9624274B2 SEQ ID NO: 192
B19	993	US9624274B2 SEQ ID NO: 193
MVM	994	US9624274B2 SEQ ID NO: 194
FPV	995	US9624274B2 SEQ ID NO: 195
CPV	996	US9624274B2 SEQ ID NO: 196
AAV6	997	US9546112B2 SEQ ID NO: 5
AAV6	998	US9457103B2 SEQ ID NO: 1
AAV2	999	US9457103B2 SEQ ID NO: 2
ShH10	1000	US9457103B2 SEQ ID NO: 3
ShH13	1001	US9457103B2 SEQ ID NO: 4
ShH10	1002	US9457103B2 SEQ ID NO: 5

ShH10	1003	US9457103B2 SEQ ID NO: 6
ShH10	1004	US9457103B2 SEQ ID NO: 7
ShH10	1005	US9457103B2 SEQ ID NO: 8
ShH10	1006	US9457103B2 SEQ ID NO: 9
rh74	1007	US9434928B2 SEQ ID NO: 1, US2015023924A1 SEQ ID NO: 2
rh74	1008	US9434928B2 SEQ ID NO: 2, US2015023924A1 SEQ ID NO: 1
AAV8	1009	US9434928B2 SEQ ID NO: 4
rh74	1010	US9434928B2 SEQ ID NO: 5
rh74 (RHM4-1)	1011	US2015023924A1 SEQ ID NO: 5, US20160375110A1 SEQ ID NO: 4
rh74 (RHM15-1)	1012	US2015023924A1 SEQ ID NO: 6, US20160375110A1 SEQ ID NO: 5
rh74 (RHM15-2)	1013	US2015023924A1 SEQ ID NO: 7, US20160375110A1 SEQ ID NO: 6
rh74 (RHM15-3/RHM15-5)	1014	US2015023924A1 SEQ ID NO: 8, US20160375110A1 SEQ ID NO: 7
rh74 (RHM15-4)	1015	US2015023924A1 SEQ ID NO: 9, US20160375110A1 SEQ ID NO: 8
rh74 (RHM15-6)	1016	US2015023924A1 SEQ ID NO: 10, US20160375110A1 SEQ ID NO: 9
rh74 (RHM4-1)	1017	US2015023924A1 SEQ ID NO: 11
rh74 (RHM15-1)	1018	US2015023924A1 SEQ ID NO: 12
rh74 (RHM15-2)	1019	US2015023924A1 SEQ ID NO: 13
rh74 (RHM15-3/RHM15-5)	1020	US2015023924A1 SEQ ID NO: 14
rh74 (RHM15-4)	1021	US2015023924A1 SEQ ID NO: 15
rh74 (RHM15-6)	1022	US2015023924A1 SEQ ID NO: 16
AAV2 (comprising lung specific polypeptide)	1023	US20160175389A1 SEQ ID NO: 9
AAV2 (comprising lung specific polypeptide)	1024	US20160175389A1 SEQ ID NO: 10
Anc80	1025	US20170051257A1 SEQ ID NO: 1
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Anc113	1037	US20170051257A1 SEQ ID NO: 13
Anc113	1038	US20170051257A1 SEQ ID NO: 14
Anc126	1039	US20170051257A1 SEQ ID NO: 15
Anc126	1040	US20170051257A1 SEQ ID NO: 16
Anc127	1041	US20170051257A1 SEQ ID NO: 17
Anc127	1042	US20170051257A1 SEQ ID NO: 18

Anc80L27	1043	US20170051257A1 SEQ ID NO: 19
Anc80L59	1044	US20170051257A1 SEQ ID NO: 20
Anc80L60	1045	US20170051257A1 SEQ ID NO: 21
Anc80L62	1046	US20170051257A1 SEQ ID NO: 22
Anc80L65	1047	US20170051257A1 SEQ ID NO: 23
Anc80L33	1048	US20170051257A1 SEQ ID NO: 24
Anc80L36	1049	US20170051257A1 SEQ ID NO: 25
Anc80L44	1050	US20170051257A1 SEQ ID NO: 26
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AAV-X1b	1054	US8283151B2 SEQ ID NO: 12
AAV-X5	1055	US8283151B2 SEQ ID NO: 13
AAV-X19	1056	US8283151B2 SEQ ID NO: 14
AAV-X21	1057	US8283151B2 SEQ ID NO: 15
AAV-X22	1058	US8283151B2 SEQ ID NO: 16
AAV-X23	1059	US8283151B2 SEQ ID NO: 17
AAV-X24	1060	US8283151B2 SEQ ID NO: 18
AAV-X25	1061	US8283151B2 SEQ ID NO: 19
AAV-X26	1062	US8283151B2 SEQ ID NO: 20
AAV-X1	1063	US8283151B2 SEQ ID NO: 21
AAV-X1b	1064	US8283151B2 SEQ ID NO: 22
AAV-X5	1065	US8283151B2 SEQ ID NO: 23
AAV-X19	1066	US8283151B2 SEQ ID NO: 24
AAV-X21	1067	US8283151B2 SEQ ID NO: 25
AAV-X22	1068	US8283151B2 SEQ ID NO: 26
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AAV-X25	1071	US8283151B2 SEQ ID NO: 29
AAV-X26	1072	US8283151B2 SEQ ID NO: 30
AAVrh8	1073	WO2016054554A1 SEQ ID NO: 8
AAVrh8VP2FC5	1074	WO2016054554A1 SEQ ID NO: 9
AAVrh8VP2FC44	1075	WO2016054554A1 SEQ ID NO: 10
AAVrh8VP2ApoB100	1076	WO2016054554A1 SEQ ID NO: 11
AAVrh8VP2RVG	1077	WO2016054554A1 SEQ ID NO: 12
AAVrh8VP2Angiopep-2 VP2	1078	WO2016054554A1 SEQ ID NO: 13
AAV9.47VP1.3	1079	WO2016054554A1 SEQ ID NO: 14
AAV9.47VP2ICAMg3	1080	WO2016054554A1 SEQ ID NO: 15
AAV9.47VP2RVG	1081	WO2016054554A1 SEQ ID NO: 16
AAV9.47VP2Angiopep-2	1082	WO2016054554A1 SEQ ID NO: 17
AAV9.47VP2A-string	1083	WO2016054554A1 SEQ ID NO: 18
AAVrh8VP2FC5 VP2	1084	WO2016054554A1 SEQ ID NO: 19
AAVrh8VP2FC44 VP2	1085	WO2016054554A1 SEQ ID NO: 20
AAVrh8VP2ApoB100 VP2	1086	WO2016054554A1 SEQ ID NO: 21
AAVrh8VP2RVG VP2	1087	WO2016054554A1 SEQ ID NO: 22

AAVrh8VP2Angiopep-2 VP2	1088	WO2016054554A1 SEQ ID NO: 23
AAV9.47VP2ICAMg3 VP2	1089	WO2016054554A1 SEQ ID NO: 24
AAV9.47VP2RVG VP2	1090	WO2016054554A1 SEQ ID NO: 25
AAV9.47VP2Angiopep-2 VP2	1091	WO2016054554A1 SEQ ID NO: 26
AAV9.47VP2A-string VP2	1092	WO2016054554A1 SEQ ID NO: 27
rAAV-B1	1093	WO2016054557A1 SEQ ID NO: 1
rAAV-B2	1094	WO2016054557A1 SEQ ID NO: 2
rAAV-B3	1095	WO2016054557A1 SEQ ID NO: 3
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rAAV-B2	1098	WO2016054557A1 SEQ ID NO: 6
rAAV-B3	1099	WO2016054557A1 SEQ ID NO: 7
rAAV-B4	1100	WO2016054557A1 SEQ ID NO: 8
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AAV9	1109	WO2016073739A1 SEQ ID NO: 3
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rAAV	1176	WO2016081811A1 SEQ ID NO: 67
rAAV	1177	WO2016081811A1 SEQ ID NO: 68
rAAV	1178	WO2016081811A1 SEQ ID NO: 69
rAAV	1179	WO2016081811A1 SEQ ID NO: 70

rAAV	1180	WO2016081811A1 SEQ ID NO: 71
rAAV	1181	WO2016081811A1 SEQ ID NO: 72
rAAV	1182	WO2016081811A1 SEQ ID NO: 73
rAAV	1183	WO2016081811A1 SEQ ID NO: 74
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rAAV	1198	WO2016081811A1 SEQ ID NO: 89
rAAV	1199	WO2016081811A1 SEQ ID NO: 90
rAAV	1200	WO2016081811A1 SEQ ID NO: 91
rAAV	1201	WO2016081811A1 SEQ ID NO: 92
rAAV	1202	WO2016081811A1 SEQ ID NO: 93
rAAV	1203	WO2016081811A1 SEQ ID NO: 94
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rAAV	1205	WO2016081811A1 SEQ ID NO: 96
rAAV	1206	WO2016081811A1 SEQ ID NO: 97
rAAV	1207	WO2016081811A1 SEQ ID NO: 98
rAAV	1208	WO2016081811A1 SEQ ID NO: 99
rAAV	1209	WO2016081811A1 SEQ ID NO: 100
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rAAV	1223	WO2016081811A1 SEQ ID NO: 114
rAAV	1224	WO2016081811A1 SEQ ID NO: 115
rAAV	1225	WO2016081811A1 SEQ ID NO: 116

rAAV	1226	WO2016081811A1 SEQ ID NO: 117
rAAV	1227	WO2016081811A1 SEQ ID NO: 118
rAAV	1228	WO2016081811A1 SEQ ID NO: 119
rAAV	1229	WO2016081811A1 SEQ ID NO: 120
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rAAV	1237	WO2016081811A1 SEQ ID NO: 128
AAV8 E532K	1238	WO2016081811A1 SEQ ID NO: 133
AAV8 E532K	1239	WO2016081811A1 SEQ ID NO: 134
rAAV4	1240	WO2016115382A1 SEQ ID NO: 2
rAAV4	1241	WO2016115382A1 SEQ ID NO: 3
rAAV4	1242	WO2016115382A1 SEQ ID NO: 4
rAAV4	1243	WO2016115382A1 SEQ ID NO: 5
rAAV4	1244	WO2016115382A1 SEQ ID NO: 6
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AAV11	1260	WO2016115382A1 SEQ ID NO: 22
AAV12	1261	WO2016115382A1 SEQ ID NO: 23
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rAAV4	1267	WO2016115382A1 SEQ ID NO: 30
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rAAV4	1269	WO2016115382A1 SEQ ID NO: 32
rAAV4	1270	WO2016115382A1 SEQ ID NO: 33
AAV2/8	1271	WO2016131981A1 SEQ ID NO: 47

AAV2/8	1272	WO2016131981A1 SEQ ID NO: 48
ancestral AAV	1273	WO2016154344A1 SEQ ID NO: 7
ancestral AAV variant C4	1274	WO2016154344A1 SEQ ID NO: 13
ancestral AAV variant C7	1275	WO2016154344A1 SEQ ID NO: 14
ancestral AAV variant G4	1276	WO2016154344A1 SEQ ID NO: 15
consensus amino acid sequence of ancestral AAV variants, C4, C7 and G4	1277	WO2016154344A1 SEQ ID NO: 16
consensus amino acid sequence of ancestral AAV variants, C4 and C7	1278	WO2016154344A1 SEQ ID NO: 17
AAV8 (with a AAV2 phospholipase domain)	1279	WO2016150403A1 SEQ ID NO: 13
AAV VR-942n	1280	US20160289275A1 SEQ ID NO: 10
AAV5-A (M569V)	1281	US20160289275A1 SEQ ID NO: 13
AAV5-A (M569V)	1282	US20160289275A1 SEQ ID NO: 14
AAV5-A (Y585V)	1283	US20160289275A1 SEQ ID NO: 16
AAV5-A (Y585V)	1284	US20160289275A1 SEQ ID NO: 17
AAV5-A (L587T)	1285	US20160289275A1 SEQ ID NO: 19
AAV5-A (L587T)	1286	US20160289275A1 SEQ ID NO: 20
AAV5-A (Y585V/L587T)	1287	US20160289275A1 SEQ ID NO: 22
AAV5-A (Y585V/L587T)	1288	US20160289275A1 SEQ ID NO: 23
AAV5-B (D652A)	1289	US20160289275A1 SEQ ID NO: 25
AAV5-B (D652A)	1290	US20160289275A1 SEQ ID NO: 26
AAV5-B (T362M)	1291	US20160289275A1 SEQ ID NO: 28
AAV5-B (T362M)	1292	US20160289275A1 SEQ ID NO: 29
AAV5-B (Q359D)	1293	US20160289275A1 SEQ ID NO: 31
AAV5-B (Q359D)	1294	US20160289275A1 SEQ ID NO: 32
AAV5-B (E350Q)	1295	US20160289275A1 SEQ ID NO: 34
AAV5-B (E350Q)	1296	US20160289275A1 SEQ ID NO: 35
AAV5-B (P533S)	1297	US20160289275A1 SEQ ID NO: 37
AAV5-B (P533S)	1298	US20160289275A1 SEQ ID NO: 38
AAV5-B (P533G)	1299	US20160289275A1 SEQ ID NO: 40
AAV5-B (P533G)	1300	US20160289275A1 SEQ ID NO: 41
AAV5-mutation in loop VII	1301	US20160289275A1 SEQ ID NO: 43
AAV5-mutation in loop VII	1302	US20160289275A1 SEQ ID NO: 44
AAV8	1303	US20160289275A1 SEQ ID NO: 47
Mut A (LK03/AAV8)	1304	WO2016181123A1 SEQ ID NO: 1
Mut B (LK03/AAV5)	1305	WO2016181123A1 SEQ ID NO: 2
Mut C (AAV8/AAV3B)	1306	WO2016181123A1 SEQ ID NO: 3
Mut D (AAV5/AAV3B)	1307	WO2016181123A1 SEQ ID NO: 4
Mut E (AAV8/AAV3B)	1308	WO2016181123A1 SEQ ID NO: 5
Mut F (AAV3B/AAV8)	1309	WO2016181123A1 SEQ ID NO: 6
AAV44.9	1310	WO2016183297A1 SEQ ID NO: 4
AAV44.9	1311	WO2016183297A1 SEQ ID NO: 5
AAVrh8	1312	WO2016183297A1 SEQ ID NO: 6
AAV44.9 (S470N)	1313	WO2016183297A1 SEQ ID NO: 9
rh74 VP1	1314	US20160375110A1 SEQ ID NO: 1

AAV-LK03 (L125I)	1315	WO2017015102A1 SEQ ID NO: 5
AAV3B (S663V+T492V)	1316	WO2017015102A1 SEQ ID NO: 6
Anc80	1317	WO2017019994A2 SEQ ID NO: 1
Anc80	1318	WO2017019994A2 SEQ ID NO: 2
Anc81	1319	WO2017019994A2 SEQ ID NO: 3
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Anc83	1323	WO2017019994A2 SEQ ID NO: 7
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Anc127	1334	WO2017019994A2 SEQ ID NO: 18
Anc80L27	1335	WO2017019994A2 SEQ ID NO: 19
Anc80L59	1336	WO2017019994A2 SEQ ID NO: 20
Anc80L60	1337	WO2017019994A2 SEQ ID NO: 21
Anc80L62	1338	WO2017019994A2 SEQ ID NO: 22
Anc80L65	1339	WO2017019994A2 SEQ ID NO: 23
Anc80L33	1340	WO2017019994A2 SEQ ID NO: 24
Anc80L36	1341	WO2017019994A2 SEQ ID NO: 25
Anc80L44	1342	WO2017019994A2 SEQ ID NO: 26
Anc80L1	1343	WO2017019994A2 SEQ ID NO: 35
Anc80L1	1344	WO2017019994A2 SEQ ID NO: 36
AAVrh10	1345	WO2017019994A2 SEQ ID NO: 41
Anc110	1346	WO2017019994A2 SEQ ID NO: 42
Anc110	1347	WO2017019994A2 SEQ ID NO: 43
AAVrh32.33	1348	WO2017019994A2 SEQ ID NO: 45
AAVrh74	1349	WO2017049031A1 SEQ ID NO: 1
AAV2	1350	WO2017053629A2 SEQ ID NO: 49
AAV2	1351	WO2017053629A2 SEQ ID NO: 50
AAV2	1352	WO2017053629A2 SEQ ID NO: 82
Parvo-like virus	1353	WO2017070476A2 SEQ ID NO: 1
Parvo-like virus	1354	WO2017070476A2 SEQ ID NO: 2
Parvo-like virus	1355	WO2017070476A2 SEQ ID NO: 3
Parvo-like virus	1356	WO2017070476A2 SEQ ID NO: 4
Parvo-like virus	1357	WO2017070476A2 SEQ ID NO: 5
Parvo-like virus	1358	WO2017070476A2 SEQ ID NO: 6
AAVrh.10	1359	WO2017070516A1 SEQ ID NO: 7
AAVrh.10	1360	WO2017070516A1 SEQ ID NO: 14

AAV2tYF	1361	WO2017070491A1 SEQ ID NO: 1
AAV-SPK	1362	WO2017075619A1 SEQ ID NO:28
AAV2.5	1363	US20170128528A1 SEQ ID NO: 13
AAV1.1	1364	US20170128528A1 SEQ ID NO: 15
AAV6.1	1365	US20170128528A1 SEQ ID NO: 17
AAV6.3.1	1366	US20170128528A1 SEQ ID NO: 18
AAV2i8	1367	US20170128528A1 SEQ ID NO: 28
AAV2i8	1368	US20170128528A1 SEQ ID NO: 29
ttAAV	1369	US20170128528A1 SEQ ID NO: 30
ttAAV-S312N	1370	US20170128528A1 SEQ ID NO: 32
ttAAV-S312N	1371	US20170128528A1 SEQ ID NO: 33
AAV6 (Y705, Y731, and T492)	1372	WO2016134337A1 SEQ ID NO: 24
AAV2	1373	WO2016134375A1 SEQ ID NO: 9
AAV2	1374	WO2016134375A1 SEQ ID NO: 10

[0095] In any of the DNA and RNA sequences referenced and/or described herein, the single letter symbol has the following description: A for adenine; C for cytosine; G for guanine; T for thymine; U for Uracil; W for weak bases such as adenine or thymine; S for strong nucleotides such as cytosine and guanine; M for amino nucleotides such as adenine and cytosine; K for keto nucleotides such as guanine and thymine; R for purines adenine and guanine; Y for pyrimidine cytosine and thymine; B for any base that is not A (e.g., cytosine, guanine, and thymine); D for any base that is not C (e.g., adenine, guanine, and thymine); H for any base that is not G (e.g., adenine, cytosine, and thymine); V for any base that is not T (e.g., adenine, cytosine, and guanine); N for any nucleotide (which is not a gap); and Z is for zero.

[0096] In any of the amino acid sequences referenced and/or described herein, the single letter symbol has the following description: G (Gly) for Glycine; A (Ala) for Alanine; L (Leu) for Leucine; M (Met) for Methionine; F (Phe) for Phenylalanine; W (Trp) for Tryptophan; K (Lys) for Lysine; Q (Gln) for Glutamine; E (Glu) for Glutamic Acid; S (Ser) for Serine; P (Pro) for Proline; V (Val) for Valine; I (Ile) for Isoleucine; C (Cys) for Cysteine; Y (Tyr) for Tyrosine; H (His) for Histidine; R (Arg) for Arginine; N (Asn) for Asparagine; D (Asp) for Aspartic Acid; T (Thr) for Threonine; B (Asx) for Aspartic acid or Asparagine; J (Xle) for Leucine or Isoleucine; O (Pyl) for Pyrrolysine; U (Sec) for Selenocysteine; X (Xaa) for any amino acid; and Z (Glx) for Glutamine or Glutamic acid.

[0097] In certain embodiments, the AAV serotype may be, or may have a sequence as described in International Patent Publication WO2015038958, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV9 (SEQ ID NO: 2 and 11 of WO2015038958 or SEQ ID NO: 132 and 131 respectively herein), PHP.B (SEQ ID NO: 8 and 9 of WO2015038958 or SEQ ID NO: 1 and 2 herein), G2B-13 (SEQ ID NO: 12 of

WO2015038958 or SEQ ID NO: 3 herein), G2B-26 (SEQ ID NO: 13 of WO2015038958 or SEQ ID NO: 1 herein), TH1.1-32 (SEQ ID NO: 14 of WO2015038958 or SEQ ID NO: 4 herein), TH1.1-35 (SEQ ID NO: 15 of WO2015038958 or SEQ ID NO: 5 herein) or variants thereof. Further, any of the targeting peptides or amino acid inserts described in WO2015038958, may be inserted into any parent AAV serotype, such as, but not limited to, AAV9 (SEQ ID NO: 131 for the DNA sequence and SEQ ID NO: 132 for the amino acid sequence). In certain embodiments, the amino acid insert is inserted between amino acids 586-592 of the parent AAV (e.g., AAV9). In another embodiment, the amino acid insert is inserted between amino acids 588-589 of the parent AAV sequence. The amino acid insert may be, but is not limited to, any of the following amino acid sequences, TLAVPFK (SEQ ID NO: 1 of WO2015038958; herein SEQ ID NO: 876), KFPVALT (SEQ ID NO: 3 of WO2015038958; herein SEQ ID NO: 877), LAVPFK (SEQ ID NO: 31 of WO2015038958; herein SEQ ID NO: 878), AVPFK (SEQ ID NO: 32 of WO2015038958; herein SEQ ID NO: 879), VPFK (SEQ ID NO: 33 of WO2015038958; herein SEQ ID NO: 880), TLAVPF (SEQ ID NO: 34 of WO2015038958; herein SEQ ID NO: 881), TLAVP (SEQ ID NO: 35 of WO2015038958; herein SEQ ID NO: 882), TLAV (SEQ ID NO: 36 of WO2015038958; herein SEQ ID NO: 883), SVSKPFL (SEQ ID NO: 28 of WO2015038958; herein SEQ ID NO: 884), FTLTTPK (SEQ ID NO: 29 of WO2015038958; herein SEQ ID NO: 885), MNATKNV (SEQ ID NO: 30 of WO2015038958; herein SEQ ID NO: 886), QSSQTPR (SEQ ID NO: 54 of WO2015038958; herein SEQ ID NO: 887), ILGTGTS (SEQ ID NO: 55 of WO2015038958; herein SEQ ID NO: 888), TRTNPEA (SEQ ID NO: 56 of WO2015038958; herein SEQ ID NO: 889), NGGTSSS (SEQ ID NO: 58 of WO2015038958; herein SEQ ID NO: 890), or YTLSQGW (SEQ ID NO: 60 of WO2015038958; herein SEQ ID NO: 891). Non-limiting examples of nucleotide sequences that may encode the amino acid inserts include the following, AAGTTTCCTGTGGCGTTGACT (for SEQ ID NO: 3 of WO2015038958; herein SEQ ID NO: 892), ACTTTGGCGGTGCCTTTTAAG (SEQ ID NO: 24 and 49 of WO2015038958; herein SEQ ID NO: 893), AGTGTGAGTAAGCCTTTTTTG (SEQ ID NO: 25 of WO2015038958; herein SEQ ID NO: 894), TTTACGTTGACGACGCCTAAG (SEQ ID NO: 26 of WO2015038958; herein SEQ ID NO: 895), ATGAATGCTACGAAGAATGTG (SEQ ID NO: 27 of WO2015038958; herein SEQ ID NO: 896), CAGTCGTCGCAGACGCCTAGG (SEQ ID NO: 48 of WO2015038958; herein SEQ ID NO: 897), ATTCTGGGGACTGGTACTTCG (SEQ ID NO: 50 and 52 of WO2015038958; herein SEQ ID NO: 898), ACGCGGACTAATCCTGAGGCT (SEQ ID NO: 51 of WO2015038958; herein SEQ ID NO: 899), AATGGGGGGACTAGTAGTTCT (SEQ ID NO: 53 of WO2015038958; herein SEQ ID

NO: 900), or TATACTTTGTCGCAGGGTTGG (SEQ ID NO: 59 of WO2015038958; herein SEQ ID NO: 901).

[0098] In certain embodiments, the AAV serotype may be, or may have a sequence as described in International Patent Publication WO2017100671, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV9 (SEQ ID NO: 45 of WO2017100671, herein SEQ ID NO: 875), PHP.N (SEQ ID NO: 46 of WO2017100671, herein SEQ ID NO: 873), PHP.S (SEQ ID NO: 47 of WO2017100671, herein SEQ ID NO: 874), or variants thereof. Further, any of the targeting peptides or amino acid inserts described in WO2017100671 may be inserted into any parent AAV serotype, such as, but not limited to, AAV9 (SEQ ID NO: 127 or SEQ ID NO: 875). In certain embodiments, the amino acid insert is inserted between amino acids 586-592 of the parent AAV (e.g., AAV9). In another embodiment, the amino acid insert is inserted between amino acids 588-589 of the parent AAV sequence. The amino acid insert may be, but is not limited to, any of the following amino acid sequences, AQTLAVPFKAQ (SEQ ID NO: 1 of WO2017100671; herein SEQ ID NO: 902), AQSVSKPFLAQ (SEQ ID NO: 2 of WO2017100671; herein SEQ ID NO: 903), AQFTLTTPKAQ (SEQ ID NO: 3 in the sequence listing of WO2017100671; herein SEQ ID NO: 904), DGTLAVPFKAQ (SEQ ID NO: 4 in the sequence listing of WO2017100671; herein SEQ ID NO: 905), ESTLAVPFKAQ (SEQ ID NO: 5 of WO2017100671; herein SEQ ID NO: 906), GGTLAVPFKAQ (SEQ ID NO: 6 of WO2017100671; herein SEQ ID NO: 907), AQTLATPFKAQ (SEQ ID NO: 7 and 33 of WO2017100671; herein SEQ ID NO: 908), ATTLATPFKAQ (SEQ ID NO: 8 of WO2017100671; herein SEQ ID NO: 909), DGTLATPFKAQ (SEQ ID NO: 9 of WO2017100671; herein SEQ ID NO: 910), GGTLATPFKAQ (SEQ ID NO: 10 of WO2017100671; herein SEQ ID NO: 911), SGSLAVPFKAQ (SEQ ID NO: 11 of WO2017100671; herein SEQ ID NO: 912), AQTLAQPFKAQ (SEQ ID NO: 12 of WO2017100671; herein SEQ ID NO: 913), AQTLQQPFKAQ (SEQ ID NO: 13 of WO2017100671; herein SEQ ID NO: 914), AQTLSNPFKAQ (SEQ ID NO: 14 of WO2017100671; herein SEQ ID NO: 915), AQTLAVPFSNP (SEQ ID NO: 15 of WO2017100671; herein SEQ ID NO: 916), QGTLAVPFKAQ (SEQ ID NO: 16 of WO2017100671; herein SEQ ID NO: 917), NQTLAVPFKAQ (SEQ ID NO: 17 of WO2017100671; herein SEQ ID NO: 918), EGSLAVPFKAQ (SEQ ID NO: 18 of WO2017100671; herein SEQ ID NO: 919), SGNLAVPFKAQ (SEQ ID NO: 19 of WO2017100671; herein SEQ ID NO: 920), EGTLAVPFKAQ (SEQ ID NO: 20 of WO2017100671; herein SEQ ID NO: 921), DSTLAVPFKAQ (SEQ ID NO: 21 in Table 1 of WO2017100671; herein SEQ ID NO: 922),

AVTLAVPFKAQ (SEQ ID NO: 22 of WO2017100671; herein SEQ ID NO: 923), AQTLSTPFKAQ (SEQ ID NO: 23 of WO2017100671; herein SEQ ID NO: 924), AQTLPQPFKAQ (SEQ ID NO: 24 and 32 of WO2017100671; herein SEQ ID NO: 925), AQTLSQPFKAQ (SEQ ID NO: 25 of WO2017100671; herein SEQ ID NO: 926), AQTLQLPFKAQ (SEQ ID NO: 26 of WO2017100671; herein SEQ ID NO: 927), AQTLTMPFKAQ (SEQ ID NO: 27, and 34 of WO2017100671 and SEQ ID NO: 35 in the sequence listing of WO2017100671; herein SEQ ID NO: 928), AQTLTTPFKAQ (SEQ ID NO: 28 of WO2017100671; herein SEQ ID NO: 929), AQYTLSQGWAQ (SEQ ID NO: 29 of WO2017100671; herein SEQ ID NO: 930), AQMNATKNVAQ (SEQ ID NO: 30 of WO2017100671; herein SEQ ID NO: 931), AQVSGGHHSAQ (SEQ ID NO: 31 of WO2017100671; herein SEQ ID NO: 932), AQTLTAPFKAQ (SEQ ID NO: 35 in Table 1 of WO2017100671; herein SEQ ID NO: 933), AQTLSKPFKAQ (SEQ ID NO: 36 of WO2017100671; herein SEQ ID NO: 934), QAVRTSL (SEQ ID NO: 37 of WO2017100671; herein SEQ ID NO: 935), YTLSQGW (SEQ ID NO: 38 of WO2017100671; herein SEQ ID NO: 891), LAKERLS (SEQ ID NO: 39 of WO2017100671; herein SEQ ID NO: 936), TLAVPFK (SEQ ID NO: 40 in the sequence listing of WO2017100671; herein SEQ ID NO: 876), SVSKPFL (SEQ ID NO: 41 of WO2017100671; herein SEQ ID NO: 884), FTLTTPK (SEQ ID NO: 42 of WO2017100671; herein SEQ ID NO: 885), MNSTKNV (SEQ ID NO: 43 of WO2017100671; herein SEQ ID NO: 937), VSGGHHS (SEQ ID NO: 44 of WO2017100671; herein SEQ ID NO: 938), SAQTLAVPFKAQAQ (SEQ ID NO: 48 of WO2017100671; herein SEQ ID NO: 939), SXXXLAVPFKAQAQ (SEQ ID NO: 49 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 940), SAQXXXVPFKAQAQ (SEQ ID NO: 50 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 941), SAQTLXXXFKAQAQ (SEQ ID NO: 51 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 942), SAQTLAVXXXAQAQ (SEQ ID NO: 52 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 943), SAQTLAVPFXXXAQ (SEQ ID NO: 53 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 944), TNHQSAQ (SEQ ID NO: 65 of WO2017100671; herein SEQ ID NO: 945), AQAQTGW (SEQ ID NO: 66 of WO2017100671; herein SEQ ID NO: 946), DGTLATPFK (SEQ ID NO: 67 of WO2017100671; herein SEQ ID NO: 947), DGTLATPFKXX (SEQ ID NO: 68 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 948), LAVPFKAQ (SEQ ID NO: 80 of WO2017100671; herein SEQ ID NO: 949), VPFKAQ (SEQ ID NO: 81 of WO2017100671; herein SEQ ID NO: 950), FKAQ (SEQ ID NO: 82 of WO2017100671; herein SEQ ID NO: 951), AQTLAV (SEQ ID NO: 83 of WO2017100671; herein SEQ ID NO: 952), AQTLAVPF

(SEQ ID NO: 84 of WO2017100671; herein SEQ ID NO: 953), QAVR (SEQ ID NO: 85 of WO2017100671; herein SEQ ID NO: 954), AVRT (SEQ ID NO: 86 of WO2017100671; herein SEQ ID NO: 955), VRTS (SEQ ID NO: 87 of WO2017100671; herein SEQ ID NO: 956), RTSL (SEQ ID NO: 88 of WO2017100671; herein SEQ ID NO: 957), QAVRT (SEQ ID NO: 89 of WO2017100671; herein SEQ ID NO: 958), AVRTS (SEQ ID NO: 90 of WO2017100671; herein SEQ ID NO: 959), VRTSL (SEQ ID NO: 91 of WO2017100671; herein SEQ ID NO: 960), QAVRTS (SEQ ID NO: 92 of WO2017100671; herein SEQ ID NO: 961), or AVRTSL (SEQ ID NO: 93 of WO2017100671; herein SEQ ID NO: 962).

[0099] Non-limiting examples of nucleotide sequences that may encode the amino acid inserts include the following, GATGGGACTTTGGCGGTGCCTTTTAAGGCACAG (SEQ ID NO: 54 of WO2017100671; herein SEQ ID NO: 963), GATGGGACGTTGGCGGTGCCTTTTAAGGCACAG (SEQ ID NO: 55 of WO2017100671; herein SEQ ID NO: 964), CAGGCGGTTAGGACGTCTTTG (SEQ ID NO: 56 of WO2017100671; herein SEQ ID NO: 965), CAGGTCTTCACGGACTCAGACTATCAG (SEQ ID NO: 57 and 78 of WO2017100671; herein SEQ ID NO: 966), CAAGTAAAACCTCTACAAATGTGGTAAAATCG (SEQ ID NO: 58 of WO2017100671; herein SEQ ID NO: 967), ACTCATCGACCAATACTTGTACTATCTCTCTAGAAC (SEQ ID NO: 59 of WO2017100671; herein SEQ ID NO: 968), GGAAGTATTCCTTGGTTTTGAACCCA (SEQ ID NO: 60 of WO2017100671; herein SEQ ID NO: 969), GGTCGCGGTTCTTGTTTGTGGAT (SEQ ID NO: 61 of WO2017100671; herein SEQ ID NO: 970), CGACCTTGAAGCGCATGAACTCCT (SEQ ID NO: 62 of WO2017100671; herein SEQ ID NO: 971), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCMNNMNNMNNMNNMNNMNNMNNTTGGGCACTCTGGTGGTTTGTC (SEQ ID NO: 63 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 972), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCMNNMNNMNNAAAAGGCACCGCCAAAGTTTG (SEQ ID NO: 69 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 973), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCMNNMNNMNNCACCGCCAAAGTTTGGGCACT (SEQ ID NO: 70 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 974), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCCTTAAAMNNMNNMNNCAAAGTTTGGGCACTCTGGTGG (SEQ ID NO: 71 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 975),

GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCCTTAAAAGGCACMNNM NNMNNTTGGGCACTCTGGTGGTTTGTG (SEQ ID NO: 72 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 976), ACTTTGGCGGTGCCTTTTAAG (SEQ ID NO: 74 of WO2017100671; herein SEQ ID NO: 893), AGTGTGAGTAAGCCTTTTTTG (SEQ ID NO: 75 of WO2017100671; herein SEQ ID NO: 894), TTTACGTTGACGACGCCTAAG (SEQ ID NO: 76 of WO2017100671; herein SEQ ID NO: 895), TATACTTTGTCGCAGGGTTGG (SEQ ID NO: 77 of WO2017100671; herein SEQ ID NO: 901), or CTTGCGAAGGAGCGGCTTTCG (SEQ ID NO: 79 of WO2017100671; herein SEQ ID NO: 977).

[0100] In certain embodiments, the AAV serotype may be, or may have a sequence as described in United States Patent No. US 9624274, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV1 (SEQ ID NO: 181 of US9624274), AAV6 (SEQ ID NO: 182 of US9624274), AAV2 (SEQ ID NO: 183 of US9624274), AAV3b (SEQ ID NO: 184 of US9624274), AAV7 (SEQ ID NO: 185 of US9624274), AAV8 (SEQ ID NO: 186 of US9624274), AAV10 (SEQ ID NO: 187 of US9624274), AAV4 (SEQ ID NO: 188 of US9624274), AAV11 (SEQ ID NO: 189 of US9624274), bAAV (SEQ ID NO: 190 of US9624274), AAV5 (SEQ ID NO: 191 of US9624274), GPV (SEQ ID NO: 192 of US9624274; herein SEQ ID NO: 992), B19 (SEQ ID NO: 193 of US9624274; herein SEQ ID NO: 993), MVM (SEQ ID NO: 194 of US9624274; herein SEQ ID NO: 994), FPV (SEQ ID NO: 195 of US9624274; herein SEQ ID NO: 995), CPV (SEQ ID NO: 196 of US9624274; herein SEQ ID NO: 996) or variants thereof. Further, any of the structural protein inserts described in US 9624274, may be inserted into, but not limited to, I-453 and I-587 of any parent AAV serotype, such as, but not limited to, AAV2 (SEQ ID NO: 183 of US9624274). The amino acid insert may be, but is not limited to, any of the following amino acid sequences, VNLTWSRASG (SEQ ID NO: 50 of US9624274; herein SEQ ID NO: 1375), EFCINHRGYWVCGD (SEQ ID NO:55 of US9624274; herein SEQ ID NO: 1376), EDGQVMDVDLS (SEQ ID NO: 85 of US9624274; herein SEQ ID NO: 1377), EKQRNGTLT (SEQ ID NO: 86 of US9624274; herein SEQ ID NO: 1378), TYQCRVTHPHLPRALMR (SEQ ID NO: 87 of US9624274; herein SEQ ID NO: 1379), RHSTTQPRKTKGSG (SEQ ID NO: 88 of US9624274; herein SEQ ID NO: 1380), DSNPRGVSAYLSR (SEQ ID NO: 89 of US9624274; herein SEQ ID NO: 1381), TITCLWDLAPSK (SEQ ID NO: 90 of US9624274; herein SEQ ID NO: 1382), KTKGSGFFVF (SEQ ID NO: 91 of US9624274; herein SEQ ID NO: 1383), THPHLPRALMRS (SEQ ID NO: 92 of US9624274; herein SEQ ID NO: 1384), GETYQCRVTHPHLPRALMRSTTK (SEQ ID NO: 93 of US9624274; herein SEQ ID NO:

1385), LPRALMRS (SEQ ID NO: 94 of US9624274; herein SEQ ID NO: 1386), INHRGYWV (SEQ ID NO: 95 of US9624274; herein SEQ ID NO: 1387), CDAGSVRTNAPD (SEQ ID NO: 60 of US9624274; herein SEQ ID NO: 1388), AKAVSNLTESRSESLQS (SEQ ID NO: 96 of US9624274; herein SEQ ID NO: 1389), SLTGDEFKKVLET (SEQ ID NO: 97 of US9624274; herein SEQ ID NO: 1390), REAVAYRFEED (SEQ ID NO: 98 of US9624274; herein SEQ ID NO: 1391), INPEIITLDG (SEQ ID NO: 99 of US9624274; herein SEQ ID NO: 1392), DISVTGAPVITATYL (SEQ ID NO: 100 of US9624274; herein SEQ ID NO: 1393), DISVTGAPVITA (SEQ ID NO: 101 of US9624274; herein SEQ ID NO: 1394), PKTVSNLTESSSESVQS (SEQ ID NO: 102 of US9624274; herein SEQ ID NO: 1395), SLMGDEFKAVLET (SEQ ID NO: 103 of US9624274; herein SEQ ID NO: 1396), QHSVAYTFEED (SEQ ID NO: 104 of US9624274; herein SEQ ID NO: 1397), INPEIITRDG (SEQ ID NO: 105 of US9624274; herein SEQ ID NO: 1398), DISLTGDPVITASYL (SEQ ID NO: 106 of US9624274; herein SEQ ID NO: 1399), DISLTGDPVITA (SEQ ID NO: 107 of US9624274; herein SEQ ID NO: 1400), DQSIDFEIDSA (SEQ ID NO: 108 of US9624274; herein SEQ ID NO: 1401), KNVSEDLPLPTFSPTLLGDS (SEQ ID NO: 109 of US9624274; herein SEQ ID NO: 1402), KNVSEDLPLPT (SEQ ID NO: 110 of US9624274; herein SEQ ID NO: 1403), CDSGRVRTDAPD (SEQ ID NO: 111 of US9624274; herein SEQ ID NO: 1404), FPEHLLVDFLQSLS (SEQ ID NO: 112 of US9624274; herein SEQ ID NO: 1405), DAEFRHDSG (SEQ ID NO: 65 of US9624274; herein SEQ ID NO: 1406), HYAAAQWDFGNTMCQL (SEQ ID NO: 113 of US9624274; herein SEQ ID NO: 1407), YAAQWDFGNTMCQ (SEQ ID NO: 114 of US9624274; herein SEQ ID NO: 1408), RSQKEGLHYT (SEQ ID NO: 115 of US9624274; herein SEQ ID NO: 1409), SSRTPSDKPVAHWANPQAE (SEQ ID NO: 116 of US9624274; herein SEQ ID NO: 1410), SRTPSDKPVAHWANP (SEQ ID NO: 117 of US9624274; herein SEQ ID NO: 1411), SSRTPSDKP (SEQ ID NO: 118 of US9624274; herein SEQ ID NO: 1412), NADGNVDYHMNSVP (SEQ ID NO: 119 of US9624274; herein SEQ ID NO: 1413), DGNVDYHMNSV (SEQ ID NO: 120 of US9624274; herein SEQ ID NO: 1414), RSFKEFLQSSLRALRQ (SEQ ID NO: 121 of US9624274; herein SEQ ID NO: 1415); FKEFLQSSLRA (SEQ ID NO: 122 of US9624274; herein SEQ ID NO: 1416), or QMWAPQWGPD (SEQ ID NO: 123 of US9624274; herein SEQ ID NO: 1417).

[0101] In certain embodiments, the AAV serotype may be, or may have a sequence as described in United States Patent No. US 9475845, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV capsid proteins comprising modification of one or more amino acids at amino acid positions 585 to 590 of the native AAV2

capsid protein. Further the modification may result in, but not limited to, the amino acid sequence RGNRQA (SEQ ID NO: 3 of US9475845; herein SEQ ID NO: 1418), SSSTDP (SEQ ID NO: 4 of US9475845; herein SEQ ID NO: 1419), SSNTAP (SEQ ID NO: 5 of US9475845; herein SEQ ID NO: 1420), SNSNLP (SEQ ID NO: 6 of US9475845; herein SEQ ID NO: 1421), SSTTAP (SEQ ID NO: 7 of US9475845; herein SEQ ID NO: 1422), AANTAA (SEQ ID NO: 8 of US9475845; herein SEQ ID NO: 1423), QQNTAP (SEQ ID NO: 9 of US9475845; herein SEQ ID NO: 1424), SAQAQA (SEQ ID NO: 10 of US9475845; herein SEQ ID NO: 1425), QANTGP (SEQ ID NO: 11 of US9475845; herein SEQ ID NO: 1426), NATTAP (SEQ ID NO: 12 of US9475845; herein SEQ ID NO: 1427), SSTAGP (SEQ ID NO: 13 and 20 of US9475845; herein SEQ ID NO: 1428), QQNTAA (SEQ ID NO: 14 of US9475845; herein SEQ ID NO: 1429), PSTAGP (SEQ ID NO: 15 of US9475845; herein SEQ ID NO: 1430), NQNTAP (SEQ ID NO: 16 of US9475845; herein SEQ ID NO: 1431), QAANAP (SEQ ID NO: 17 of US9475845; herein SEQ ID NO: 1432), SIVGLP (SEQ ID NO: 18 of US9475845; herein SEQ ID NO: 1433), AASTAA (SEQ ID NO: 19, and 27 of US9475845; herein SEQ ID NO: 1434), SQNTTA (SEQ ID NO: 21 of US9475845; herein SEQ ID NO: 1435), QQDTAP (SEQ ID NO: 22 of US9475845; herein SEQ ID NO: 1436), QTNTGP (SEQ ID NO: 23 of US9475845; herein SEQ ID NO: 1437), QTNGAP (SEQ ID NO: 24 of US9475845; herein SEQ ID NO: 1438), QQNAAP (SEQ ID NO: 25 of US9475845; herein SEQ ID NO: 1439), or AANTQA (SEQ ID NO: 26 of US9475845; herein SEQ ID NO: 1440). In certain embodiments, the amino acid modification is a substitution at amino acid positions 262 through 265 in the native AAV2 capsid protein or the corresponding position in the capsid protein of another AAV with a targeting sequence. The targeting sequence may be, but is not limited to, any of the amino acid sequences, NGRAHA (SEQ ID NO: 38 of US9475845; herein SEQ ID NO: 1441), QPEHSST (SEQ ID NO: 39 and 50 of US9475845; herein SEQ ID NO: 1442), VNTANST (SEQ ID NO: 40 of US9475845; herein SEQ ID NO: 1443), HGPMQKS (SEQ ID NO: 41 of US9475845; herein SEQ ID NO: 1444), PHKPPLA (SEQ ID NO: 42 of US9475845; herein SEQ ID NO: 1445), IKNNEMW (SEQ ID NO: 43 of US9475845; herein SEQ ID NO: 1446), RNLDTPM (SEQ ID NO: 44 of US9475845; herein SEQ ID NO: 1447), VDSHRQS (SEQ ID NO: 45 of US9475845; herein SEQ ID NO: 1448), YDSKTKT (SEQ ID NO: 46 of US9475845; herein SEQ ID NO: 1449), SQLPHQK (SEQ ID NO: 47 of US9475845; herein SEQ ID NO: 1450), STMQQNT (SEQ ID NO: 48 of US9475845; herein SEQ ID NO: 1451), TERYMTQ (SEQ ID NO: 49 of US9475845; herein SEQ ID NO: 1452), DASLSTS (SEQ ID NO: 51 of US9475845; herein SEQ ID NO: 1453), DLPNKKT (SEQ ID NO: 52 of US9475845; herein SEQ ID NO: 1454), DLTAARL (SEQ ID NO: 53 of US9475845; herein SEQ ID NO: 1455), EPHQFNY (SEQ ID

NO: 54 of US9475845; herein SEQ ID NO: 1456), EPQSNHT (SEQ ID NO: 55 of US9475845; herein SEQ ID NO: 1457), MSSWPSQ (SEQ ID NO: 56 of US9475845; herein SEQ ID NO: 1458), NPKHNAT (SEQ ID NO: 57 of US9475845; herein SEQ ID NO: 1459), PDGMRTT (SEQ ID NO: 58 of US9475845; herein SEQ ID NO: 1460), PNNNKTT (SEQ ID NO: 59 of US9475845; herein SEQ ID NO: 1461), QSTTHDS (SEQ ID NO: 60 of US9475845; herein SEQ ID NO: 1462), TGSKQKQ (SEQ ID NO: 61 of US9475845; herein SEQ ID NO: 1463), SLKHQAL (SEQ ID NO: 62 of US9475845; herein SEQ ID NO: 1464), SPIDGEQ (SEQ ID NO: 63 of US9475845; herein SEQ ID NO: 1465), WIFPWIQL (SEQ ID NO: 64 and 112 of US9475845; herein SEQ ID NO: 1466), CDCRGDCFC (SEQ ID NO: 65 of US9475845; herein SEQ ID NO: 1467), CNGRC (SEQ ID NO: 66 of US9475845; herein SEQ ID NO: 1468), CPRECES (SEQ ID NO: 67 of US9475845; herein SEQ ID NO: 1469), CTTHWGFTLC (SEQ ID NO: 68 and 123 of US9475845; herein SEQ ID NO: 1470), CGRRAGGSC (SEQ ID NO: 69 of US9475845; herein SEQ ID NO: 1471), CKGGRAKDC (SEQ ID NO: 70 of US9475845; herein SEQ ID NO: 1472), CVPELGHEC (SEQ ID NO: 71 and 115 of US9475845; herein SEQ ID NO: 1473), CRRETAWAK (SEQ ID NO: 72 of US9475845; herein SEQ ID NO: 1474), VSWFSHRYSPFAVS (SEQ ID NO: 73 of US9475845; herein SEQ ID NO: 1475), GYRDGYAGPILYN (SEQ ID NO: 74 of US9475845; herein SEQ ID NO: 1476), XXXYXXX (SEQ ID NO: 75 of US9475845; herein SEQ ID NO: 1477), YXNW (SEQ ID NO: 76 of US9475845; herein SEQ ID NO: 1478), RPLPPLP (SEQ ID NO: 77 of US9475845; herein SEQ ID NO: 1479), APPLPPR (SEQ ID NO: 78 of US9475845; herein SEQ ID NO: 1480), DVFYPYPYASGS (SEQ ID NO: 79 of US9475845; herein SEQ ID NO: 1481), MYWYPY (SEQ ID NO: 80 of US9475845; herein SEQ ID NO: 1482), DITWDQLWDLMK (SEQ ID NO: 81 of US9475845; herein SEQ ID NO: 1483), CWDDXWLC (SEQ ID NO: 82 of US9475845; herein SEQ ID NO: 1484), EWCEYLGGYLRCYA (SEQ ID NO: 83 of US9475845; herein SEQ ID NO: 1485), YXCXXGPXTWXCXP (SEQ ID NO: 84 of US9475845; herein SEQ ID NO: 1486), IEGPTLRQWLAARA (SEQ ID NO: 85 of US9475845; herein SEQ ID NO: 1487), LWXXX (SEQ ID NO: 86 of US9475845; herein SEQ ID NO: 1488), XFXXYLW (SEQ ID NO: 87 of US9475845; herein SEQ ID NO: 1489), SSIISHFRWGLCD (SEQ ID NO: 88 of US9475845; herein SEQ ID NO: 1490), MSRPACPPNDKYE (SEQ ID NO: 89 of US9475845; herein SEQ ID NO: 1491), CLRSGRGC (SEQ ID NO: 90 of US9475845; herein SEQ ID NO: 1492), CHWMFSPWC (SEQ ID NO: 91 of US9475845; herein SEQ ID NO: 1493), WXXF (SEQ ID NO: 92 of US9475845; herein SEQ ID NO: 1494), CSSRLDAC (SEQ ID NO: 93 of US9475845; herein SEQ ID NO: 1495), CLPVASC (SEQ ID NO: 94 of US9475845; herein SEQ ID NO: 1496), CGFECVRQCPERC (SEQ ID NO: 95 of US9475845; herein SEQ ID NO:

1497), CVALCREACGEGC (SEQ ID NO: 96 of US9475845; herein SEQ ID NO: 1498), SWCEPGWCR (SEQ ID NO: 97 of US9475845; herein SEQ ID NO: 1499), YSGKWGW (SEQ ID NO: 98 of US9475845; herein SEQ ID NO: 1500), GLSGGRS (SEQ ID NO: 99 of US9475845; herein SEQ ID NO: 1501), LMLPRAD (SEQ ID NO: 100 of US9475845; herein SEQ ID NO: 1502), CSCFRDVCC (SEQ ID NO: 101 of US9475845; herein SEQ ID NO: 1503), CRDVVSVIC (SEQ ID NO: 102 of US9475845; herein SEQ ID NO: 1504), MARSGL (SEQ ID NO: 103 of US9475845; herein SEQ ID NO: 1505), MARAKE (SEQ ID NO: 104 of US9475845; herein SEQ ID NO: 1506), MSRTMS (SEQ ID NO: 105 of US9475845; herein SEQ ID NO: 1507), KCCYSL (SEQ ID NO: 106 of US9475845; herein SEQ ID NO: 1508), MYWGDSHWLQYWYE (SEQ ID NO: 107 of US9475845; herein SEQ ID NO: 1509), MQLPLAT (SEQ ID NO: 108 of US9475845; herein SEQ ID NO: 1510), EWLS (SEQ ID NO: 109 of US9475845; herein SEQ ID NO: 1511), SNEW (SEQ ID NO: 110 of US9475845; herein SEQ ID NO: 1512), TNYL (SEQ ID NO: 111 of US9475845; herein SEQ ID NO: 1513), WDLAWMFRLPVG (SEQ ID NO: 113 of US9475845; herein SEQ ID NO: 1514), CTVALPGGYVRVC (SEQ ID NO: 114 of US9475845; herein SEQ ID NO: 1515), CVAYCIEHHCWTC (SEQ ID NO: 116 of US9475845; herein SEQ ID NO: 1516), CVFAHNYDYLVC (SEQ ID NO: 117 of US9475845; herein SEQ ID NO: 1517), CVFTSNYAFC (SEQ ID NO: 118 of US9475845; herein SEQ ID NO: 1518), VHSPNKK (SEQ ID NO: 119 of US9475845; herein SEQ ID NO: 1519), CRGDGWC (SEQ ID NO: 120 of US9475845; herein SEQ ID NO: 1520), XRGCDX (SEQ ID NO: 121 of US9475845; herein SEQ ID NO: 1521), PXXX (SEQ ID NO: 122 of US9475845; herein SEQ ID NO: 1522), SGKGPRQITAL (SEQ ID NO: 124 of US9475845; herein SEQ ID NO: 1523), AAAAAAAAAXXXXX (SEQ ID NO: 125 of US9475845; herein SEQ ID NO: 1524), VYMSPF (SEQ ID NO: 126 of US9475845; herein SEQ ID NO: 1525), ATWLPPR (SEQ ID NO: 127 of US9475845; herein SEQ ID NO: 1526), HTMYYHHYQHHL (SEQ ID NO: 128 of US9475845; herein SEQ ID NO: 1527), SEVGCRAGPLQWLCEKYFG (SEQ ID NO: 129 of US9475845; herein SEQ ID NO: 1528), CGLLPVGRPDRNVWRWLC (SEQ ID NO: 130 of US9475845; herein SEQ ID NO: 1529), CKGQCDRFKGLPWEC (SEQ ID NO: 131 of US9475845; herein SEQ ID NO: 1530), SGRSA (SEQ ID NO: 132 of US9475845; herein SEQ ID NO: 1531), WGFP (SEQ ID NO: 133 of US9475845; herein SEQ ID NO: 1532), AEPMPHSLNFSQYLWYT (SEQ ID NO: 134 of US9475845; herein SEQ ID NO: 1533), WAYXSP (SEQ ID NO: 135 of US9475845; herein SEQ ID NO: 1534), IELLQAR (SEQ ID NO: 136 of US9475845; herein SEQ ID NO: 1535), AYTKCSRQWRTCMTTH (SEQ ID NO: 137 of US9475845; herein SEQ ID NO: 1536), PQNSKIPGPTFLDPH (SEQ ID NO: 138 of

US9475845; herein SEQ ID NO: 1537), SMEPALPDWWWKMFK (SEQ ID NO: 139 of US9475845; herein SEQ ID NO: 1538), ANTPCGPYTHDCPVKR (SEQ ID NO: 140 of US9475845; herein SEQ ID NO: 1539), TACHQHVRMVRP (SEQ ID NO: 141 of US9475845; herein SEQ ID NO: 1540), VPWMEPAYQRFL (SEQ ID NO: 142 of US9475845; herein SEQ ID NO: 1541), DPRATPGS (SEQ ID NO: 143 of US9475845; herein SEQ ID NO: 1542), FRPNRAQDYNTN (SEQ ID NO: 144 of US9475845; herein SEQ ID NO: 1543), CTKNSYLMC (SEQ ID NO: 145 of US9475845; herein SEQ ID NO: 1544), CXXTXXXGXGC (SEQ ID NO: 146 of US9475845; herein SEQ ID NO: 1545), CPIEDRPMC (SEQ ID NO: 147 of US9475845; herein SEQ ID NO: 1546), HEWSYLAPYPWF (SEQ ID NO: 148 of US9475845; herein SEQ ID NO: 1547), MCPKHPLGC (SEQ ID NO: 149 of US9475845; herein SEQ ID NO: 1548), RMWPSSTVNLSAGRR (SEQ ID NO: 150 of US9475845; herein SEQ ID NO: 1549), SAKTAVSQRVWLPSHRGGEP (SEQ ID NO: 151 of US9475845; herein SEQ ID NO: 1550), KSREHVNNSACPSKRITAAL (SEQ ID NO: 152 of US9475845; herein SEQ ID NO: 1551), EGFR (SEQ ID NO: 153 of US9475845; herein SEQ ID NO: 1552), AGLGVR (SEQ ID NO: 154 of US9475845; herein SEQ ID NO: 1553), GTRQGHTMRLGVSDG (SEQ ID NO: 155 of US9475845; herein SEQ ID NO: 1554), IAGLATPGWSHWLAL (SEQ ID NO: 156 of US9475845; herein SEQ ID NO: 1555), SMSIARL (SEQ ID NO: 157 of US9475845; herein SEQ ID NO: 1556), HTFEPGV (SEQ ID NO: 158 of US9475845; herein SEQ ID NO: 1557), NTSLKRISNKRIRRK (SEQ ID NO: 159 of US9475845; herein SEQ ID NO: 1558), LRIKRKRRKRKKTRK (SEQ ID NO: 160 of US9475845; herein SEQ ID NO: 1559), GGG, GFS, LWS, EGG, LLV, LSP, LBS, AGG, GRR, GGH and GTV.

[0102] In certain embodiments, the AAV serotype may be, or may have a sequence as described in United States Publication No. US 20160369298, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, site-specific mutated capsid protein of AAV2 (SEQ ID NO: 97 of US 20160369298; herein SEQ ID NO: 1560) or variants thereof, wherein the specific site is at least one site selected from sites R447, G453, S578, N587, N587+1, S662 of VP1 or fragment thereof.

[0103] Further, any of the mutated sequences described in US 20160369298, may be or may have, but not limited to, any of the following sequences SDSGASN (SEQ ID NO: 1 and SEQ ID NO: 231 of US20160369298; herein SEQ ID NO: 1561), SPSGASN (SEQ ID NO: 2 of US20160369298; herein SEQ ID NO: 1562), SHSGASN (SEQ ID NO: 3 of US20160369298; herein SEQ ID NO: 1563), SRSGASN (SEQ ID NO: 4 of US20160369298; herein SEQ ID NO: 1564), SKSGASN (SEQ ID NO: 5 of US20160369298; herein SEQ ID NO: 1565), SNSGASN

(SEQ ID NO: 6 of US20160369298; herein SEQ ID NO: 1566), SGSGASN (SEQ ID NO: 7 of US20160369298; herein SEQ ID NO: 1567), SASGASN (SEQ ID NO: 8, 175, and 221 of US20160369298; herein SEQ ID NO: 1568), SESGTSN (SEQ ID NO: 9 of US20160369298; herein SEQ ID NO: 1569), STTGGSN (SEQ ID NO: 10 of US20160369298; herein SEQ ID NO: 1570), SSAGSTN (SEQ ID NO: 11 of US20160369298; herein SEQ ID NO: 1571), NNDSQA (SEQ ID NO: 12 of US20160369298; herein SEQ ID NO: 1572), NNRNQA (SEQ ID NO: 13 of US20160369298; herein SEQ ID NO: 1573), NNNKQA (SEQ ID NO: 14 of US20160369298; herein SEQ ID NO: 1574), NAKRQA (SEQ ID NO: 15 of US20160369298; herein SEQ ID NO: 1575), NDEHQA (SEQ ID NO: 16 of US20160369298; herein SEQ ID NO: 1576), NTSQKA (SEQ ID NO: 17 of US20160369298; herein SEQ ID NO: 1577), YYLSRTNTPSGTDTQSRLVFSQAGA (SEQ ID NO: 18 of US20160369298; herein SEQ ID NO: 1578), YYLSRTNTDSGTETQSGLDFSQAGA (SEQ ID NO: 19 of US20160369298; herein SEQ ID NO: 1579), YYLSRTNTESGTPTQSALEFSQAGA (SEQ ID NO: 20 of US20160369298; herein SEQ ID NO: 1580), YYLSRTNTHSGTHTQSPLHFSQAGA (SEQ ID NO: 21 of US20160369298; herein SEQ ID NO: 1581), YYLSRTNTSSGTITISHLIFSQAGA (SEQ ID NO: 22 of US20160369298; herein SEQ ID NO: 1582), YYLSRTNTRSGIMTKSSLMFSQAGA (SEQ ID NO: 23 of US20160369298; herein SEQ ID NO: 1583), YYLSRTNTKSGRKTLSNLSFSQAGA (SEQ ID NO: 24 of US20160369298; herein SEQ ID NO: 1584), YYLSRTNDGSGPVTPSKLRFSQRGA (SEQ ID NO: 25 of US20160369298; herein SEQ ID NO: 1585), YYLSRTNAASGHATHSDLKFSQPGA (SEQ ID NO: 26 of US20160369298; herein SEQ ID NO: 1586), YYLSRTNGQAGSLTMSELGFSQVGA (SEQ ID NO: 27 of US20160369298; herein SEQ ID NO: 1587), YYLSRTNSTGGNQTTSQLLFSQLSA (SEQ ID NO: 28 of US20160369298; herein SEQ ID NO: 1588), YFLSRTNNNTGLNTNSTLNFSQGRA (SEQ ID NO: 29 of US20160369298; herein SEQ ID NO: 1589), SKTGADNNNSEYSWTG (SEQ ID NO: 30 of US20160369298; herein SEQ ID NO: 1590), SKTDADNNNSEYSWTG (SEQ ID NO: 31 of US20160369298; herein SEQ ID NO: 1591), SKTEADNNNSEYSWTG (SEQ ID NO: 32 of US20160369298; herein SEQ ID NO: 1592), SKTPADNNNSEYSWTG (SEQ ID NO: 33 of US20160369298; herein SEQ ID NO: 1593), SKTHADNNNSEYSWTG (SEQ ID NO: 34 of US20160369298; herein SEQ ID NO: 1594), SKTQADNNNSEYSWTG (SEQ ID NO: 35 of US20160369298; herein SEQ ID NO: 1595), SKTIADNNNSEYSWTG (SEQ ID NO: 36 of US20160369298; herein SEQ ID NO: 1596), SKTMADNNNSEYSWTG (SEQ ID NO: 37 of US20160369298; herein SEQ ID NO: 1597), SKTRADNNNSEYSWTG (SEQ ID NO: 38 of US20160369298; herein SEQ ID NO: 1598), SKTNADNNNSEYSWTG (SEQ ID NO: 39 of

US20160369298; herein SEQ ID NO: 1599), SKTVGRNNNSEYSWTG (SEQ ID NO: 40 of US20160369298; herein SEQ ID NO: 1600), SKTADRNNNSEYSWTG (SEQ ID NO: 41 of US20160369298; herein SEQ ID NO: 1601), SKKLSQNNNSKYSWQG (SEQ ID NO: 42 of US20160369298; herein SEQ ID NO: 1602), SKPTTGNNNSDYSWPG (SEQ ID NO: 43 of US20160369298; herein SEQ ID NO: 1603), STQKNENNNSNYSWPG (SEQ ID NO: 44 of US20160369298; herein SEQ ID NO: 1604), HKDDEGKF (SEQ ID NO: 45 of US20160369298; herein SEQ ID NO: 1605), HKDDNRKF (SEQ ID NO: 46 of US20160369298; herein SEQ ID NO: 1606), HKDDTNKF (SEQ ID NO: 47 of US20160369298; herein SEQ ID NO: 1607), HEDSDKNF (SEQ ID NO: 48 of US20160369298; herein SEQ ID NO: 1608), HRDGADSF (SEQ ID NO: 49 of US20160369298; herein SEQ ID NO: 1609), HGDNKSRF (SEQ ID NO: 50 of US20160369298; herein SEQ ID NO: 1610), KQGSEKTNVDFEEV (SEQ ID NO: 51 of US20160369298; herein SEQ ID NO: 1611), KQGSEKTNVDSEEV (SEQ ID NO: 52 of US20160369298; herein SEQ ID NO: 1612), KQGSEKTNVDVEEV (SEQ ID NO: 53 of US20160369298; herein SEQ ID NO: 1613), KQGSDKTNVDDAGV (SEQ ID NO: 54 of US20160369298; herein SEQ ID NO: 1614), KQGSSKTNVDPREV (SEQ ID NO: 55 of US20160369298; herein SEQ ID NO: 1615), KQGSRKTNVDHKQV (SEQ ID NO: 56 of US20160369298; herein SEQ ID NO: 1616), KQGSKGGNVDTNRV (SEQ ID NO: 57 of US20160369298; herein SEQ ID NO: 1617), KQGSGEANVDNGDV (SEQ ID NO: 58 of US20160369298; herein SEQ ID NO: 1618), KQDAAADNIDYDHV (SEQ ID NO: 59 of US20160369298; herein SEQ ID NO: 1619), KQSGTRSNAAASSV (SEQ ID NO: 60 of US20160369298; herein SEQ ID NO: 1620), KENTNTNDTELTNV (SEQ ID NO: 61 of US20160369298; herein SEQ ID NO: 1621), QRGNNVAATADVNT (SEQ ID NO: 62 of US20160369298; herein SEQ ID NO: 1622), QRGNNEAATADVNT (SEQ ID NO: 63 of US20160369298; herein SEQ ID NO: 1623), QRGNNPAATADVNT (SEQ ID NO: 64 of US20160369298; herein SEQ ID NO: 1624), QRGNNHAATADVNT (SEQ ID NO: 65 of US20160369298; herein SEQ ID NO: 1625), QEENNIAATPGVNT (SEQ ID NO: 66 of US20160369298; herein SEQ ID NO: 1626), QPPNNMAATHEVNT (SEQ ID NO: 67 of US20160369298; herein SEQ ID NO: 1627), QHHNNSAATTIVNT (SEQ ID NO: 68 of US20160369298; herein SEQ ID NO: 1628), QTTNNRAAFNMVET (SEQ ID NO: 69 of US20160369298; herein SEQ ID NO: 1629), QKKNNNAASKKVAT (SEQ ID NO: 70 of US20160369298; herein SEQ ID NO: 1630), QGGNNKAADDAVKT (SEQ ID NO: 71 of US20160369298; herein SEQ ID NO: 1631), QAAKGGAADDAVKT (SEQ ID NO: 72 of US20160369298; herein SEQ ID NO: 1632), QDDRAAAANESVDT (SEQ ID NO: 73 of

US20160369298; herein SEQ ID NO: 1633), QQQHDDAAYQRVHT (SEQ ID NO: 74 of US20160369298; herein SEQ ID NO: 1634), QSSSSLAAVSTVQT (SEQ ID NO: 75 of US20160369298; herein SEQ ID NO: 1635), QNNQTTAAIRNVTT (SEQ ID NO: 76 of US20160369298; herein SEQ ID NO: 1636), NYNKKSDNVDFT (SEQ ID NO: 77 of US20160369298; herein SEQ ID NO: 1637), NYNKKSENVDFT (SEQ ID NO: 78 of US20160369298; herein SEQ ID NO: 1638), NYNKKSLNVDFT (SEQ ID NO: 79 of US20160369298; herein SEQ ID NO: 1639), NYNKKSPNVDFT (SEQ ID NO: 80 of US20160369298; herein SEQ ID NO: 1640), NYSKKSHCVDFT (SEQ ID NO: 81 of US20160369298; herein SEQ ID NO: 1641), NYRKTIYVDFT (SEQ ID NO: 82 of US20160369298; herein SEQ ID NO: 1642), NYKEKKDVHFT (SEQ ID NO: 83 of US20160369298; herein SEQ ID NO: 1643), NYGHRAIVQFT (SEQ ID NO: 84 of US20160369298; herein SEQ ID NO: 1644), NYANHQFVVCT (SEQ ID NO: 85 of US20160369298; herein SEQ ID NO: 1645), NYDDDPTGVLLT (SEQ ID NO: 86 of US20160369298; herein SEQ ID NO: 1646), NYDDPTGVLLT (SEQ ID NO: 87 of US20160369298; herein SEQ ID NO: 1647), NFEQQNSVEWT (SEQ ID NO: 88 of US20160369298; herein SEQ ID NO: 1648), SQSGASN (SEQ ID NO: 89 and SEQ ID NO: 241 of US20160369298; herein SEQ ID NO: 1649), NNGSQA (SEQ ID NO: 90 of US20160369298; herein SEQ ID NO: 1650), YYLSRTNTPSGTTTWSRLQFSQAGA (SEQ ID NO: 91 of US20160369298; herein SEQ ID NO: 1651), SKTSADNNNSEYSWTG (SEQ ID NO: 92 of US20160369298; herein SEQ ID NO: 1652), HKDDEEKF (SEQ ID NO: 93, 209, 214, 219, 224, 234, 239, and 244 of US20160369298; herein SEQ ID NO: 1653), KQGSEKTNVDIEEV (SEQ ID NO: 94 of US20160369298; herein SEQ ID NO: 1654), QRGNNQAATADVNT (SEQ ID NO: 95 of US20160369298; herein SEQ ID NO: 1655), NYNKKSVNVDFT (SEQ ID NO: 96 of US20160369298; herein SEQ ID NO: 1656), SQSGASNYNTPSGTTTQSRLQFSTSADNNNSEYSWTGATKYH (SEQ ID NO: 106 of US20160369298; herein SEQ ID NO: 1657), SASGASNFNSEGGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 107 of US20160369298; herein SEQ ID NO: 1658), SQSGASNYNTPSGTTTQSRLQFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 108 of US20160369298; herein SEQ ID NO: 1659), SASGASNYNTPSGTTTQSRLQFSTSADNNNSEFSWPGATTYH (SEQ ID NO: 109 of US20160369298; herein SEQ ID NO: 1660), SQSGASNFNSEGGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 110 of US20160369298; herein SEQ ID NO: 1661),

SASGASNYNTPSGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 111 of US20160369298; herein SEQ ID NO: 1662), SQSGASNYNTPSGTTTQSRLQFSTSADNNNSDFSWTGATKYH (SEQ ID NO: 112 of US20160369298; herein SEQ ID NO: 1663), SGAGASNFNSEGGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 113 of US20160369298; herein SEQ ID NO: 1664), SGAGASN (SEQ ID NO: 176 of US20160369298; herein SEQ ID NO: 1665), NSEGGSLTQSSLGFS (SEQ ID NO: 177, 185, 193 and 202 of US20160369298; herein SEQ ID NO: 1666), TDGENNNSDFS (SEQ ID NO: 178 of US20160369298; herein SEQ ID NO: 1667), SEFSWPGATT (SEQ ID NO: 179 of US20160369298; herein SEQ ID NO: 1668), TSADNNNSDFSWT (SEQ ID NO: 180 of US20160369298; herein SEQ ID NO: 1669), SQSGASNY (SEQ ID NO: 181, 187, and 198 of US20160369298; herein SEQ ID NO: 1670), NTPSGTTTQSRLQFS (SEQ ID NO: 182, 188, 191, and 199 of US20160369298; herein SEQ ID NO: 1671), TSADNNNSEYSWTGATKYH (SEQ ID NO: 183 of US20160369298; herein SEQ ID NO: 1672), SASGASNF (SEQ ID NO: 184 of US20160369298; herein SEQ ID NO: 1673), TDGENNNSDFSWTGATKYH (SEQ ID NO: 186, 189, 194, 197, and 203 of US20160369298; herein SEQ ID NO: 1674), SASGASNY (SEQ ID NO: 190 and SEQ ID NO: 195 of US20160369298; herein SEQ ID NO: 1675), TSADNNNSEFSWPGATTYH (SEQ ID NO: 192 of US20160369298; herein SEQ ID NO: 1676), NTPSGSLTQSSLGFS (SEQ ID NO: 196 of US20160369298; herein SEQ ID NO: 1677), TSADNNNSDFSWTGATKYH (SEQ ID NO: 200 of US20160369298; herein SEQ ID NO: 1678), SGAGASNF (SEQ ID NO: 201 of US20160369298; herein SEQ ID NO: 1679), CTCCAGVVSVVSMRSRVCVNSGCAGCTDHCVVSRNSGTCVMSACACAA (SEQ ID NO: 204 of US20160369298; herein SEQ ID NO: 1680), CTCCAGAGAGGCAACAGACAAGCAGCTACCGCAGATGTCAACACACAA (SEQ ID NO: 205 of US20160369298; herein SEQ ID NO: 1681), SAAGASN (SEQ ID NO: 206 of US20160369298; herein SEQ ID NO: 1682), YFLSRTNTESGSTTQSTLRFSQAG (SEQ ID NO: 207 of US20160369298; herein SEQ ID NO: 1683), SKTSADNNNSDFS (SEQ ID NO: 208, 228, and 253 of US20160369298; herein SEQ ID NO: 1684), KQGSEKTDVDIDKV (SEQ ID NO: 210 of US20160369298; herein SEQ ID NO: 1685), STAGASN (SEQ ID NO: 211 of US20160369298; herein SEQ ID NO: 1686), YFLSRTNTTSGIETQSTLRFSQAG (SEQ ID NO: 212 and SEQ ID NO: 247 of US20160369298; herein SEQ ID NO: 1687), SKTDGENNNSDFS (SEQ ID NO: 213 and SEQ ID NO: 248 of US20160369298; herein SEQ ID NO: 1688), KQGAAADDVEIDGV (SEQ ID NO: 215 and SEQ ID NO: 250 of US20160369298; herein SEQ ID NO: 1689), SEAGASN (SEQ ID NO: 216 of US20160369298;

herein SEQ ID NO: 1690), YYLSRTNTPSGTTTQSRLQFSQAG (SEQ ID NO: 217, 232 and 242 of US20160369298; herein SEQ ID NO: 1691), SKTSADNNNSEYS (SEQ ID NO: 218, 233, 238, and 243 of US20160369298; herein SEQ ID NO: 1692), KQGSEKTNVDIEKV (SEQ ID NO: 220, 225 and 245 of US20160369298; herein SEQ ID NO: 1693), YFLSRTNDASGSDTKSTLLFSQAG (SEQ ID NO: 222 of US20160369298; herein SEQ ID NO: 1694), STTPSENNNSEYS (SEQ ID NO: 223 of US20160369298; herein SEQ ID NO: 1695), SAAGATN (SEQ ID NO: 226 and SEQ ID NO: 251 of US20160369298; herein SEQ ID NO: 1696), YFLSRTNGEAGSATLSELRFSQAG (SEQ ID NO: 227 of US20160369298; herein SEQ ID NO: 1697), HGDDADRF (SEQ ID NO: 229 and SEQ ID NO: 254 of US20160369298; herein SEQ ID NO: 1698), KQGAEKSDVEVDRV (SEQ ID NO: 230 and SEQ ID NO: 255 of US20160369298; herein SEQ ID NO: 1699), KQDSGGDNIDIDQV (SEQ ID NO: 235 of US20160369298; herein SEQ ID NO: 1700), SDAGASN (SEQ ID NO: 236 of US20160369298; herein SEQ ID NO: 1701), YFLSRTNTEGGHDTQSTLRFSQAG (SEQ ID NO: 237 of US20160369298; herein SEQ ID NO: 1702), KEDGGGSDVAIDEV (SEQ ID NO: 240 of US20160369298; herein SEQ ID NO: 1703), SNAGASN (SEQ ID NO: 246 of US20160369298; herein SEQ ID NO: 1704), and YFLSRTNGEAGSATLSELRFSQPG (SEQ ID NO: 252 of US20160369298; herein SEQ ID NO: 1705). Non-limiting examples of nucleotide sequences that may encode the amino acid mutated sites include the following, AGCVVMDCAGGARSCASCAAC (SEQ ID NO: 97 of US20160369298; herein SEQ ID NO: 1706), AACRACRRSMRSMAGGCA (SEQ ID NO: 98 of US20160369298; herein SEQ ID NO: 1707), CACRRGGACRRCRMSRRSARSTTT (SEQ ID NO: 99 of US20160369298; herein SEQ ID NO: 1708), TATTTCTTGAGCAGAACAAACRVCVVSRSCGGAMNCVHSACGMHSTCAVVSCTTVDS TTTTCTCAGSBCRGSGCG (SEQ ID NO: 100 of US20160369298; herein SEQ ID NO: 1709), TCAAMAMMAVNSRVCSRSAACAACAACAGTRASTTCTCGTGGMMAGGA (SEQ ID NO: 101 of US20160369298; herein SEQ ID NO: 1710), AAGSAARRCRSCRVSRVARVCRATRYCGMSNHCRVMVRSGTC (SEQ ID NO: 102 of US20160369298; herein SEQ ID NO: 1711), CAGVVSVVSMRSRVCVNSGCAGCTDHCVVSRNSGTCVMSACA (SEQ ID NO: 103 of US20160369298; herein SEQ ID NO: 1712), AACTWCRVSVASMVSVHSDDTGTGSWSTKSACT (SEQ ID NO: 104 of US20160369298; herein SEQ ID NO: 1713), TTGTTGAACATCACCACGTGACGCACGTTC (SEQ ID NO: 256 of US20160369298; herein SEQ ID NO: 1714), TCCCCGTGGTTCTACTACATAATGTGGCCG (SEQ ID NO: 257 of US20160369298; herein

SEQ ID NO: 1715), TTCCACACTCCGTTTTGGATAATGTTGAAC (SEQ ID NO: 258 of US20160369298; herein SEQ ID NO: 1716), AGGGACATCCCCAGCTCCATGCTGTGGTCG (SEQ ID NO: 259 of US20160369298; herein SEQ ID NO: 1717), AGGGACAACCCCTCCGACTCGCCCTAATCC (SEQ ID NO: 260 of US20160369298; herein SEQ ID NO: 1718), TCCTAGTAGAAGACACCCTCTCACTGCCCG (SEQ ID NO: 261 of US20160369298; herein SEQ ID NO: 1719), AGTACCATGTACACCCACTCTCCCAGTGCC (SEQ ID NO: 262 of US20160369298; herein SEQ ID NO: 1720), ATATGGACGTTCATGCTGATCACCATACCG (SEQ ID NO: 263 of US20160369298; herein SEQ ID NO: 1721), AGCAGGAGCTCCTTGGCCTCAGCGTGCGAG (SEQ ID NO: 264 of US20160369298; herein SEQ ID NO: 1722), ACAAGCAGCTTCACTATGACAACCACTGAC (SEQ ID NO: 265 of US20160369298; herein SEQ ID NO: 1723), CAGCCTAGGAACTGGCTTCCTGGACCCTGTTACCGCCAGCAGAGAGTCTCAAMAMM AVNSRVCSRSAACAACAACAGTRASTTCTCCTGGMMAGGAGCTACCAAGTACCACC TCAATGGCAGAGACTCTCTGGTGAATCCCGGACCAGCTATGGCAAGCCACRRGGAC RRCRMSRRSARSTTTTTTCCTCAGAGCGGGGTTCTCATCTTTGGGAAGSAARRCRSCR VSRVARVCRATRYCGMSNHCRVMVRSGTCATGATTACAGACGAAGAGGAGATCTGG AC (SEQ ID NO: 266 of US20160369298; herein SEQ ID NO: 1724), TGGGACAATGGCGGTCGTCTCTCAGAGTTKTKKT (SEQ ID NO: 267 of US20160369298; herein SEQ ID NO: 1725), AGAGGACCKKTCCTCGATGGTTCATGGTGGAGTTA (SEQ ID NO: 268 of US20160369298; herein SEQ ID NO: 1726), CCACTTAGGGCCTGGTCGATACCGTTCGGTG (SEQ ID NO: 269 of US20160369298; herein SEQ ID NO: 1727), and TCTCGCCCCAAGAGTAGAAACCCTTCSTTYYG (SEQ ID NO: 270 of US20160369298; herein SEQ ID NO: 1728).

[0104] In some embodiments, the AAV serotype may comprise an ocular cell targeting peptide as described in International Patent Publication WO2016134375, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to SEQ ID NO: 9, and SEQ ID NO:10 of WO2016134375. Further, any of the ocular cell targeting peptides or amino acids described in WO2016134375, may be inserted into any parent AAV serotype, such as, but not limited to, AAV2 (SEQ ID NO:8 of WO2016134375; herein SEQ ID NO: 1729), or AAV9 (SEQ ID NO: 11 of WO2016134375; herein SEQ ID NO: 1730). In some embodiments, modifications, such as insertions are made in AAV2 proteins at P34-A35, T138-A139, A139-P140, G453- T454, N587-R588, and/or R588-Q589. In certain embodiments, insertions are made

at D384, G385, 1560, T561, N562, E563, E564, E565, N704, and/or Y705 of AAV9. The ocular cell targeting peptide may be, but is not limited to, any of the following amino acid sequences, GSTPPPM (SEQ ID NO: 1 of WO2016134375; herein SEQ ID NO: 1731), or GETRAPL (SEQ ID NO: 4 of WO2016134375; herein SEQ ID NO: 1732).

[0105] In some embodiments, the AAV serotype may be modified as described in the United States Publication US 20170145405 the contents of which are herein incorporated by reference in their entirety. AAV serotypes may include, modified AAV2(e.g., modifications at Y444F, Y500F, Y730F and/or S662V), modified AAV3 (e.g., modifications at Y705F, Y731F and/or T492V), and modified AAV6 (e.g., modifications at S663V and/or T492V).

[0106] In some embodiments, the AAV serotype may be modified as described in the International Publication WO2017083722 the contents of which are herein incorporated by reference in their entirety. AAV serotypes may include, AAV1 (Y705+731F+T492V), AAV2 (Y444+500+730F+T491V), AAV3 (Y705+731F), AAV5, AAV 5(Y436+693+719F), AAV6 (VP3 variant Y705F/Y731F/T492V), AAV8 (Y733F), AAV9, AAV9 (VP3 variant Y731F), and AAV10 (Y733F).

[0107] In some embodiments, the AAV serotype may comprise, as described in International Patent Publication WO2017015102, the contents of which are herein incorporated by reference in their entirety, an engineered epitope comprising the amino acids SPAKFA (SEQ ID NO: 24 of WO2017015102; herein SEQ ID NO: 1733) or NKDKLN (SEQ ID NO:2 of WO2017015102; herein SEQ ID NO: 1734). The epitope may be inserted in the region of amino acids 665 to 670 based on the numbering of the VP1 capsid of AAV8 (SEQ ID NO:3 of WO2017015102) and/or residues 664 to 668 of AAV3B (SEQ ID NO:3).

[0108] In certain embodiments, the AAV serotype may be, or may have a sequence as described in International Patent Publication WO2017058892, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV variants with capsid proteins that may comprise a substitution at one or more (e.g., 2, 3, 4, 5, 6, or 7) of amino acid residues 262-268, 370- 379, 451 -459, 472-473, 493-500, 528-534, 547-552, 588- 597, 709-710, 716-722 of AAV1, in any combination, or the equivalent amino acid residues in AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAVrh32.33, bovine AAV or avian AAV. The amino acid substitution may be, but is not limited to, any of the amino acid sequences described in WO2017058892. In certain embodiments, the AAV may comprise an amino acid substitution at residues 256L, 258K, 259Q, 261S, 263A, 264S, 265T, 266G, 272H, 385S, 386Q, S472R, V473D, N500E 547S, 709A, 710N, 716D, 717N, 718N, 720L, A456T, Q457T, N458Q, K459S, T492S, K493A, S586R, S587G, S588N, T589R

and/or 722T of AAV1 (SEQ ID NO: 1 of WO2017058892) in any combination, 244N, 246Q, 248R, 249E, 250I, 251K, 252S, 253G, 254S, 255V, 256D, 263Y, 377E, 378N, 453L, 456R, 532Q, 533P, 535N, 536P, 537G, 538T, 539T, 540A, 541T, 542Y, 543L, 546N, 653V, 654P, 656S, 697Q, 698F, 704D, 705S, 706T, 707G, 708E, 709Y and/or 710R of AAV5 (SEQ ID NO:5 of WO2017058892) in any combination, 248R, 316V, 317Q, 318D, 319S, 443N, 530N, 531S, 532Q 533P, 534A, 535N, 540A, 541 T, 542Y, 543L, 545G, 546N, 697Q, 704D, 706T, 708E, 709Yand/or 710R of AAV5 (SEQ ID NO: 5 of WO2017058892) in any combination, 264S, 266G, 269N, 272H, 457Q, 588S and/or 589I of AAV6 (SEQ ID NO:6 WO2017058892) in any combination, 457T, 459N, 496G, 499N, 500N, 589Q, 590N and/or 592A of AAV8 (SEQ ID NO: 8 WO2017058892) in any combination,451I, 452N, 453G, 454S, 455G, 456Q, 457N and/or 458Q of AAV9 (SEQ ID NO: 9 WO2017058892) in any combination.

[0109] In some embodiments, the AAV may include a sequence of amino acids at positions 155, 156 and 157 of VP1 or at positions 17, 18, 19 and 20 of VP2, as described in International Publication No. WO 2017066764, the contents of which are herein incorporated by reference in their entirety. The sequences of amino acid may be, but not limited to, N-S-S, S-X-S, S-S-Y, N-X-S, N-S-Y, S-X-Y and N-X-Y, where N, X and Y are, but not limited to, independently non-serine, or non-threonine amino acids, wherein the AAV may be, but not limited to AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 and AAV12. In some embodiments, the AAV may include a deletion of at least one amino acid at positions 156, 157 or 158 of VP1 or at positions 19, 20 or 21 of VP2, wherein the AAV may be, but not limited to AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 and AAV12.

[0110] In certain embodiments, the AAV serotype may be as described in Jackson et al (Frontiers in Molecular Neuroscience 9:154 (2016)), the contents of which are herein incorporated by reference in their entirety. In some embodiments, the AAV serotype is PHP.B or AAV9. In some embodiments, the AAV serotype is paired with a synapsin promoter to enhance neuronal transduction, as compared to when more ubiquitous promoters are used (i.e., CBA or CMV).

[0111] In certain embodiments, the AAV may be a serotype generated by Cre-recombination-based AAV targeted evolution (CREATE) as described by Deverman et al., (Nature Biotechnology 34(2):204-209 (2016)), Chan et al., (Nature Neuroscience 20(8):1172-1179 (2017)), and in International Patent Application Publication Nos. WO2015038958 and WO2017100671, the contents of each of which are herein incorporated by reference in their entirety. In certain embodiments, AAV serotypes generated in this manner have improved CNS

transduction and/or neuronal and astrocytic tropism, as compared to other AAV serotypes. As non-limiting examples, the AAV serotype may include a targeting peptide such as, but not limited to, PHP.B, PHP.B2, PHP.B3, PHP.A, PHP.S, PHP.N, G2A12, G2A15, G2A3, G2B4, and G2B5.

[0112] In certain embodiments, the AAV serotype may be as described in Jackson et al (Frontiers in Molecular Neuroscience 9:154 (2016)), the contents of which are herein incorporated by reference in their entirety.

[0113] In some embodiments, the AAV serotype is PHP.B. In some embodiments, the AAV serotype is paired with a synapsin promoter to enhance neuronal transduction, as compared to when more ubiquitous promoters are used (i.e., CBA or CMV).

[0114] In some embodiments, the AAV serotype is PHP.N. In certain embodiments, the AAV serotype is a serotype comprising the AAVPHP.N (PHP.N) peptide, or a variant thereof. In certain embodiments the AAV serotypes is a serotype comprising the AAVPHP.B (PHP.B) peptide, or a variant thereof. In certain embodiments, the AAV serotype is a serotype comprising the AAVPHP.A (PHP.A) peptide, or a variant thereof. In certain embodiments, the AAV serotype is a serotype comprising the PHP.S peptide, or a variant thereof. In certain embodiments, the AAV serotype is a serotype comprising the PHP.B2 peptide, or a variant thereof. In certain embodiments, the AAV serotype is a serotype comprising the PHP.B3 peptide, or a variant thereof. In certain embodiments, the AAV serotype is a serotype comprising the G2B4 peptide, or a variant thereof. In certain embodiments, the AAV serotype is a serotype comprising the G2B5 peptide, or a variant thereof. In certain embodiments the AAV capsid is one that allows for blood brain barrier penetration following intravenous administration.

[0115] In certain embodiments, the AAV serotype may comprise a capsid amino acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of the those described above.

[0116] In certain embodiments, the AAV serotype may comprise a capsid nucleic acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of the those described above.

[0117] In certain embodiments, the initiation codon for translation of the AAV VP1 capsid protein may be CTG, TTG, or GTG as described in US Patent No. US8163543, the contents of which are herein incorporated by reference in its entirety.

[0118] The present disclosure refers to structural capsid proteins (including VP1, VP2 and VP3) which are encoded by capsid (Cap) genes. These capsid proteins form an outer protein structural shell (i.e. capsid) of a viral vector such as AAV. VP capsid proteins synthesized from Cap polynucleotides generally include a methionine as the first amino acid in the peptide sequence (Met1), which is associated with the start codon (AUG or ATG) in the corresponding Cap nucleotide sequence. However, it is common for a first-methionine (Met1) residue or generally any first amino acid (AA1) to be cleaved off after or during polypeptide synthesis by protein processing enzymes such as Met-aminopeptidases. This "Met/AA-clipping" process often correlates with a corresponding acetylation of the second amino acid in the polypeptide sequence (e.g., alanine, valine, serine, threonine, etc.). Met-clipping commonly occurs with VP1 and VP3 capsid proteins but can also occur with VP2 capsid proteins.

[0119] Where the Met/AA-clipping is incomplete, a mixture of one or more (one, two or three) VP capsid proteins comprising the viral capsid may be produced, some of which may include a Met1/AA1 amino acid (Met+/AA+) and some of which may lack a Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-). For further discussion regarding Met/AA-clipping in capsid proteins, see Jin, et al. Direct Liquid Chromatography/Mass Spectrometry Analysis for Complete Characterization of Recombinant Adeno-Associated Virus Capsid Proteins. *Hum Gene Ther Methods*. 2017 Oct. 28(5):255-267; Hwang, et al. N-Terminal Acetylation of Cellular Proteins Creates Specific Degradation Signals. *Science*. 2010 February 19. 327(5968): 973–977; the contents of which are each incorporated herein by reference in its entirety.

[0120] According to the present invention, references to capsid proteins is not limited to either clipped (Met-/AA-) or unclipped (Met+/AA+) and may, in context, refer to independent capsid proteins, viral capsids comprised of a mixture of capsid proteins, and/or polynucleotide sequences (or fragments thereof) which encode, describe, produce or result in capsid proteins of the present disclosure. A direct reference to a "capsid protein" or "capsid polypeptide" (such as VP1, VP2 or VP2) may also comprise VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) as well as corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-).

[0121] Further according to the present disclosure, a reference to a specific SEQ ID NO: (whether a protein or nucleic acid) which comprises or encodes, respectively, one or more capsid

proteins which include a Met1/AA1 amino acid (Met+/AA+) should be understood to teach the VP capsid proteins which lack the Met1/AA1 amino acid as upon review of the sequence, it is readily apparent any sequence which merely lacks the first listed amino acid (whether or not Met1/AA1).

[0122] In certain embodiments, reference to a VP1 polypeptide sequence which is 736 amino acids in length and which includes a "Met1" amino acid (Met+) encoded by the AUG/ATG start codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length and which does not include the "Met1" amino acid (Met-) of the 736 amino acid Met+ sequence. As a second non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length and which includes an "AA1" amino acid (AA1+) encoded by any NNN initiator codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length and which does not include the "AA1" amino acid (AA1-) of the 736 amino acid AA1+ sequence.

[0123] References to viral capsids formed from VP capsid proteins (such as reference to specific AAV capsid serotypes), can incorporate VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA1+), corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA1-clipping (Met-/AA1-), and combinations thereof (Met+/AA1+ and Met-/AA1-).

[0124] In certain embodiments, an AAV capsid serotype can include VP1 (Met+/AA1+), VP1 (Met-/AA1-), or a combination of VP1 (Met+/AA1+) and VP1 (Met-/AA1-). An AAV capsid serotype can also include VP3 (Met+/AA1+), VP3 (Met-/AA1-), or a combination of VP3 (Met+/AA1+) and VP3 (Met-/AA1-); and can also include similar optional combinations of VP2 (Met+/AA1) and VP2 (Met-/AA1-).

Viral Genome Component: Inverted Terminal Repeats (ITRs)

[0125] The AAV particles of the present disclosure comprise a viral genome with at least one ITR region and a payload region. In certain embodiments, the viral genome has two ITRs. These two ITRs flank the payload region at the 5' and 3' ends. The ITRs function as origins of replication comprising recognition sites for replication. ITRs comprise sequence regions which can be complementary and symmetrically arranged. ITRs incorporated into viral genomes of the disclosure may be comprised of naturally occurring polynucleotide sequences or recombinantly derived polynucleotide sequences.

[0126] The ITRs may be derived from the same serotype as the capsid, selected from any of the serotypes listed in Table 1, or a derivative thereof. The ITR may be of a different serotype than the capsid. In certain embodiments, the AAV particle has more than one ITR. In a non-

limiting example, the AAV particle has a viral genome comprising two ITRs. In certain embodiments, the ITRs are of the same serotype as one another. In another embodiment, the ITRs are of different serotypes. Non-limiting examples include zero, one or both of the ITRs having the same serotype as the capsid. In certain embodiments both ITRs of the viral genome of the AAV particle are AAV2 ITRs.

[0127] Independently, each ITR may be about 100 to about 150 nucleotides in length. An ITR may be about 100-105 nucleotides in length, 106-110 nucleotides in length, 111-115 nucleotides in length, 116-120 nucleotides in length, 121-125 nucleotides in length, 126-130 nucleotides in length, 131-135 nucleotides in length, 136-140 nucleotides in length, 141-145 nucleotides in length or 146-150 nucleotides in length. In certain embodiments, the ITRs are 140-142 nucleotides in length. Non-limiting examples of ITR length are 102, 130, 140, 141, 142, 145 nucleotides in length, and those having at least 95% identity thereto.

Viral Genome Component: Promoters

[0128] In certain embodiments, the payload region of the viral genome comprises at least one element to enhance the transgene target specificity and expression (See e.g., Powell et al. Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy, 2015; the contents of which are herein incorporated by reference in its entirety). Non-limiting examples of elements to enhance the transgene target specificity and expression include promoters, endogenous miRNAs, post-transcriptional regulatory elements (PREs), polyadenylation (PolyA) signal sequences and upstream enhancers (USEs), CMV enhancers and introns.

[0129] A person skilled in the art may recognize that expression of the polypeptides of the disclosure in a target cell may require a specific promoter, including but not limited to, a promoter that is species specific, inducible, tissue-specific, or cell cycle-specific (Parr et al., *Nat. Med.* 3:1145-9 (1997); the contents of which are herein incorporated by reference in their entirety).

[0130] In certain embodiments, the promoter is deemed to be efficient when it drives expression of the polypeptide(s) encoded in the payload region of the viral genome of the AAV particle. In certain embodiments, that polypeptide is AADC.

[0131] In certain embodiments, the promoter is a promoter deemed to be efficient when it drives expression in the cell being targeted.

[0132] In certain embodiments, the promoter is a promoter having a tropism for the cell being targeted.

[0133] In certain embodiments, the promoter drives expression of the payload for a period of time in targeted tissues. Expression driven by a promoter may be for a period of 1 hour, 2, hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 3 weeks, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years or more than 10 years. Expression may be for 1-5 hours, 1-12 hours, 1-2 days, 1-5 days, 1-2 weeks, 1-3 weeks, 1-4 weeks, 1-2 months, 1-4 months, 1-6 months, 2-6 months, 3-6 months, 3-9 months, 4-8 months, 6-12 months, 1-2 years, 1-5 years, 2-5 years, 3-6 years, 3-8 years, 4-8 years or 5-10 years. In certain embodiments, the promoter is a weak promoter for sustained expression of a payload in nervous tissues.

[0134] In certain embodiments, the promoter drives expression of the polypeptides of the disclosure for at least 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, 15 years, 16 years, 17 years, 18 years, 19 years, 20 years, 21 years, 22 years, 23 years, 24 years, 25 years, 26 years, 27 years, 28 years, 29 years, 30 years, 31 years, 32 years, 33 years, 34 years, 35 years, 36 years, 37 years, 38 years, 39 years, 40 years, 41 years, 42 years, 43 years, 44 years, 45 years, 46 years, 47 years, 48 years, 49 years, 50 years, 55 years, 60 years, 65 years, or more than 65 years.

[0135] Promoters may be naturally occurring or non-naturally occurring. Non-limiting examples of promoters include viral promoters, plant promoters and mammalian promoters. In some embodiments, the promoters may be human promoters. In some embodiments, the promoter may be truncated.

[0136] Promoters which drive or promote expression in most tissues include, but are not limited to, human elongation factor 1α-subunit (EF1α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β-actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC). Tissue-specific expression elements can be used to restrict expression to certain cell types such as, but not limited to, muscle specific promoters, B cell promoters, monocyte promoters, leukocyte promoters, macrophage promoters, pancreatic acinar cell promoters, endothelial cell promoters, lung tissue promoters, astrocyte promoters, or nervous

system promoters which can be used to restrict expression to neurons, astrocytes, or oligodendrocytes.

[0137] Non-limiting examples of muscle-specific promoters include mammalian muscle creatine kinase (MCK) promoter, mammalian desmin (DES) promoter, mammalian troponin I (TNNI2) promoter, and mammalian skeletal alpha-actin (ASKA) promoter (see, e.g. U.S. Patent Publication US 20110212529, the contents of which are herein incorporated by reference in their entirety)

[0138] Non-limiting examples of tissue-specific expression elements for neurons include neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF-β), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β-globin minigene nβ2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2) promoters. Non-limiting examples of tissue-specific expression elements for astrocytes include glial fibrillary acidic protein (GFAP) and EAAT2 promoters. A non-limiting example of a tissue-specific expression element for oligodendrocytes includes the myelin basic protein (MBP) promoter.

[0139] In certain embodiments, the promoter may be less than 1 kb. The promoter may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800 or more than 800 nucleotides. The promoter may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800 or 700-800.

[0140] In certain embodiments, the promoter may be a combination of two or more components of the same or different starting or parental promoters such as, but not limited to, CMV and CBA. Each component may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800 or more than 800. Each component may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800 or 700-800.

In certain embodiments, the promoter is a combination of a 382 nucleotide CMV-enhancer sequence and a 260 nucleotide CBA-promoter sequence.

[0141] In certain embodiments, the viral genome comprises a ubiquitous promoter. Non-limiting examples of ubiquitous promoters include CMV, CBA (including derivatives CAG, CBh, etc.), EF-1α, PGK, UBC, GUSB (hGBp), and UCOE (promoter of HNRPA2B1-CBX3).

[0142] Yu et al. (Molecular Pain 2011, 7:63; the contents of which are herein incorporated by reference in their entirety) evaluated the expression of eGFP under the CAG, EFIα, PGK and UBC promoters in rat DRG cells and primary DRG cells using lentiviral vectors and found that UBC showed weaker expression than the other 3 promoters and only 10-12% glial expression was seen for all promoters. Soderblom et al. (E. Neuro 2015; the contents of which are herein incorporated by reference in its entirety) evaluated the expression of eGFP in AAV8 with CMV and UBC promoters and AAV2 with the CMV promoter after injection in the motor cortex. Intranasal administration of a plasmid containing a UBC or EFIα promoter showed a sustained airway expression greater than the expression with the CMV promoter (See e.g., Gill et al., Gene Therapy 2001, Vol. 8, 1539-1546; the contents of which are herein incorporated by reference in their entirety). Husain et al. (Gene Therapy 2009; the contents of which are herein incorporated by reference in its entirety) evaluated an HβH construct with a hGUSB promoter, a HSV-1LAT promoter and an NSE promoter and found that the HβH construct showed weaker expression than NSE in mouse brain. Passini and Wolfe (J. Virol. 2001, 12382-12392, the contents of which are herein incorporated by reference in its entirety) evaluated the long term effects of the HβH vector following an intraventricular injection in neonatal mice and found that there was sustained expression for at least 1 year. Low expression in all brain regions was found by Xu et al. (Gene Therapy 2001, 8, 1323-1332; the contents of which are herein incorporated by reference in their entirety) when NFL and NFH promoters were used as compared to the CMV-lacZ, CMV-luc, EF, GFAP, hENK, nAChR, PPE, PPE + wpre, NSE (0.3 kb), NSE (1.8 kb) and NSE (1.8 kb + wpre). Xu et al. found that the promoter activity in descending order was NSE (1.8 kb), EF, NSE (0.3 kb), GFAP, CMV, hENK, PPE, NFL and NFH. NFL is a 650 nucleotide promoter and NFH is a 920 nucleotide promoter which are both absent in the liver but NFH is abundant in the sensory proprioceptive neurons, brain and spinal cord and NFH is present in the heart. SCN8A is a 470 nucleotide promoter which expresses throughout the DRG, spinal cord and brain with particularly high expression seen in the hippocampal neurons and cerebellar Purkinje cells, cortex, thalamus and hypothalamus (See e.g., Drews et al. *Identification of evolutionary conserved, functional noncoding elements in the promoter region of the sodium channel gene SCN8A,* Mamm Genome (2007) 18:723-731; and Raymond et al. *Expression of*

Alternatively Spliced Sodium Channel α-subunit genes, Journal of Biological Chemistry (2004) 279(44) 46234-46241; the contents of each of which are herein incorporated by reference in their entireties).

[0143] Any of promoters taught by the aforementioned Yu, Soderblom, Gill, Husain, Passini, Xu, Drews or Raymond may be used in the present disclosures.

[0144] In certain embodiments, the promoter is not cell specific.

[0145] In certain embodiments, the promoter is an ubiquitin c (UBC) promoter. The UBC promoter may have a size of 300-350 nucleotides. In certain embodiments, the UBC promoter is 332 nucleotides.

[0146] In certain embodiments, the promoter is a β-glucuronidase (GUSB) promoter. The GUSB promoter may have a size of 350-400 nucleotides. In certain embodiments, the GUSB promoter is 378 nucleotides.

[0147] In certain embodiments, the promoter is a neurofilament light (NFL) promoter. The NFL promoter may have a size of 600-700 nucleotides. In certain embodiments, the NFL promoter is 650 nucleotides.

[0148] In certain embodiments, the promoter is a neurofilament heavy (NFH) promoter. The NFH promoter may have a size of 900-950 nucleotides. In certain embodiments, the NFH promoter is 920 nucleotides.

[0149] In certain embodiments, the promoter is a SCN8A promoter. The SCN8A promoter may have a size of 450-500 nucleotides. In certain embodiments, the SCN8A promoter is 470 nucleotides.

[0150] In certain embodiments, the promoter is a frataxin (FXN) promoter. The FXN promoter may also be referred to as the FRDA promoter.

[0151] In certain embodiments, the promoter is a phosphoglycerate kinase 1 (PGK) promoter.

[0152] In certain embodiments, the promoter is a chicken β-actin (CBA) promoter.

[0153] In certain embodiments, the promoter is a cytomegalovirus (CMV) promoter.

[0154] In certain embodiments, the promoter is a H1 promoter.

[0155] In certain embodiments, the promoter is an engineered promoter.

[0156] In certain embodiments, the promoter is a liver or a skeletal muscle promoter. Non-limiting examples of liver promoters include human α-1-antitrypsin (hAAT) and thyroxine binding globulin (TBG). Non-limiting examples of skeletal muscle promoters include Desmin, MCK or synthetic C5-12.

[0157] In certain embodiments, the promoter is a RNA pol III promoter. In certain embodiments, the RNA pol III promoter is U6. In certain embodiments, the RNA pol III promoter is H1.

[0158] In certain embodiments, the viral genome comprises two promoters. In certain embodiments, the promoters are an EF1α promoter and a CMV promoter.

[0159] In certain embodiments, the viral genome comprises an enhancer element, a promoter and/or a 5'UTR intron. The enhancer element, also referred to herein as an "enhancer," may be, but is not limited to, a CMV enhancer, the promoter may be, but is not limited to, a CMV, CBA, UBC, GUSB, NSE, Synapsin, MeCP2, and GFAP promoter and the 5'UTR/intron may be, but is not limited to, SV40, and CBA-MVM. In certain embodiments, the enhancer, promoter and/or intron used in combination may be: (1) CMV enhancer, CMV promoter, SV40 5'UTR intron; (2) CMV enhancer, CBA promoter, SV 40 5'UTR intron; (3) CMV enhancer, CBA promoter, CBA-MVM 5'UTR intron; (4) UBC promoter; (5) GUSB promoter; (6) NSE promoter; (7) Synapsin promoter; (8) MeCP2 promoter and (9) GFAP promoter.

[0160] In certain embodiments, the viral genome comprises an engineered promoter.

[0161] In another embodiment, the viral genome comprises a promoter from a naturally expressed protein.

[0162] In certain embodiments, a region located approximately ~5 kb upstream of the first exon of the payload in order to allow for expression of the payload with the promoter. (See e.g., Puspasari et al. *Long Range Regulation of Human FXN Gene Expression,* PLOS ONE, 2011; the contents of which is herein incorporated by reference in its entirety; a 17 bp region located approximately 4.9 kb upstream of the first exon of the frataxin gene in order to allow for expression with the FRDA promoter).

[0163] In certain embodiments, the vector genome may comprise a promoter such as, but not limited to, CMV or U6. In certain embodiments, the promoter for the AAV particles comprising the payload of the present disclosure is a CMV promoter. In certain embodiments, the promoter for the AAV particles comprising the payload of the present disclosure is a U6 promoter.

[0164] In certain embodiments, the vector genome may comprise a CMV and a U6 promoter.

[0165] In certain embodiments, the vector genome may comprise a CBA promoter.

Viral Genome Component: Untranslated Regions (UTRs)

[0166] By definition, wild type untranslated regions (UTRs) of a gene are transcribed but not translated. Generally, the 5' UTR starts at the transcription start site and ends at the start codon and the 3' UTR starts immediately following the stop codon and continues until the termination signal for transcription.

[0167] Features typically found in abundantly expressed genes of specific target organs may be engineered into UTRs to enhance the stability and protein production. In certain embodiments, a 5' UTR from mRNA normally expressed in the liver (e.g., albumin, serum amyloid A, Apolipoprotein A/B/E, transferrin, alpha fetoprotein, erythropoietin, or Factor VIII) may be used in the viral genomes of the AAV particles of the disclosure to enhance expression in hepatic cell lines or liver.

[0168] While not wishing to be bound by theory, wild-type 5′ untranslated regions (UTRs) include features which play roles in translation initiation. Kozak sequences, which are commonly known to be involved in the process by which the ribosome initiates translation of many genes, are usually included in 5' UTRs. Kozak sequences have the consensus CCR(A/G)CCAUGG, where R is a purine (adenine or guanine) three bases upstream of the start codon (ATG), which is followed by another 'G'.

[0169] In certain embodiments, the 5'UTR in the viral genome includes a Kozak sequence.

[0170] In certain embodiments, the 5'UTR in the viral genome does not include a Kozak sequence.

[0171] While not wishing to be bound by theory, wild-type 3′ UTRs are known to have stretches of Adenosines and Uridines embedded therein. These AU rich signatures are particularly prevalent in genes with high rates of turnover. Based on their sequence features and functional properties, the AU rich elements (AREs) can be separated into three classes (Chen et al, 1995, the contents of which are herein incorporated by reference in its entirety): Class I AREs, such as, but not limited to, c-Myc and MyoD, contain several dispersed copies of an AUUUA motif within U-rich regions. Class II AREs, such as, but not limited to, GM-CSF and TNF-a, possess two or more overlapping UUAUUUA(U/A)(U/A) nonamers. Class III ARES, such as, but not limited to, c-Jun and Myogenin, are less well defined. These U rich regions do not contain an AUUUA motif. Most proteins binding to the AREs are known to destabilize the messenger, whereas members of the ELAV family, most notably HuR, have been documented to increase the stability of mRNA. HuR binds to AREs of all the three classes. Engineering the HuR specific binding sites into the 3′ UTR of nucleic acid molecules will lead to HuR binding and thus, stabilization of the message *in vivo*.

[0172] Introduction, removal or modification of 3′ UTR AU rich elements (AREs) can be used to modulate the stability of polynucleotides. When engineering specific polynucleotides, e.g., payload regions of viral genomes, one or more copies of an ARE can be introduced to make polynucleotides less stable and thereby curtail translation and decrease production of the

resultant protein. Likewise, AREs can be identified and removed or mutated to increase the intracellular stability and thus increase translation and production of the resultant protein.

[0173] In certain embodiments, the 3' UTR of the viral genome may include an oligo(dT) sequence for templated addition of a poly-A tail.

[0174] In certain embodiments, the viral genome may include at least one miRNA seed, binding site or full sequence. microRNAs (or miRNA or miR) are 19-25 nucleotide noncoding RNAs that bind to the sites of nucleic acid targets and down-regulate gene expression either by reducing nucleic acid molecule stability or by inhibiting translation. A microRNA sequence comprises a "seed" region, i.e., a sequence in the region of positions 2-8 of the mature microRNA, which sequence has perfect Watson-Crick complementarity to the miRNA target sequence of the nucleic acid.

[0175] In certain embodiments, the viral genome may be engineered to include, alter or remove at least one miRNA binding site, sequence or seed region.

[0176] Any UTR from any gene known in the art may be incorporated into the viral genome of the AAV particle. These UTRs, or portions thereof, may be placed in the same orientation as in the gene from which they were selected or they may be altered in orientation or location. In certain embodiments, the UTR used in the viral genome of the AAV particle may be inverted, shortened, lengthened, made with one or more other 5′ UTRs or 3′ UTRs known in the art. As used herein, the term "altered" as it relates to a UTR, means that the UTR has been changed in some way in relation to a reference sequence. For example, a 3′ or 5′ UTR may be altered relative to a wild type or native UTR by the change in orientation or location as taught above or may be altered by the inclusion of additional nucleotides, deletion of nucleotides, swapping or transposition of nucleotides.

[0177] In certain embodiments, the viral genome of the AAV particle comprises at least one artificial UTRs which is not a variant of a wild type UTR.

[0178] In certain embodiments, the viral genome of the AAV particle comprises UTRs which have been selected from a family of transcripts whose proteins share a common function, structure, feature or property.

Viral Genome Component: Polyadenylation Sequence

[0179] In certain embodiments, the viral genome of the AAV particles of the present disclosure comprise at least one polyadenylation sequence. The viral genome of the AAV particle may comprise a polyadenylation sequence between the 3' end of the payload coding sequence and the 5' end of the 3'ITR.

[0180] In certain embodiments, the polyadenylation sequence or "polyA sequence" may range from absent to about 500 nucleotides in length. The polyadenylation sequence may be, but is not limited to, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, and 500 nucleotides in length.

[0181] In certain embodiments, the polyadenylation sequence is 50-100 nucleotides in length.

[0182] In certain embodiments, the polyadenylation sequence is 50-150 nucleotides in length.

[0183] In certain embodiments, the polyadenylation sequence is 50-160 nucleotides in length.

[0184] In certain embodiments, the polyadenylation sequence is 50-200 nucleotides in length.

[0185] In certain embodiments, the polyadenylation sequence is 60-100 nucleotides in length.

[0186] In certain embodiments, the polyadenylation sequence is 60-150 nucleotides in length.

[0187] In certain embodiments, the polyadenylation sequence is 60-160 nucleotides in length.

[0188] In certain embodiments, the polyadenylation sequence is 60-200 nucleotides in length.

[0189] In certain embodiments, the polyadenylation sequence is 70-100 nucleotides in length.

[0190] In certain embodiments, the polyadenylation sequence is 70-150 nucleotides in length.

[0191] In certain embodiments, the polyadenylation sequence is 70-160 nucleotides in length.

[0192] In certain embodiments, the polyadenylation sequence is 70-200 nucleotides in length.

[0193] In certain embodiments, the polyadenylation sequence is 80-100 nucleotides in length.

[0194] In certain embodiments, the polyadenylation sequence is 80-150 nucleotides in length.

[0195] In certain embodiments, the polyadenylation sequence is 80-160 nucleotides in length.

[0196] In certain embodiments, the polyadenylation sequence is 80-200 nucleotides in length.

[0197] In certain embodiments, the polyadenylation sequence is 90-100 nucleotides in length.

[0198] In certain embodiments, the polyadenylation sequence is 90-150 nucleotides in length.

[0199] In certain embodiments, the polyadenylation sequence is 90-160 nucleotides in length.

[0200] In certain embodiments, the polyadenylation sequence is 90-200 nucleotides in length.

Viral Genome Component: Introns

[0201] In certain embodiments, the payload region comprises at least one element to enhance the expression such as one or more introns or portions thereof. Non-limiting examples of introns include, MVM (67-97 bps), F.IX truncated intron 1 (300 bps), β-globin SD/immunoglobulin heavy chain splice acceptor (250 bps), adenovirus splice donor/immunoglobin splice acceptor (500 bps), SV40 late splice donor/splice acceptor (19S/16S) (180 bps) and hybrid adenovirus splice donor/IgG splice acceptor (230 bps).

[0202] In certain embodiments, the intron or intron portion may be 100-500 nucleotides in length. The intron may have a length of 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500. The intron may have a length between 80-100, 80-120, 80-140, 80-160, 80-180, 80-200, 80-250, 80-300, 80-350, 80-400, 80-450, 80-500, 200-300, 200-400, 200-500, 300-400, 300-500, or 400-500.

[0203] In certain embodiments, the vector genome comprises at least one element to enhance the transgene target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, 2015; the contents of which are herein incorporated by reference in its entirety) such as an intron. Non-limiting examples of introns include, MVM (67-97 bps), F.IX truncated intron 1 (300 bps), β-globin SD/immunoglobulin heavy chain splice acceptor (250 bps), adenovirus splice

donor/immunoglobin splice acceptor (500 bps), SV40 late splice donor/splice acceptor (19S/16S) (180 bps) and hybrid adenovirus splice donor/IgG splice acceptor (230 bps).

[0204] In certain embodiments, the intron may be 100-500 nucleotides in length. The intron may have a length of 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500. The intron may have a length between 80-100, 80-120, 80-140, 80-160, 80-180, 80-200, 80-250, 80-300, 80-350, 80-400, 80-450, 80-500, 200-300, 200-400, 200-500, 300-400, 300-500, or 400-500.

Viral Genome Component: Filler Sequence

[0205] In certain embodiments, the viral genome comprises one or more filler sequences.

[0206] In certain embodiments, the viral genome comprises one or more filler sequences in order to have the length of the viral genome be the optimal size for packaging. In certain embodiments, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 2.3 kb. In certain embodiments, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 4.6 kb.

[0207] In certain embodiments, the viral genome is a single stranded (ss) viral genome and comprises one or more filler sequences which have a length about between 0.1 kb - 3.8 kb, such as, but not limited to, 0.1 kb, 0.2 kb, 0.3 kb, 0.4 kb, 0.5 kb, 0.6 kb, 0.7 kb, 0.8 kb, 0.9 kb, 1 kb, 1.1 kb, 1.2 kb, 1.3 kb, 1.4 kb, 1.5 kb, 1.6 kb, 1.7 kb, 1.8 kb, 1.9 kb, 2 kb, 2.1 kb, 2.2 kb, 2.3 kb, 2.4 kb, 2.5 kb, 2.6 kb, 2.7 kb, 2.8 kb, 2.9 kb, 3 kb, 3.1 kb, 3.2 kb, 3.3 kb, 3.4 kb, 3.5 kb, 3.6 kb, 3.7 kb, or 3.8 kb. In certain embodiments, the total length filler sequence in the vector genome is 3.1 kb. In certain embodiments, the total length filler sequence in the vector genome is 2.7 kb. In certain embodiments, the total length filler sequence in the vector genome is 0.8 kb. In certain embodiments, the total length filler sequence in the vector genome is 0.4 kb. In certain embodiments, the length of each filler sequence in the vector genome is 0.8 kb. In certain embodiments, the length of each filler sequence in the vector genome is 0.4 kb.

[0208] In certain embodiments, the viral genome is a self-complementary (sc) viral genome and comprises one or more filler sequences which have a length about between 0.1 kb – 1.5 kb, such as, but not limited to, 0.1 kb, 0.2 kb, 0.3 kb, 0.4 kb, 0.5 kb, 0.6 kb, 0.7 kb, 0.8 kb, 0.9 kb, 1 kb, 1.1 kb, 1.2 kb, 1.3 kb, 1.4 kb, or 1.5 kb. In certain embodiments, the total length filler sequence in the vector genome is 0.8 kb. In certain embodiments, the total length filler sequence in the vector genome is 0.4 kb. In certain embodiments, the length of each filler sequence in the

vector genome is 0.8 kb. In certain embodiments, the length of each filler sequence in the vector genome is 0.4 kb

[0209] In certain embodiments, the viral genome comprises any portion of a filler sequence. The viral genome may comprise 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of a filler sequence.

[0210] In certain embodiments, the viral genome is a single stranded (ss) viral genome and comprises one or more filler sequences in order to have the length of the viral genome be about 4.6 kb. In certain embodiments, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the 5' ITR sequence. In certain embodiments, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to a promoter sequence. In certain embodiments, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the polyadenylation signal sequence. In certain embodiments, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to the 3' ITR sequence. In certain embodiments, the viral genome comprises at least one filler sequence, and the filler sequence is located between two intron sequences. In certain embodiments, the viral genome comprises at least one filler sequence, and the filler sequence is located within an intron sequence. In certain embodiments, the viral genome comprises two filler sequences, and the first filler sequence is located 3' to the 5' ITR sequence and the second filler sequence is located 3' to the polyadenylation signal sequence. In certain embodiments, the viral genome comprises two filler sequences, and the first filler sequence is located 5' to a promoter sequence and the second filler sequence is located 3' to the polyadenylation signal sequence. In certain embodiments, the viral genome comprises two filler sequences, and the first filler sequence is located 3' to the 5' ITR sequence and the second filler sequence is located 5' to the 5' ITR sequence.

[0211] In certain embodiments, the viral genome is a self-complementary (sc) viral genome and comprises one or more filler sequences in order to have the length of the viral genome be about 2.3 kb. In certain embodiments, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the 5' ITR sequence. In certain embodiments, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to a promoter sequence. In certain embodiments, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the polyadenylation signal sequence. In certain embodiments, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to the 3' ITR sequence. In certain embodiments, the viral genome comprises at least one filler

sequence, and the filler sequence is located between two intron sequences. In certain embodiments, the viral genome comprises at least one filler sequence, and the filler sequence is located within an intron sequence. In certain embodiments, the viral genome comprises two filler sequences, and the first filler sequence is located 3' to the 5' ITR sequence and the second filler sequence is located 3' to the polyadenylation signal sequence. In certain embodiments, the viral genome comprises two filler sequences, and the first filler sequence is located 5' to a promoter sequence and the second filler sequence is located 3' to the polyadenylation signal sequence. In certain embodiments, the viral genome comprises two filler sequences, and the first filler sequence is located 3' to the 5' ITR sequence and the second filler sequence is located 5' to the 5' ITR sequence.

[0212] In certain embodiments, the viral genome may comprise one or more filler sequences between one of more regions of the viral genome. In certain embodiments, the filler region may be located before a region such as, but not limited to, a payload region, an inverted terminal repeat (ITR), a promoter region, an intron region, an enhancer region, a polyadenylation signal sequence region, a multiple cloning site (MCS) region, and/or an exon region. In certain embodiments, the filler region may be located after a region such as, but not limited to, a payload region, an inverted terminal repeat (ITR), a promoter region, an intron region, an enhancer region, a polyadenylation signal sequence region, a multiple cloning site (MCS) region, and/or an exon region. In certain embodiments, the filler region may be located before and after a region such as, but not limited to, a payload region, an inverted terminal repeat (ITR), a promoter region, an intron region, an enhancer region, a polyadenylation signal sequence region, a multiple cloning site (MCS) region, and/or an exon region.

[0213] In certain embodiments, the viral genome may comprise one or more filler sequences which bifurcates at least one region of the viral genome. The bifurcated region of the viral genome may comprise 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of the of the region to the 5' of the filler sequence region. In certain embodiments, the filler sequence may bifurcate at least one region so that 10% of the region is located 5' to the filler sequence and 90% of the region is located 3' to the filler sequence. In certain embodiments, the filler sequence may bifurcate at least one region so that 20% of the region is located 5' to the filler sequence and 80% of the region is located 3' to the filler sequence. In certain embodiments, the filler sequence may bifurcate at least one region so that 30% of the region is located 5' to the filler sequence and 70% of the region is located 3' to the filler sequence. In certain embodiments, the filler sequence may bifurcate at least one region so that 40% of the region is located 5' to the filler sequence and 60%

of the region is located 3' to the filler sequence. In certain embodiments, the filler sequence may bifurcate at least one region so that 50% of the region is located 5' to the filler sequence and 50% of the region is located 3' to the filler sequence. In certain embodiments, the filler sequence may bifurcate at least one region so that 60% of the region is located 5' to the filler sequence and 40% of the region is located 3' to the filler sequence. In certain embodiments, the filler sequence may bifurcate at least one region so that 70% of the region is located 5' to the filler sequence and 30% of the region is located 3' to the filler sequence. In certain embodiments, the filler sequence may bifurcate at least one region so that 80% of the region is located 5' to the filler sequence and 20% of the region is located 3' to the filler sequence. In certain embodiments, the filler sequence may bifurcate at least one region so that 90% of the region is located 5' to the filler sequence and 10% of the region is located 3' to the filler sequence.

[0214] In certain embodiments, the viral genome comprises a filler sequence after the 5' ITR.

[0215] In certain embodiments, the viral genome comprises a filler sequence after the promoter region. In certain embodiments, the viral genome comprises a filler sequence after the payload region. In certain embodiments, the viral genome comprises a filler sequence after the intron region. In certain embodiments, the viral genome comprises a filler sequence after the enhancer region. In certain embodiments, the viral genome comprises a filler sequence after the polyadenylation signal sequence region. In certain embodiments, the viral genome comprises a filler sequence after the MCS region. In certain embodiments, the viral genome comprises a filler sequence after the exon region.

[0216] In certain embodiments, the viral genome comprises a filler sequence before the promoter region. In certain embodiments, the viral genome comprises a filler sequence before the payload region. In certain embodiments, the viral genome comprises a filler sequence before the intron region. In certain embodiments, the viral genome comprises a filler sequence before the enhancer region. In certain embodiments, the viral genome comprises a filler sequence before the polyadenylation signal sequence region. In certain embodiments, the viral genome comprises a filler sequence before the MCS region. In certain embodiments, the viral genome comprises a filler sequence before the exon region.

[0217] In certain embodiments, the viral genome comprises a filler sequence before the 3' ITR.

[0218] In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the promoter region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the payload region. In certain embodiments, a filler sequence may be located between two regions,

such as, but not limited to, the 5' ITR and the intron region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the enhancer region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the polyadenylation signal sequence region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the MCS region.

[0219] In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the exon region.

[0220] In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the payload region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the intron region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the enhancer region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the polyadenylation signal sequence region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the MCS region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the exon region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the 3' ITR.

[0221] In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the intron region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the enhancer region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the polyadenylation signal sequence region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the MCS region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the exon region.

[0222] In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the 3' ITR.

[0223] In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the enhancer region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the intron region and

the polyadenylation signal sequence region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the MCS region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the exon region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the 3' ITR. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the polyadenylation signal sequence region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the MCS region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the exon region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the 3' ITR.

[0224] In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the polyadenylation signal sequence region and the MCS region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the polyadenylation signal sequence region and the exon region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the polyadenylation signal sequence region and the 3' ITR.

[0225] In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the MCS region and the exon region. In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the MCS region and the 3' ITR.

[0226] In certain embodiments, a filler sequence may be located between two regions, such as, but not limited to, the exon region and the 3' ITR.

[0227] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and payload region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second

filler sequence may be located between the promoter region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may

comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the exon region and 3' ITR.

[0228] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler

sequence may be located between the promoter region and payload region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler

sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be

located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the exon region and 3' ITR.

[0229] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and payload region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the

first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain

embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the exon region and 3' ITR.

[0230] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and payload region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first

filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the enhancer

region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the exon region and 3' ITR.

[0231] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and payload region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence

region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and

polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a

viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[0232] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and payload region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located

between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a

viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[0233] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and payload region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the

5' ITR and exon region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the

first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[0234] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the

first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be

located between the promoter region and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the exon region and 3' ITR.

[0235] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter

region and intron region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be

located between the promoter region and intron region, and the second filler sequence may be located between the exon region and 3' ITR.

[0236] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the

promoter region and enhancer region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the exon region and 3' ITR.

[0237] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first

filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be

located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[0238] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the

promoter region and exon region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the

polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[0239] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located

between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the MCS region

and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[0240] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and intron region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the

first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the exon region and 3' ITR.

[0241] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be

located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the MCS region

and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the exon region and 3' ITR.

[0242] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon

region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the exon region and 3' ITR.

[0243] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the

payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[0244] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload

region and MCS region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[0245] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler

sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the MCS region

and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[0246] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and enhancer region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region.

In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the exon region and 3' ITR.

[0247] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and

3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the exon region and 3' ITR.

[0248] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and exon region. In

certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[0249] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[0250] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the enhancer region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[0251] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the enhancer region and MCS region. In certain

embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the enhancer region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the enhancer region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the exon region and 3' ITR.

[0252] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second

filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[0253] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[0254] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler

sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[0255] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the exon region and 3' ITR.

[0256] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and MCS region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[0257] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and exon region, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[0258] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and 3' ITR, and the second filler sequence may be located between the MCS region and exon region. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and 3' ITR, and the second filler sequence may be located between the MCS region and 3' ITR. In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and 3' ITR, and the second filler sequence may be located between the exon region and 3' ITR.

[0259] In certain embodiments, a viral genome may comprise two filler sequences, the first filler sequence may be located between the MCS region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[0260] AAV Production

[0261] The present disclosure provides methods for the generation of parvoviral particles, *e.g.* AAV particles, by viral genome replication in a viral replication cell.

[0262] In accordance with the disclosure, the viral genome comprising a payload region will be incorporated into the AAV particle produced in the viral replication cell. Methods of making AAV particles are well known in the art and are described in e.g., United States Patent Nos. US6204059, US5756283, US6258595, US6261551, US6270996, US6281010, US6365394, US6475769, US6482634, US6485966, US6943019, US6953690, US7022519, US7238526, US7291498 and US7491508, US5064764, US6194191, US6566118, US8137948; or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597; Methods In Molecular Biology, ed. Richard, Humana Press, NJ (1995); O'Reilly et al., Baculovirus Expression Vectors, A Laboratory Manual, Oxford Univ. Press (1994); Samulski et

al.,*J. Vir.*63:3822-8 (1989); Kajigaya et al., *Proc. Nat'l. Acad. Sci. USA* 88: 4646-50 (1991); Ruffing et al., *J. Vir.* 66:6922-30 (1992); Kimbauer et al., *Vir.,* 219:37-44 (1996); Zhao et al., *Vir.*272:382-93 (2000); the contents of each of which are herein incorporated by reference in their entirety. In certain embodiments, the AAV particles are made using the methods described in WO2015191508, the contents of which are herein incorporated by reference in their entirety.

[0263] Viral replication cells commonly used for production of recombinant AAV particles include but are not limited to 293 cells, COS cells, HeLa cells, KB cells, and other mammalian cell lines as described in U.S. Pat. Nos. US6156303, US5387484, US5741683, US5691176, and US5688676; U.S. patent publication No. 2002/0081721, and International Patent Publication Nos. WO 00/47757, WO 00/24916, and WO 96/17947, the contents of each of which are herein incorporated by reference in their entireties.

[0264] In some embodiments, the present disclosure provides a method for producing an AAV particle having enhanced (increased, improved) transduction efficiency comprising the steps of: 1) co-transfecting competent bacterial cells with a bacmid vector and either a viral construct vector and/or AAV payload construct vector, 2) isolating the resultant viral construct expression vector and AAV payload construct expression vector and separately transfecting viral replication cells, 3) isolating and purifying resultant payload and viral construct particles comprising viral construct expression vector or AAV payload construct expression vector, 4) co-infecting a viral replication cell with both the AAV payload and viral construct particles comprising viral construct expression vector or AAV payload construct expression vector, and 5) harvesting and purifying the AAV particle comprising a viral genome.

[0265] In some embodiments, the present disclosure provides a method for producing an AAV particle comprising the steps of 1) simultaneously co-transfecting mammalian cells, such as, but not limited to HEK293 cells, with a payload region, a construct expressing rep and cap genes and a helper construct, 2) harvesting and purifying the AAV particle comprising a viral genome. In some embodiments, the AAV particle is produced by transient transfection of an adherent HEK293 cell line using three or more bacteria-produced plasmids. In some embdodiments, the resulting AAV particles can be purified by ion exchange chromatography, ultracentrifugation or a combination thereof.

[0266] In some embodiments, the viral genome of the AAV particle of the disclosure optionally encodes a selectable marker. The selectable marker may comprise a cell-surface marker, such as any protein expressed on the surface of the cell including, but not limited to receptors, CD markers, lectins, integrins, or truncated versions thereof.

[0267] In some embodiments, selectable marker reporter genes as described in International application No. WO 96/23810; Heim et al., Current Biology 2:178-182 (1996); Heim et al., Proc. Natl. Acad. Sci. USA (1995); or Heim et al., Science 373:663-664 (1995); WO 96/30540, the contents of each of which are incorporated herein by reference in their entireties).

Genome Size

[0268] In certain embodiments, the AAV particle which comprises a payload described herein may be single stranded or double stranded vector genome. The size of the vector genome may be small, medium, large or the maximum size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0269] In certain embodiments, the vector genome which comprises a payload described herein may be a small single stranded vector genome. A small single stranded vector genome may be 2.7 to 3.5 kb in size such as about 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, and 3.5 kb in size. In certain embodiments, the small single stranded vector genome may be 3.2 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0270] In certain embodiments, the vector genome which comprises a payload described herein may be a small double stranded vector genome. A small double stranded vector genome may be 1.3 to 1.7 kb in size such as about 1.3, 1.4, 1.5, 1.6, and 1.7 kb in size. In certain embodiments, the small double stranded vector genome may be 1.6 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0271] In certain embodiments, the vector genome which comprises a payload described herein may be a medium single stranded vector genome. A medium single stranded vector genome may be 3.6 to 4.3 kb in size such as about 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2 and 4.3 kb in size. In certain embodiments, the medium single stranded vector genome may be 4.0 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0272] In certain embodiments, the vector genome which comprises a payload described herein may be a medium double stranded vector genome. A medium double stranded vector genome may be 1.8 to 2.1 kb in size such as about 1.8, 1.9, 2.0, and 2.1 kb in size. In certain embodiments, the medium double stranded vector genome may be 2.0 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0273] In certain embodiments, the vector genome which comprises a payload described herein may be a large single stranded vector genome. A large single stranded vector genome may be 4.4 to 6.0 kb in size such as about 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 and 6.0 kb in size. In certain embodiments, the large single stranded vector genome may be 4.7 kb in size. In certain embodiments, the large single stranded vector genome may be

4.8 kb in size. As yet another non-limiting example, the large single stranded vector genome may be 6.0 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0274] In certain embodiments, the vector genome which comprises a payload described herein may be a large double stranded vector genome. A large double stranded vector genome may be 2.2 to 3.0 kb in size such as about 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 and 3.0 kb in size. In certain embodiments, the large double stranded vector genome may be 2.4 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

Payloads of the Disclosure

[0275] The AAV particles of the present disclosure comprise at least one payload region. As used herein, "payload" or "payload region" refers to one or more polynucleotides or polynucleotide regions encoded by or within a viral genome or an expression product of such polynucleotide or polynucleotide region, e.g., a transgene, a polynucleotide encoding a polypeptide or multi-polypeptide or a modulatory nucleic acid or regulatory nucleic acid. Payloads of the present disclosure typically encode polypeptides or fragments or variants thereof.

[0276] The payload region may be constructed in such a way as to reflect a region similar to or mirroring the natural organization of an mRNA.

[0277] The payload region may comprise a combination of coding and non-coding nucleic acid sequences.

[0278] In some embodiments, the AAV payload region may encode a coding or non-coding RNA.

[0279] In certain embodiments, the AAV particle comprises a viral genome with a payload region comprising nucleic acid sequences encoding more than one polypeptide of interest. In such an embodiment, a viral genome encoding more than one polypeptide may be replicated and packaged into a viral particle. A target cell transduced with a viral particle comprising more than one polypeptide may express each of the polypeptides in a single cell.

[0280] In certain embodiments, the payload region may comprise one or more of the components as shown in FIG. 1. The payload region **110** is located within the viral genome **100**. At the 5' and/or the 3' end of the payload region **110** there may be at least one inverted terminal repeat (ITR) **120**. Within the payload region, there is a promoter region **130**, an intron region **140** and a coding region **150**.

[0281] Where the AAV particle payload region encodes a polypeptide, the polypeptide may be a peptide or protein. The viral genomes encoding polypeptides described herein may be useful

in the fields of human disease, viruses, infections veterinary applications and a variety of *in vivo* and *in vitro* settings.

[0282] In some embodiments, the AAV particles are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of neurological diseases and/or disorders.

[0283] In some embodiments, the AAV particles are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Parkinson's Disease.

[0284] In some embodiments, the AAV particles are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of diseases of the central nervous system.

The nature of the polypeptides and variants

[0285] Amino acid sequences encoded by payload regions of the viral genomes of the disclosure may be translated as a whole polypeptide, a plurality of polypeptides or fragments of polypeptides, which independently may be encoded by one or more nucleic acids, fragments of nucleic acids or variants of any of the aforementioned. As used herein, "polypeptide" means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. In some instances, the polypeptide encoded is smaller than about 50 amino acids and the polypeptide is then termed a peptide. If the polypeptide is a peptide, it will be at least about 2, 3, 4, or at least 5 amino acid residues long. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. They may also comprise single chain or multichain polypeptides and may be associated or linked. The term polypeptide may also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

[0286] The term "polypeptide variant" refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Ordinarily, variants will possess at least about 50% identity (homology) to a native or reference sequence, and preferably, they will be at least about 80%, more preferably at least about 90% identical (homologous) to a native or reference sequence.

[0287] In some embodiments "variant mimics" are provided. As used herein, the term "variant mimic" is one which contains one or more amino acids which would mimic an activated

sequence. For example, glutamate may serve as a mimic for phosphoro-threonine and/or phosphoro-serine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic, e.g., phenylalanine may act as an inactivating substitution for tyrosine; or alanine may act as an inactivating substitution for serine.

[0288] The term "amino acid sequence variant" refers to molecules with some differences in their amino acid sequences as compared to a native or starting sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence. "Native" or "starting" sequence should not be confused with a wild type sequence. As used herein, a native or starting sequence is a relative term referring to an original molecule against which a comparison may be made. "Native" or "starting" sequences or molecules may represent the wild-type (that sequence found in nature) but do not have to be the wild-type sequence.

[0289] Ordinarily, variants will possess at least about 70% homology to a native sequence, and preferably, they will be at least about 80%, more preferably at least about 90% homologous to a native sequence. "Homology" as it applies to amino acid sequences is defined as the percentage of residues in the candidate amino acid sequence that are identical with the residues in the amino acid sequence of a second sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology. Methods and computer programs for the alignment are well known in the art. It is understood that homology depends on a calculation of percent identity but may differ in value due to gaps and penalties introduced in the calculation.

[0290] By "homologs" as it applies to amino acid sequences is meant the corresponding sequence of other species having substantial identity to a second sequence of a second species.

[0291] "Analogs" is meant to include polypeptide variants which differ by one or more amino acid alterations, e.g., substitutions, additions or deletions of amino acid residues that still maintain the properties of the parent polypeptide.

[0292] Sequence tags or amino acids, such as one or more lysines, can be added to the peptide sequences of the disclosure (e.g., at the N-terminal or C-terminal ends). Sequence tags can be used for peptide purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal or N-terminal residues) may alternatively be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence which is soluble, or linked to a solid support.

[0293] "Substitutional variants" when referring to proteins are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. The substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more amino acids have been substituted in the same molecule.

[0294] As used herein the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

[0295] "Insertional variants" when referring to proteins are those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a native or starting sequence. "Immediately adjacent" to an amino acid means connected to either the alpha-carboxy or alpha-amino functional group of the amino acid.

[0296] "Deletional variants" when referring to proteins, are those with one or more amino acids in the native or starting amino acid sequence removed. Ordinarily, deletional variants will have one or more amino acids deleted in a particular region of the molecule.

[0297] As used herein, the term "derivative" is used synonymously with the term "variant" and refers to a molecule that has been modified or changed in any way relative to a reference molecule or starting molecule. In some embodiments, derivatives include native or starting proteins that have been modified with an organic proteinaceous or non-proteinaceous derivatizing agent, and post-translational modifications. Covalent modifications are traditionally introduced by reacting targeted amino acid residues of the protein with an organic derivatizing agent that is capable of reacting with selected side-chains or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. The resultant covalent derivatives are useful in programs directed at identifying residues

important for biological activity, for immunoassays, or for the preparation of anti-protein antibodies for immunoaffinity purification of the recombinant glycoprotein. Such modifications are within the ordinary skill in the art and are performed without undue experimentation.

[0298] Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues may be present in the proteins used in accordance with the present disclosure.

[0299] Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)).

[0300] "Features" when referring to proteins are defined as distinct amino acid sequence-based components of a molecule. Features of the proteins of the present disclosure include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini or any combination thereof.

[0301] As used herein when referring to proteins the term "surface manifestation" refers to a polypeptide based component of a protein appearing on an outermost surface.

[0302] As used herein when referring to proteins the term "local conformational shape" means a polypeptide based structural manifestation of a protein which is located within a definable space of the protein.

[0303] As used herein when referring to proteins the term "fold" means the resultant conformation of an amino acid sequence upon energy minimization. A fold may occur at the secondary or tertiary level of the folding process. Examples of secondary level folds include beta sheets and alpha helices. Examples of tertiary folds include domains and regions formed due to aggregation or separation of energetic forces. Regions formed in this way include hydrophobic and hydrophilic pockets, and the like.

[0304] As used herein the term "turn" as it relates to protein conformation means a bend which alters the direction of the backbone of a peptide or polypeptide and may involve one, two, three or more amino acid residues.

[0305] As used herein when referring to proteins the term "loop" refers to a structural feature of a peptide or polypeptide which reverses the direction of the backbone of a peptide or polypeptide and comprises four or more amino acid residues. Oliva et al. have identified at least 5 classes of protein loops (J. Mol Biol 266 (4): 814-830; 1997).

[0306] As used herein when referring to proteins the term "half-loop" refers to a portion of an identified loop having at least half the number of amino acid residues as the loop from which it is derived. It is understood that loops may not always contain an even number of amino acid residues. Therefore, in those cases where a loop contains or is identified to comprise an odd number of amino acids, a half-loop of the odd-numbered loop will comprise the whole number portion or next whole number portion of the loop (number of amino acids of the loop/2+/-0.5 amino acids). For example, a loop identified as a 7 amino acid loop could produce half-loops of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4).

[0307] As used herein when referring to proteins the term "domain" refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity, serving as a site for protein-protein interactions).

[0308] As used herein when referring to proteins the term "half-domain" means portion of an identified domain having at least half the number of amino acid residues as the domain from which it is derived. It is understood that domains may not always contain an even number of amino acid residues. Therefore, in those cases where a domain contains or is identified to comprise an odd number of amino acids, a half-domain of the odd-numbered domain will comprise the whole number portion or next whole number portion of the domain (number of amino acids of the domain/2+/-0.5 amino acids). For example, a domain identified as a 7 amino acid domain could produce half-domains of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4). It is also understood that sub-domains may be identified within domains or half-domains, these subdomains possessing less than all of the structural or functional properties identified in the domains or half domains from which they were derived. It is also understood that the amino acids that comprise any of the domain types herein need not be contiguous along the backbone of the polypeptide (i.e., nonadjacent amino acids may fold structurally to produce a domain, half-domain or subdomain).

[0309] As used herein when referring to proteins the terms "site" as it pertains to amino acid based embodiments is used synonymous with "amino acid residue" and "amino acid side chain". A site represents a position within a peptide or polypeptide that may be modified, manipulated, altered, derivatized or varied within the polypeptide based molecules of the present disclosure.

[0310] As used herein the terms "termini or terminus" when referring to proteins refers to an extremity of a peptide or polypeptide. Such extremity is not limited only to the first or final site of the peptide or polypeptide but may include additional amino acids in the terminal regions. The polypeptide based molecules of the present disclosure may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH2)) and a C-terminus

(terminated by an amino acid with a free carboxyl group (COOH)). Proteins of the disclosure are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These sorts of proteins will have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

[0311] Once any of the features have been identified or defined as a component of a molecule of the disclosure, any of several manipulations and/or modifications of these features may be performed by moving, swapping, inverting, deleting, randomizing or duplicating. Furthermore, it is understood that manipulation of features may result in the same outcome as a modification to the molecules of the disclosure. For example, a manipulation which involves deleting a domain would result in the alteration of the length of a molecule just as modification of a nucleic acid to encode less than a full length molecule would.

[0312] Modifications and manipulations can be accomplished by methods known in the art such as site directed mutagenesis. The resulting modified molecules may then be tested for activity using in vitro or in vivo assays such as those described herein or any other suitable screening assay known in the art.

Payload: AADC polynucleotide constructs

[0313] According to the present disclosure, aromatic L-amino acid decarboxylase (AADC; also known as dopa decarboxylase and DDC) polynucleotides are provided which function alone or in combination with additional nucleic acid sequence(s) to encode the AADC protein. As used herein an "AADC polynucleotide" is any nucleic acid polymer which encodes an AADC protein and when present in a vector, plasmid or translatable construct, expresses such AADC protein in a cell, tissue, organ or organism.

[0314] AADC polynucleotides include precursor molecules which are processed inside the cell. AADC polynucleotides or the processed forms thereof may be encoded in a plasmid, vector, genome or other nucleic acid expression vector for delivery to a cell.

[0315] In some embodiments AADC polynucleotides are designed as components of AAV viral genomes and packaged in AAV particles which are processed within the cell to produce the wild type AADC protein.

[0316] In some embodiments, the AADC polynucleotide may be the payload of the AAV particle.

[0317] As used herein, the wild type AADC protein may be any of the naturally occurring isoforms or variants from the *DDC gene*. Multiple alternatively spliced transcript variants encoding different isoforms of AADC have been identified. Specifically, the *DDC gene*

produces seven transcript variants that encode six distinct isoforms. DDC transcript variants 1 and 2 both encode AADC isoform 1. In some embodiments, the AADC polynucleotides encode DDC transcript variant 2, thereby encoding a native AADC isoform 1 (NCBI Reference Sequence: NP_000781.1). This sequence is given here:
MNASEFRRRGKEMVDYVANYMEGIEGRQVYPDVEPGYLRPLIPAAAPQEPDTFEDIIND
VEKIIMPGVTHWHSPYFFAYFPTASSYPAMLADMLCGAIGCIGFSWAASPACTELETVM
MDWLGKMLELPKAFLNEKAGEGGGVIQGSASEATLVALLAARTKVIHRLQAASPELTQ
AAIMEKLVAYSSDQAHSSVERAGLIGGVKLKAIPSDGNFAMRASALQEALERDKAAGLI
PFFMVATLGTTTCCSFDNLLEVGPICNKEDIWLHVDAAYAGSAFICPEFRHLLNGVEFAD
SFNFNPHKWLLVNFDCSAMWVKKRTDLTGAFRLDPTYLKHSHQDSGLITDYRHWQIPL
GRRFRSLKMWFVFRMYGVKGLQAYIRKHVQLSHEFESLVRQDPRFEICVEVILGLVCFR
LKGSNKVNEALLQRINSAKKIHLVPCHLRDKFVLRFAICSRTVESAHVQRAWEHIKELA
ADVLRAERE (SEQ ID NO: 978)

[0318] The AADC polynucleotides of the disclosure, may be engineered to contain modular elements and/or sequence motifs assembled to create AADC polynucleotide constructs.

[0319] According to the present disclosure, AADC polynucleotides are provided. Such polynucleotides comprise nucleic acid polymers which comprise a region of linked nucleosides encoding one or more isoforms or variants of the AADC protein.

[0320] In some embodiments, the AADC polynucleotide comprises a codon optimized transcript encoding an AADC protein.

[0321] In some embodiments, the AADC polynucleotide comprises a sequence region encoding one or more wild type isoforms or variants of an AADC protein. Such polynucleotides may also comprise a sequence region encoding any one or more of the following: a 5' ITR, a cytomegalovirus (CMV) Enhancer, a CMV Promoter, an ie1 exon 1, an ie1 intron1, an hbBglobin intron2, an hBglobin exon 3, a 5' UTR, a 3' UTR, an hGH poly(A) signal, and/or a 3' ITR. Such sequence regions are taught herein or may be any of those known in the art.

[0322] In some embodiments, the AADC polynucleotide comprises a SEQ ID NO: 979 or a fragment or variant thereof. This AADC polynucleotide sequence is given here:

[0323] 5'cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgc
ccggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttccttgtagttaatgattaacccgccatgct
acttatctacgtagccatgcgtcgacataacgcgtatatctagacgttacataacttacggtaaatggcccgcctggctgaccgcccaacgac
ccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaa
ctgcccacttggcagtacatcaagtgtatcatatgccaagtacgcccccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc
agtacatgaccttatgggactttcctacttggcagtacatctagtattagtcatcgctattaccatggtgatgcggttttggcagtacatcaatgg

gcgtggatagcggtttgactcacggggatttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatgtcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcagagctcgtttagtgaaccgtcagatcgcctggagacgccatccacgctgttttgacctccatagaagacaccgggaccgatccagcctccgcggattcgaatcccggccgggaacggtgcattggaacgcggattccccgtgccaagagtgacgtaagtaccgcctatagagtctataggcccacaaaaaatgctttcttctttaatatactttttgtttatcttatttctaatactttccctaatctctttctttcagggcaataatgatacaatgtatcatgcctctttgcaccatttctaaagaataacagtgataatttctgggttaaggcaatagcaatatttctgcatataaatatttctgcatataaattgtaactgatgtaagaggtttcatattgctaatagcagctacaatccagctaccattctgcttttatttatggttgggataaggctggattatctgagtccaagctaggcccttttgctaatcatgttcatacctcttatcttcctcccacagctcctgggcaacgtgctggtctgtgtgctggcccatcactttggcaaagaattgggattcgaacatcgattgaattccccggggatccaccatgaacgcaagtgaattccgaaggagagggaaggagatggtggattacgtggccaactacatggaaggcattgagggacgccaggtctaccctgacgtggagccccgggtacctgcggccgctgatccctgccgctgccccctcaggagccagacacgtttgaggacatcatcaacgacgttgagaagataatcatgcctggggtgacgcactggcacagcccctacttcttcgcctacttccccactgccagctcgtacccggccatgcttgcggacatgctgtgcggggccattggctgcatcggcttctcctgggcggcaagcccagcatgcacagagctggagactgtgatgatggactggctcgggaagatgctggaactaccaaaggcatttttgaatgagaaagctggagaaggggggaggagtgatccagggaagtgccagtgaagccaccctggtggccctgctggccgctcggaccaaagtgatccatcggctgcaggcagcgtccccagagctcacacaggccgctatcatggagaagctggtggcttactcatccgatcaggcacactcctcagtggaaagagctgggttaattggtggagtgaaattaaaagccatcccctcagatggcaacttcgccatgcgtgcgtctgccctgcaggaagccctggagagagacaaagcggctggcctgattccttttctttatggttgccaccctggggaccacaacatgctgctcctttgacaatctcttagaagtcggtcctatctgcaacaaggaagacatatggctgcacgttgatgcagcctacgcaggcagtgcattcatctgccctgagttccggcaccttctgaatggagtggagtttgcagattcattcaactttaatccccacaaatggctattggtgaattttgactgttctgccatgtgggtgaaaaagagaacagacttaacgggagcctttagactggaccccacttacctgaagcacagccatcaggattcagggcttatcactgactaccggcattggcagataccactgggcagaagatttcgctctttgaaaatgtggtttgtatttaggatgtatggagtcaaaggactgcaggcttatatccgcaagcatgtccagctgtcccatgagttttgagtcactggtgcgccaggatccccgctttgaaatctgtgtggaagtcattctggggcttgtctgctttcggctaaagggttccaacaaagtgaatgaagctcttctgcaaagaataaacagtgccaaaaaaatccacttggttccatgtcacctcagggacaagtttgtcctgcgctttgccatctgttctcgcacggtggaatctgcccatgtgcagcgggcctgggaacacatcaaagagctggcggccgacgtgctgcgagcagagaggagtaggagtgaagccaggacctgcagaagcttgcctcgagcagcgctgctcgagagatctacgggtggcatccctgtgacccctccccagtgcctctcctggccctggaagttgccactccagtgcccaccagccttgtcctaataaaattaagttgcatcattttgtctgactaggtgtccttctataatattatggggtggaggggggtggtatggagcaaggggcaagttgggaagacaacctgtagggcctgcggggtctattgggaaccaagctggagtgcagtggcacaatcttggctcactgcaatctccgcctcctgggttcaagcgattctcctgcctcagcctcccgagttgttgggattccaggcatgcatgaccaggctcagctaatttttgtttttttggtagagacggggtttcaccatattggccaggctggtctccaactcctaatctcaggtgatctacccacctttggcctcccaaattgctgggattacaggcgtgaaccactgctcccttccctgtccttactagatttaaatatgtcgtgcatcgatgctacgtagataagtagcatggcgggttaatcattaactacagaggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg3' (SEQ ID NO: 979)

[0324] In some embodiments, an AADC polynucleotide that comprises a SEQ ID NO: 979 or a fragment or variant thereof is part of an AAV particle comprising an AAV2 capsid serotype.

[0325] In certain embodiments, an AADC polynucleotide comprises a ribonucleotide form of SEQ ID NO: 979.

[0326] In certain embodiments, the AADC polynucleotide comprises a sequence which has a percent identity to any of SEQ ID NO: 979 or a fragment or variant thereof. The AADC polynucleotide may have 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% identity to any of SEQ ID NO: 979 or a fragment or variant thereof. The AADC polynucleotide may have 1-10%, 10-20%, 30-40%, 50-60%, 50-70%, 50-80%, 50-90%, 50-99%, 50-100%, 60-70%, 60-80%, 60-90%, 60-99%, 60-100%, 70-80%, 70-90%, 70-99%, 70-100%, 80-85%, 80-90%, 80-95%, 80-99%, 80-100%, 90-95%, 90-99%, or 90-100% to any of SEQ ID NO: 979 or a fragment or variant thereof. In certain embodiments, the AADC polynucleotide comprises a sequence which as 80% identity to any of SEQ ID NO: 979 or a fragment or variant thereof. In certain embodiments, the AADC polynucleotide comprises a sequence which as 85% identity to any of SEQ ID NO: 979 or a fragment or variant thereof. In certain embodiments, the AADC polynucleotide comprises a sequence which as 90% identity to any of SEQ ID NO: 979 or a fragment or variant thereof. In certain embodiments, the AADC polynucleotide comprises a sequence which as 95% identity to any of SEQ ID NO: 979 or a fragment or variant thereof. In certain embodiments, the AADC polynucleotide comprises a sequence which as 99% identity to any of SEQ ID NO: 979 or a fragment or variant thereof.

[0327] In some embodiments, the coding region of the AADC polynucleotide is 1440 nucleotides in length. Such an AADC polynucleotide may, for example, be codon optimized over all or a portion of the polynucleotide.

[0328] In some embodiments, the AADC polynucleotide comprises any of SEQ ID NO: 979 or a fragment or variant thereof but lacking the 5' and/or 3' ITRs. Such a polynucleotide may be incorporated into a plasmid or vector and utilized to express the encoded AADC protein.

[0329] In certain embodiments, the AADC polynucleotides may be produced in insect cells (e.g., Sf9 cells).

[0330] In certain embodiments, the AADC polynucleotides may be produced using triple transfection.

[0331] In certain embodiments, the AADC polynucleotide may comprise an open reading frame of an AADC mRNA, for example, a codon optimized open reading frame of an AADC mRNA, at least one 5'ITR and at least one 3'ITR where the one or more of the 5'ITRs may be

located at the 5'end of the promoter region and one or more 3' ITRs may be located at the 3' end of the poly(A) signal. The AADC mRNA may comprise a promoter region, a 5'untranslated region (UTR), a 3'UTR and a poly(A) signal. The promoter region may include, but is not limited to, enhancer element, a promoter element, a first exon region, a first intron region, a second intron region and a second exon region. In certain embodiments, the enhancer element and the promoter element are derived from CMV. In certain embodiments, the first exon region is ie1 exon 1 or fragments thereof, the first intron region is ie1 intron 1 or fragments thereof, the second intron region is hbBglobin intron 2 or fragments thereof and the second exon region is hbBglobin exon 3 or fragments thereof. As yet another non-limiting example, the poly(A) signal is derived from human growth hormone.

[0332] In certain embodiments, at least one element may be used with the AADC polynucleotides described herein to enhance the transgene target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, 2015; the contents of which are herein incorporated by reference in its entirety). Non-limiting examples of elements to enhance the transgene target specificity and expression include promoters, endogenous miRNAs, post-transcriptional regulatory elements (PREs), polyadenylation (PolyA) signal sequences and upstream enhancers (USEs), CMV enhancers and introns.

[0333] In certain embodiments, at least one element may be used with the AADC polynucleotides described herein to enhance the transgene target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, 2015; the contents of which are herein incorporated by reference in its entirety) such as promoters.

[0334] In certain embodiments, the AADC polynucleotide is encoded in a plasmid or vector, which may be derived from an adeno-associated virus (AAV).

[0335] In certain embodiments, the AAV particle of the disclosure comprises a recombinant AAV2 with a viral genome encoding a human AADC.

[0336] In certain embodiments, the AAV particle of the disclosure is VY-AADC01.

[0337] In certain embodiments, the AAV particle of the disclosure is VY-AADC02.

[0338] In certain embodiments, the AAV particle of the disclosure has a CAS (Chemical Abstracts Service) Registry Number of 2226647-27-2.

II. FORMULATION AND DELIVERY

Pharmaceutical Compositions

[0339] According to the present disclosure the AAV particles may be prepared as pharmaceutical compositions (e.g. formulations). It will be understood that such compositions necessarily comprise one or more active ingredients and, most often, a pharmaceutically acceptable excipient.

[0340] Relative amounts of the active ingredient (e.g. AAV particle), a pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.0001% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.0001% and 100%, e.g., between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

[0341] In some embodiments, the AAV particle pharmaceutical compositions described herein may comprise at least one payload. In certain embodiments, the pharmaceutical compositions may contain an AAV particle with 1, 2, 3, 4 or 5 payloads.

[0342] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, e.g., to non-human animals, e.g. non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, rats, birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

[0343] In some embodiments, compositions are administered to humans, human patients or subjects.

Formulations

[0344] Formulations of the present disclosure can include, without limitation, saline, liposomes, lipid nanoparticles, polymers, peptides, proteins, cells transfected with AAV particles (e.g., for transfer or transplantation into a subject) and combinations thereof.

[0345] Formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. As used herein the term "pharmaceutical composition" refers to compositions comprising at least one active ingredient and optionally one or more pharmaceutically acceptable excipients.

[0346] In general, such preparatory methods include the step of associating the active ingredient with an excipient and/or one or more other accessory ingredients. As used herein, the phrase "active ingredient" generally refers either to an AAV particle carrying a payload region encoding the polypeptides of the disclosure or to the end product encoded by a viral genome of by an AAV particle as described herein.

[0347] Formulations of the AAV particles and pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

[0348] A pharmaceutical composition in accordance with the present disclosure may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" refers to a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[0349] In certain embodiments, the AAV particles of the disclosure may be formulated in PBS, in combination with an ethylene oxide/propylene oxide copolymer (also known as pluronic or poloxamer).

[0350] In certain embodiments, the AAV particles of the disclosure may be formulated in PBS with 0.001% w/v pluronic acid (F-68) (poloxamer 188) at a pH of about 7.0.

[0351] In certain embodiments, the AAV particles of the disclosure may be formulated in PBS with 0.001% w/v pluronic acid (F-68) (poloxamer 188) at a pH of about 7.3.

[0352] In certain embodiments, the AAV particles of the disclosure may be formulated in PBS with 0.001% w/v pluronic acid (F-68) (poloxamer 188) at a pH of about 7.4.

[0353] In certain embodiments, the AAV particles of the disclosure may be formulated in a solution comprising sodium chloride, sodium phosphate and an ethylene oxide/propylene oxide copolymer.

[0354] In certain embodiments, the AAV particles of the disclosure may be formulated in a solution comprising sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic and poloxamer 188/pluronic acid (F-68).

[0355] In certain embodiments, the AAV particles of the disclosure may be formulated in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188 (i.e. pluronic acid F-68), at a pH of about 7.3. In certain embodiments, the AAV particles of the disclosure may be formulated at a target concentration of $\geq 3.0 \times 10^{12}$ vg/mL in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3. In certain embodiments, the AAV particles of the disclosure may be formulated at a target concentration of $3.5\text{-}5.5 \times 10^{12}$ vg/mL in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3. In certain embodiments, the AAV particles of the disclosure may be formulated at a target concentration of $4.5\text{-}5.5 \times 10^{12}$ vg/mL in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3. In certain embodiments, the AAV particles of the disclosure may be formulated at a target concentration of 4.9×10^{12} vg/mL in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3. In certain embodiments, the AAV particles of the disclosure may be formulated at a target concentration of $2.0\text{-}3.5 \times 10^{12}$ vg/mL in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3. In certain embodiments, the AAV particles of the disclosure may be formulated at a target concentration of $2.4\text{-}2.8 \times 10^{12}$ vg/mL in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3. In certain embodiments, the AAV particles of the disclosure may be formulated at a target concentration of 2.6×10^{12} vg/mL in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3.

[0356] In certain embodiments, the AAV particles of the disclosure may be administered at a target concentration of $2.0\text{-}3.5 \times 10^{12}$ vg/mL in a solution comprising about 180mM sodium

chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3. In certain embodiments, the AAV particles of the disclosure may be administered at a target concentration of 2.4-2.8 x 10^{12} vg/mL in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3. In certain embodiments, the AAV particles of the disclosure may be administered at a target concentration of 2.6 x 10^{12} vg/mL in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% w/v poloxamer 188, at a pH of about 7.3.

[0357] The concentration of sodium chloride in the final solution may be 150mM-200mM. As non-limiting examples, the concentration of sodium chloride in the final solution may be 150mM, 160mM, 170mM, 180mM, 190mM or 200mM. The concentration of sodium phosphate in the final solution may be 1mM-50mM. As non-limiting examples, the concentration of sodium phosphate in the final solution may be 1mM, 2mM, 3mM, 4mM, 5mM, 6mM, 7mM, 8mM, 9mM, 10mM, 15mM, 20mM, 25mM, 30mM, 40mM, or 50mM. The concentration of poloxamer 188 (pluronic acid (F-68)) may be 0.0001%-1%. As non-limiting examples, the concentration of poloxamer 188 (pluronic acid (F-68)) may be 0.0001%, 0.0005%, 0.001%, 0.005%, 0.01%, 0.05%, 0.1%, 0.5%, or 1% w/v. The final solution may have a pH of 6.8-7.7. Non-limiting examples for the pH of the final solution include a pH of 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, or 7.7.

[0358] In certain embodiments, the AAV particles of the disclosure may be formulated in a solution comprising about 1.05% sodium chloride, about 0.212% sodium phosphate dibasic, heptahydrate, about 0.025% sodium phosphate monobasic, monohydrate, and 0.001% poloxamer 188, at a pH of about 7.4. In certain embodiments, the concentration of AAV particle in this formulated solution may be about 0.001%. The concentration of sodium chloride in the final solution may be 0.1-2.0%, with non-limiting examples of 0.1%, 0.25%, 0.5%, 0.75%, 0.95%, 0.96%, 0.97%, 0.98%, 0.99%, 1.00%, 1.01%, 1.02%, 1.03%, 1.04%, 1.05%, 1.06%, 1.07%, 1.08%, 1.09%, 1.10%, 1.25%, 1.5%, 1.75%, or 2%. The concentration of sodium phosphate dibasic in the final solution may be 0.100-0.300% with non-limiting examples including 0.100%, 0.125%, 0.150%, 0.175%, 0.200%, 0.210%, 0.211%, 0.212%, 0.213%, 0.214%, 0.215%, 0.225%, 0.250%, 0.275%, 0.300%. The concentration of sodium phosphate monobasic in the final solution may be 0.010-0.050%, with non-limiting examples of 0.010%, 0.015%, 0.020%, 0.021%, 0.022%, 0.023%, 0.024%, 0.025%, 0.026%, 0.027%, 0.028%, 0.029%, 0.030%, 0.035%, 0.040%, 0.045%, or 0.050%. The concentration of poloxamer 188 (pluronic acid (F-68)) may be 0.0001%-1%. As non-limiting examples, the concentration of poloxamer 188 (pluronic acid (F-68)) may be 0.0001%, 0.0005%, 0.001%, 0.005%, 0.01%, 0.05%, 0.1%, 0.5%,

or 1%. The final solution may have a pH of 6.8-7.7. Non-limiting examples for the pH of the final solution include a pH of 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, or 7.7.

[0359] In certain embodiments, the formulation comprises components with the following CAS (Chemical Abstracts Services) Registry Numbers, 7647-14-15 (sodium chloride), 7782-85-6 (sodium phosphate dibasic, heptahydrate), 10049-21-5 (sodium phosphate monobasic, monohydrate), 9003-11-6 (poloxamer 188) and 2226647-27-2 (recombinant adeno-associated virus 2 vector VY-AADC02 human aromatic amino acid decarboxylase-specifying).

[0360] In some embodiments, the AAV formulations described herein may contain sufficient AAV particles for expression of at least one expressed functional payload. In certain embodiments, the AAV particles may contain viral genomes encoding 1, 2, 3, 4 or 5 functional payloads.

[0361] In certain embodiments, AAV formulations of the present disclosure may be formulated with a target concentration of AAV vectors (vg/mL) and administered at a different target concentration of AAV vectors. In certain embodiments, an AAV formulations may be formulated at a target concentration of AAV vectors (vg/mL) and then concentrated to be administered at a higher target concentration of AAV vectors. In certain embodiments, an AAV formulations may be formulated at a target concentration of AAV vectors (vg/mL) and then diluted to be administered at a lower target concentration of AAV vectors.

[0362] According to the present disclosure AAV particles may be formulated for CNS delivery. Agents that cross the brain blood barrier may be used. For example, some cell penetrating peptides that can target molecules to the brain blood barrier endothelium may be used for formulation (e.g., Mathupala, *Expert Opin Ther Pat.*, 2009, 19, 137-140; the content of which is incorporated herein by reference in its entirety).

Excipients and Diluents

[0363] The AAV particles of the disclosure can be formulated using one or more excipients or diluents to (1) increase stability; (2) increase cell transfection or transduction; (3) permit the sustained or delayed release of the payload; (4) alter the biodistribution (e.g., target the viral particle to specific tissues or cell types); (5) increase the translation of encoded protein; (6) alter the release profile of encoded protein and/or (7) allow for regulatable expression of the payload of the disclosure.

[0364] In some embodiments, a pharmaceutically acceptable excipient may be at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use for humans and for veterinary use. In some embodiments, an excipient may be approved by United States Food and Drug Administration. In some

embodiments, an excipient may be of pharmaceutical grade. In some embodiments, an excipient may meet the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[0365] Excipients, as used herein, include, but are not limited to, any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparing the composition are known in the art (see Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro, Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference in its entirety). The use of a conventional excipient medium may be contemplated within the scope of the present disclosure, except insofar as any conventional excipient medium may be incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

[0366] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and/or combinations thereof.

[0367] In certain embodiments, the AAV particles may be formulated in a hydrogel prior to administration. Hydrogels have a degree of flexibility which is similar to natural tissue as a result of their significant water content.

[0368] In another embodiment, a hydrogel may be administered to a subject prior to the administration of an AAV particle formulation. In certain embodiments, the site of administration of the hydrogel may be within 3 inches (e.g., within 2.9, 2.8, 2.7, 2.6, 2.5, 2.4, 2.3, 2.2., 2.1, 2.0, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1 or less than 0.1 inches) of the site of administration of the AAV particle formulation.

Inactive Ingredients

[0369] In some embodiments, AAV particle formulations may comprise at least one inactive ingredient. As used herein, the term "inactive ingredient" refers to one or more agents that do not contribute to the activity of the active ingredient of the pharmaceutical composition included in formulations. In some embodiments, all, none or some of the inactive ingredients which may be used in the formulations of the present disclosure may be approved by the US Food and Drug Administration (FDA).

[0370] In certain embodiments, the AAV particle pharmaceutical compositions comprise at least one inactive ingredient such as, but not limited to, 1,2,6-Hexanetriol; 1,2-Dimyristoyl-Sn-Glycero-3-(Phospho-S-(1-Glycerol)); 1,2-Dimyristoyl-Sn-Glycero-3-Phosphocholine; 1,2-Dioleoyl-Sn-Glycero-3-Phosphocholine; 1,2-Dipalmitoyl-Sn-Glycero-3-(Phospho-Rac-(1-Glycerol)); 1,2-Distearoyl-Sn-Glycero-3-(Phospho-Rac-(1-Glycerol)); 1,2-Distearoyl-Sn-Glycero-3-Phosphocholine; 1-O-Tolylbiguanide; 2-Ethyl-1,6-Hexanediol; Acetic Acid; Acetic Acid, Glacial; Acetic Anhydride; Acetone; Acetone Sodium Bisulfite; Acetylated Lanolin Alcohols; Acetylated Monoglycerides; Acetylcysteine; Acetyltryptophan, DL-; Acrylates Copolymer; Acrylic Acid-Isooctyl Acrylate Copolymer; Acrylic Adhesive 788; Activated Charcoal; Adcote 72A103; Adhesive Tape; Adipic Acid; Aerotex Resin 3730; Alanine; Albumin Aggregated; Albumin Colloidal; Albumin Human; Alcohol; Alcohol, Dehydrated; Alcohol, Denatured; Alcohol, Diluted; Alfadex; Alginic Acid; Alkyl Ammonium Sulfonic Acid Betaine; Alkyl Aryl Sodium Sulfonate; Allantoin; Allyl .Alpha.-Ionone; Almond Oil; Alpha-Terpineol; Alpha-Tocopherol; Alpha-Tocopherol Acetate, Dl-; Alpha-Tocopherol, Dl-; Aluminum Acetate; Aluminum Chlorhydroxy Allantoinate; Aluminum Hydroxide; Aluminum Hydroxide - Sucrose, Hydrated; Aluminum Hydroxide Gel; Aluminum Hydroxide Gel F 500; Aluminum Hydroxide Gel F 5000; Aluminum Monostearate; Aluminum Oxide; Aluminum Polyester; Aluminum Silicate; Aluminum Starch Octenylsuccinate; Aluminum Stearate; Aluminum Subacetate; Aluminum Sulfate Anhydrous; Amerchol C; Amerchol-Cab; Aminomethylpropanol; Ammonia; Ammonia Solution; Ammonia Solution, Strong; Ammonium Acetate; Ammonium Hydroxide; Ammonium Lauryl Sulfate; Ammonium Nonoxynol-4 Sulfate; Ammonium Salt Of C-12-C-15 Linear Primary Alcohol Ethoxylate; Ammonium Sulfate; Ammonyx; Amphoteric-2; Amphoteric-9; Anethole; Anhydrous Citric Acid; Anhydrous Dextrose; Anhydrous Lactose; Anhydrous Trisodium Citrate; Aniseed Oil; Anoxid Sbn; Antifoam; Antipyrine; Apaflurane; Apricot Kernel Oil Peg-6 Esters; Aquaphor; Arginine; Arlacel; Ascorbic Acid; Ascorbyl Palmitate; Aspartic Acid; Balsam Peru; Barium Sulfate; Beeswax; Beeswax, Synthetic; Beheneth-10; Bentonite; Benzalkonium Chloride; Benzenesulfonic Acid; Benzethonium Chloride; Benzododecinium Bromide; Benzoic Acid; Benzyl Alcohol; Benzyl Benzoate; Benzyl Chloride; Betadex; Bibapcitide; Bismuth Subgallate; Boric Acid; Brocrinat; Butane; Butyl Alcohol; Butyl Ester Of Vinyl Methyl Ether/Maleic Anhydride Copolymer (125000 Mw); Butyl Stearate; Butylated Hydroxyanisole; Butylated Hydroxytoluene; Butylene Glycol; Butylparaben; Butyric Acid; C20-40 Pareth-24; Caffeine; Calcium; Calcium Carbonate; Calcium Chloride; Calcium Gluceptate; Calcium Hydroxide; Calcium Lactate; Calcobutrol; Caldiamide Sodium; Caloxetate Trisodium; Calteridol Calcium; Canada Balsam; Caprylic/Capric Triglyceride;

Caprylic/Capric/Stearic Triglyceride; Captan; Captisol; Caramel; Carbomer 1342; Carbomer 1382; Carbomer 934; Carbomer 934p; Carbomer 940; Carbomer 941; Carbomer 980; Carbomer 981; Carbomer Homopolymer Type B (Allyl Pentaerythritol Crosslinked); Carbomer Homopolymer Type C (Allyl Pentaerythritol Crosslinked); Carbon Dioxide; Carboxy Vinyl Copolymer; Carboxymethylcellulose; Carboxymethylcellulose Sodium; Carboxypolymethylene; Carrageenan; Carrageenan Salt; Castor Oil; Cedar Leaf Oil; Cellulose; Cellulose, Microcrystalline; Cerasynt-Se; Ceresin; Ceteareth-12; Ceteareth-15; Ceteareth-30; Cetearyl Alcohol/Ceteareth-20; Cetearyl Ethylhexanoate; Ceteth-10; Ceteth-2; Ceteth-20; Ceteth-23; Cetostearyl Alcohol; Cetrimonium Chloride; Cetyl Alcohol; Cetyl Esters Wax; Cetyl Palmitate; Cetylpyridinium Chloride; Chlorobutanol; Chlorobutanol Hemihydrate; Chlorobutanol, Anhydrous; Chlorocresol; Chloroxylenol; Cholesterol; Choleth; Choleth-24; Citrate; Citric Acid; Citric Acid Monohydrate; Citric Acid, Hydrous; Cocamide Ether Sulfate; Cocamine Oxide; Coco Betaine; Coco Diethanolamide; Coco Monoethanolamide; Cocoa Butter; Coco-Glycerides; Coconut Oil; Coconut Oil, Hydrogenated; Coconut Oil/Palm Kernel Oil Glycerides, Hydrogenated; Cocoyl Caprylocaprate; Cola Nitida Seed Extract; Collagen; Coloring Suspension; Corn Oil; Cottonseed Oil; Cream Base; Creatine; Creatinine; Cresol; Croscarmellose Sodium; Crospovidone; Cupric Sulfate; Cupric Sulfate Anhydrous; Cyclomethicone; Cyclomethicone/Dimethicone Copolyol; Cysteine; Cysteine Hydrochloride; Cysteine Hydrochloride Anhydrous; Cysteine, Dl-; D&C Red No. 28; D&C Red No. 33; D&C Red No. 36; D&C Red No. 39; D&C Yellow No. 10; Dalfampridine; Daubert 1-5 Pestr (Matte) 164z; Decyl Methyl Sulfoxide; Dehydag Wax Sx; Dehydroacetic Acid; Dehymuls E; Denatonium Benzoate; Deoxycholic Acid; Dextran; Dextran 40; Dextrin; Dextrose; Dextrose Monohydrate; Dextrose Solution; Diatrizoic Acid; Diazolidinyl Urea; Dichlorobenzyl Alcohol; Dichlorodifluoromethane; Dichlorotetrafluoroethane; Diethanolamine; Diethyl Pyrocarbonate; Diethyl Sebacate; Diethylene Glycol Monoethyl Ether; Diethylhexyl Phthalate; Dihydroxyaluminum Aminoacetate; Diisopropanolamine; Diisopropyl Adipate; Diisopropyl Dilinoleate; Dimethicone 350; Dimethicone Copolyol; Dimethicone Mdx4-4210; Dimethicone Medical Fluid 360; Dimethyl Isosorbide; Dimethyl Sulfoxide; Dimethylaminoethyl Methacrylate - Butyl Methacrylate - Methyl Methacrylate Copolymer; Dimethyldioctadecylammonium Bentonite; Dimethylsiloxane/Methylvinylsiloxane Copolymer; Dinoseb Ammonium Salt; Dipalmitoylphosphatidylglycerol, Dl-; Dipropylene Glycol; Disodium Cocoamphodiacetate; Disodium Laureth Sulfosuccinate; Disodium Lauryl Sulfosuccinate; Disodium Sulfosalicylate; Disofenin; Divinylbenzene Styrene Copolymer; Dmdm Hydantoin; Docosanol; Docusate Sodium; Duro-Tak 280-2516; Duro-Tak 387-2516; Duro-Tak 80-1196; Duro-Tak 87-2070;

Duro-Tak 87-2194; Duro-Tak 87-2287; Duro-Tak 87-2296; Duro-Tak 87-2888; Duro-Tak 87-2979; Edetate Calcium Disodium; Edetate Disodium; Edetate Disodium Anhydrous; Edetate Sodium; Edetic Acid; Egg Phospholipids; Entsufon; Entsufon Sodium; Epilactose; Epitetracycline Hydrochloride; Essence Bouquet 9200; Ethanolamine Hydrochloride; Ethyl Acetate; Ethyl Oleate; Ethylcelluloses; Ethylene Glycol; Ethylene Vinyl Acetate Copolymer; Ethylenediamine; Ethylenediamine Dihydrochloride; Ethylene-Propylene Copolymer; Ethylene-Vinyl Acetate Copolymer (28% Vinyl Acetate); Ethylene-Vinyl Acetate Copolymer (9% Vinylacetate); Ethylhexyl Hydroxystearate; Ethylparaben; Eucalyptol; Exametazime; Fat, Edible; Fat, Hard; Fatty Acid Esters; Fatty Acid Pentaerythriol Ester; Fatty Acids; Fatty Alcohol Citrate; Fatty Alcohols; Fd&C Blue No. 1; Fd&C Green No. 3; Fd&C Red No. 4; Fd&C Red No. 40; Fd&C Yellow No. 10 (Delisted); Fd&C Yellow No. 5; Fd&C Yellow No. 6; Ferric Chloride; Ferric Oxide; Flavor 89-186; Flavor 89-259; Flavor Df-119; Flavor Df-1530; Flavor Enhancer; Flavor Fig 827118; Flavor Raspberry Pfc-8407; Flavor Rhodia Pharmaceutical No. Rf 451; Fluorochlorohydrocarbons; Formaldehyde; Formaldehyde Solution; Fractionated Coconut Oil; Fragrance 3949-5; Fragrance 520a; Fragrance 6.007; Fragrance 91-122; Fragrance 9128-Y; Fragrance 93498g; Fragrance Balsam Pine No. 5124; Fragrance Bouquet 10328; Fragrance Chemoderm 6401-B; Fragrance Chemoderm 6411; Fragrance Cream No. 73457; Fragrance Cs-28197; Fragrance Felton 066m; Fragrance Firmenich 47373; Fragrance Givaudan Ess 9090/1c; Fragrance H-6540; Fragrance Herbal 10396; Fragrance Nj-1085; Fragrance P O Fl-147; Fragrance Pa 52805; Fragrance Pera Derm D; Fragrance Rbd-9819; Fragrance Shaw Mudge U-7776; Fragrance Tf 044078; Fragrance Ungerer Honeysuckle K 2771; Fragrance Ungerer N5195; Fructose; Gadolinium Oxide; Galactose; Gamma Cyclodextrin; Gelatin; Gelatin, Crosslinked; Gelfoam Sponge; Gellan Gum (Low Acyl); Gelva 737; Gentisic Acid; Gentisic Acid Ethanolamide; Gluceptate Sodium; Gluceptate Sodium Dihydrate; Gluconolactone; Glucuronic Acid; Glutamic Acid, Dl-; Glutathione; Glycerin; Glycerol Ester Of Hydrogenated Rosin; Glyceryl Citrate; Glyceryl Isostearate; Glyceryl Laurate; Glyceryl Monostearate; Glyceryl Oleate; Glyceryl Oleate/Propylene Glycol; Glyceryl Palmitate; Glyceryl Ricinoleate; Glyceryl Stearate; Glyceryl Stearate - Laureth-23; Glyceryl Stearate/Peg Stearate; Glyceryl Stearate/Peg-100 Stearate; Glyceryl Stearate/Peg-40 Stearate; Glyceryl Stearate-Stearamidoethyl Diethylamine; Glyceryl Trioleate; Glycine; Glycine Hydrochloride; Glycol Distearate; Glycol Stearate; Guanidine Hydrochloride; Guar Gum; Hair Conditioner (18n195-1m); Heptane; Hetastarch; Hexylene Glycol; High Density Polyethylene; Histidine; Human Albumin Microspheres; Hyaluronate Sodium; Hydrocarbon; Hydrocarbon Gel, Plasticized; Hydrochloric Acid; Hydrochloric Acid, Diluted; Hydrocortisone; Hydrogel Polymer; Hydrogen Peroxide;

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 157

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 157

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

PCT/US2019/032384
VOYAGER THERAPEUTICS, INC.

222 330 m10/m24
March 2020

AMENDED CLAIMS

1. A method of administering a pharmaceutical composition to a subject, the method comprising: administering to the subject a pharmaceutical composition comprising an adeno-associated virus (AAV) which comprises an AAV2 capsid and a vector genome, wherein the vector genome comprises a nucleotide sequence which has at least 99% identity to SEQ ID NO: 979.

2. The method of claim 1, wherein the vector genome comprises SEQ ID NO: 979.

3. The method of claim 1, wherein the vector genome consists of SEQ ID NO: 979.

4. The method of any one of claims 1-3, wherein pharmaceutical composition is administered to the subject by posterior surgical infusion into at least one putamen of the subject; and wherein the average total putaminal coverage from the posterior administration is at least 50%.

5. The method of claim 4, wherein the posterior administration of the pharmaceutical composition is bilateral to both the right putamen and the left putamen of the subject during a single procedure.

6. The method of claim 5, wherein the average total putaminal coverage of the pharmaceutical composition after the posterior administration is 50-65%.

7. The method of claim 5, wherein the average total putaminal coverage of the pharmaceutical composition after the posterior administration is 50-60%.

8. The method of claim 5, wherein the average total putaminal coverage of the pharmaceutical composition after the posterior administration is 55-65%.

9. The method of any one of claims 1-8, wherein the surgical time is 7-10 hours.

10. The method of any one of claims 1-9, wherein the infusion time is 2.5-4.5 hours.

11. The method of any one of claims 1-3, wherein the pharmaceutical composition is administered to the subject by transfrontal surgical infusion into at least one putamen of the subject; and wherein the average total putaminal coverage from the posterior administration is 30-50%.

12. The method of claim 11, wherein the transfrontal administration of the pharmaceutical composition is bilateral to both the right putamen and the left putamen of the subject during a single procedure.

13. The method of claim 12, wherein the average total putaminal coverage from the transfrontal administration is 35-50%.

14. The method of claim 12, wherein the average total putaminal coverage from the transfrontal administration is 40-50%.

15. The method of any one of claims 1-14, wherein the pharmaceutical composition comprises an AAV concentration of between 2.0×10^{12} vg/ml and 3.0×10^{12} vg/ml.

16. The method of any one of claims 1-14, wherein the pharmaceutical composition comprises an AAV concentration of between 2.4×10^{12} vg/ml and 2.8×10^{12} vg/ml.

17. The method of any one of claims 1-14, wherein the pharmaceutical composition comprises an AAV concentration of about 2.6×10^{12} vg/ml.

18. The method of any one of claims 1-17, wherein the pharmaceutical composition is administered at a volume of up to 1800 µL per putamen.

19. The method of any one of claims 1-17, wherein the pharmaceutical composition is administered at a volume of up to 1500 μL per putamen.

20. The method of any one of claims 1-19, wherein the pharmaceutical composition is administered at a total viral dosage of 2.0×10^{12} vg to 9.4×10^{12} vg.

21. The method of any one of claims 1-19, wherein the pharmaceutical composition is administered at a total viral dosage of 3.5×10^{12} vg to 8.0×10^{12} vg.

22. The method of any one of claims 1-21, wherein the pharmaceutical composition is a formulation comprising sodium chloride, sodium phosphate and pluronic acid F-68, and wherein the formulation has a pH between 7.0-7.5.

23. The method of claim 22, wherein the formulation comprises 150-200 mM sodium chloride, 8-12 mM sodium phosphate and 0.001-0.01% w/v pluronic acid F-68, at a pH between 7.2-7.4.

24. The method of claim 22, wherein the formulation comprises 180 mM sodium chloride, 10 mM sodium phosphate and 0.001% w/v pluronic acid F-68, at a pH of 7.3.

25. A method of treating a neurological disease in a subject, the method comprising: administering to the subject a pharmaceutical composition according to the method of any one of claims 1-24.

26. The method of claim 25, wherein the neurological disease is Parkinson's Disease.

27. The method of claim 25 or claim 26, wherein the administration of the pharmaceutical composition is sufficient to produce a therapeutically effective outcome.

AMENDED SHEET

Date Reçue/Date Received 2020-11-03

28. The method of claim 27, wherein the therapeutically effective outcome comprises an increase in AADC enzyme activity relative to baseline of more than 50%, as measured by PET ^{18}F-Dopa analysis 2-7 months after administration.

29. The method of claim 28, wherein the increase in AADC enzyme activity relative to baseline is between 50%-85%.

30. The method of claim 28, wherein the increase in AADC enzyme activity relative to baseline is between 60%-85%.

31. The method of claim 28, wherein the increase in AADC enzyme activity relative to baseline is between 70%-85%.

32. The method of any one of claims 27-31, wherein the therapeutically effective outcome comprises a reduced UPDRS III score in the "ON" medication state relative to baseline of up to 20%, as measured 6 months after administration.

33. The method of claim 32, wherein the reduction in UPDRS III score in the "ON" medication state relative to baseline is between 15%-20% at 6 months.

34. The method of any one of claims 27-33, wherein the therapeutically effective outcome comprises a reduced UPDRS III score in the "ON" medication state relative to baseline of up to 30%, as measured 12 months after administration.

35. The method of claim 34, wherein the reduction in UPDRS III score in the "ON" medication state relative to baseline is between 20%-30% at 12 months.

36. The method of claim 34 or claim 35, wherein the patient has a baseline UPDRS III "ON" score greater than 10.

37. The method of claim 34 or claim 35, wherein the patient has a baseline UPDRS III "ON" score between 10 and 14.

38. The method of any one of claims 27-37, wherein the therapeutically effective outcome comprises a reduced UPDRS III score in the "OFF" medication state relative to baseline of up to 26%, as measured 6 months after administration.

39. The method of claim 38, wherein the reduction in UPDRS III score in the "OFF" medication state relative to baseline is between 20%-26% at 6 months.

40. The method of any one of claims 27-39, wherein the therapeutically effective outcome comprises a reduced UPDRS III score in the "OFF" medication state relative to baseline of up to 33%, as measured 12 months after administration.

41. The method of claim 40, wherein the reduction in UPDRS III score in the "OFF" medication state relative to baseline is between 25%-33% at 12 months.

42. The method of claim 40 or claim 41, wherein the patient has a baseline UPDRS III "OFF" score greater than 30.

43. The method of claim 40 or claim 41, wherein the patient has a baseline UPDRS III "OFF" score between 30 and 36.5.

44. The method of any one of claims 27-43, wherein the therapeutically effective outcome comprises an increase in diary ON-time without troublesome dyskinesia of at least 3.0 hours relative to baseline, as measured by Hauser motor diary at 6 months.

45. The method of claim 44, wherein the increase in diary ON-time without troublesome dyskinesia relative to baseline is between 3.0 hours to 3.9 hours at 6 months.

46. The method of any one of claims 27-45, wherein the therapeutically effective outcome comprises an increase in diary ON-time without troublesome dyskinesia of at least 2.5 hours relative to baseline, as measured by Hauser motor diary at 12 months.

47. The method of claim 46, wherein the increase in diary ON-time without troublesome dyskinesia relative to baseline is between 2.5 hours to 3.0 hours at 12 months.

48. The method of any one of claims 27-47, wherein the therapeutically effective outcome comprises a decrease in diary OFF-time of at least 3.0 hours relative to baseline, as measured by Hauser motor diary at 6 months.

49. The method of claim 48, wherein the decrease in diary OFF-time relative to baseline is between 3.0 hours to 3.9 hours at 6 months.

50. The method of any one of claims 27-49, wherein the therapeutically effective outcome comprises a decrease in diary OFF-time of at least 2.5 hours relative to baseline, as measured by Hauser motor diary at 12 months.

51. The method of claim 50, wherein the decrease in diary OFF-time relative to baseline is between 2.5 hours to 3.0 hours at 12 months.

FIG. 1

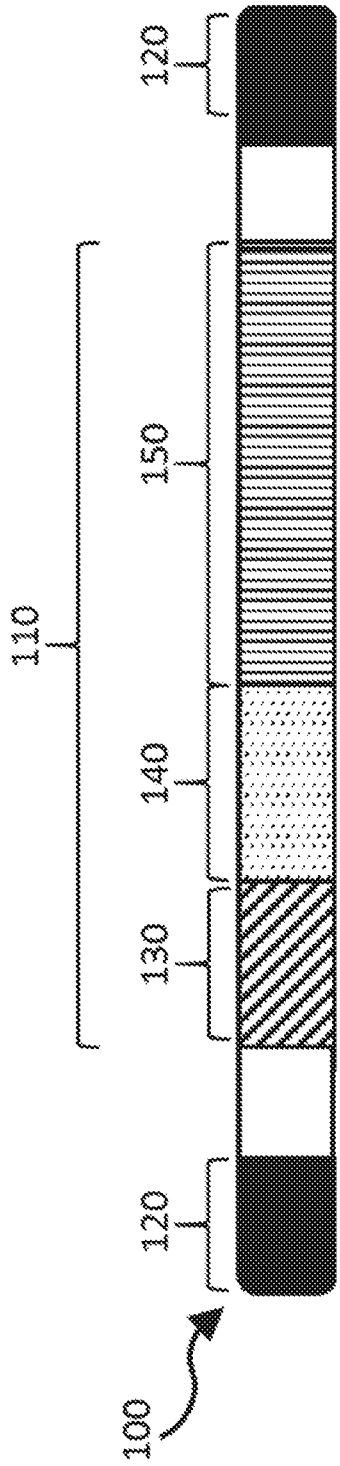


FIG. 2

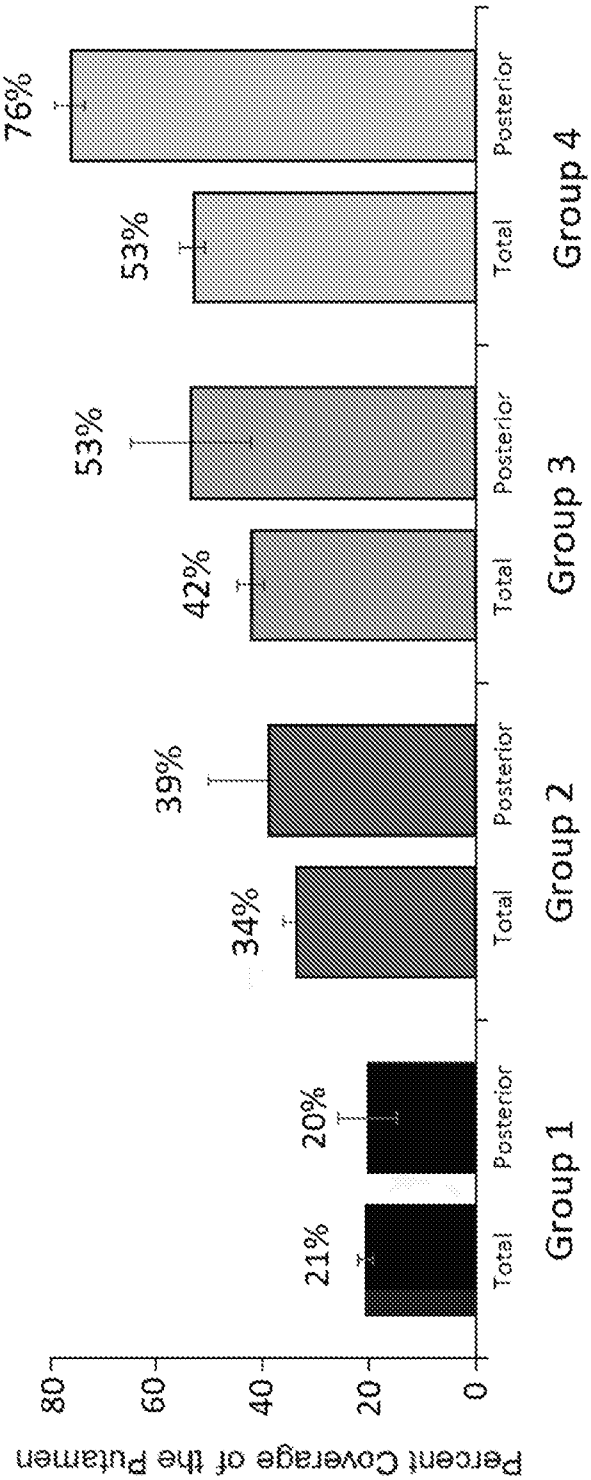

Percent Coverage of the Putamen
0
20
40
60
80
21%
20%
34%
39%
42%
53%
53%
76%
Total
Posterior
Group 1
Group 2
Group 3
Group 4

FIG. 3

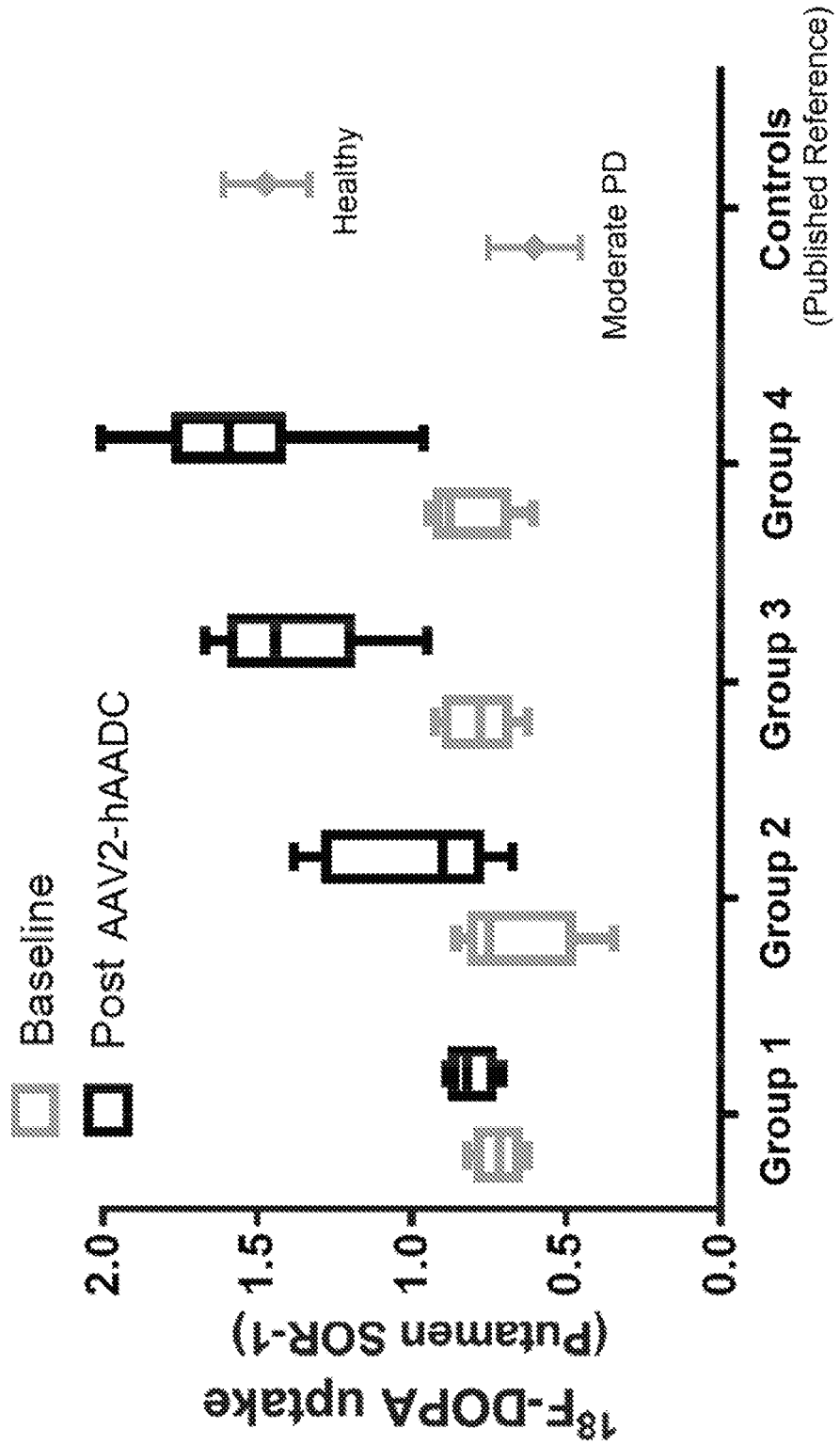

^{18}F-DOPA uptake
(Putamen SOR-1)
2.0
1.5
1.0
0.5
0.0
Baseline
Post AAV2-hAADC
Healthy
Moderate PD
Group 1
Group 2
Group 3
Group 4
Controls
(Published Reference)

FIG. 4

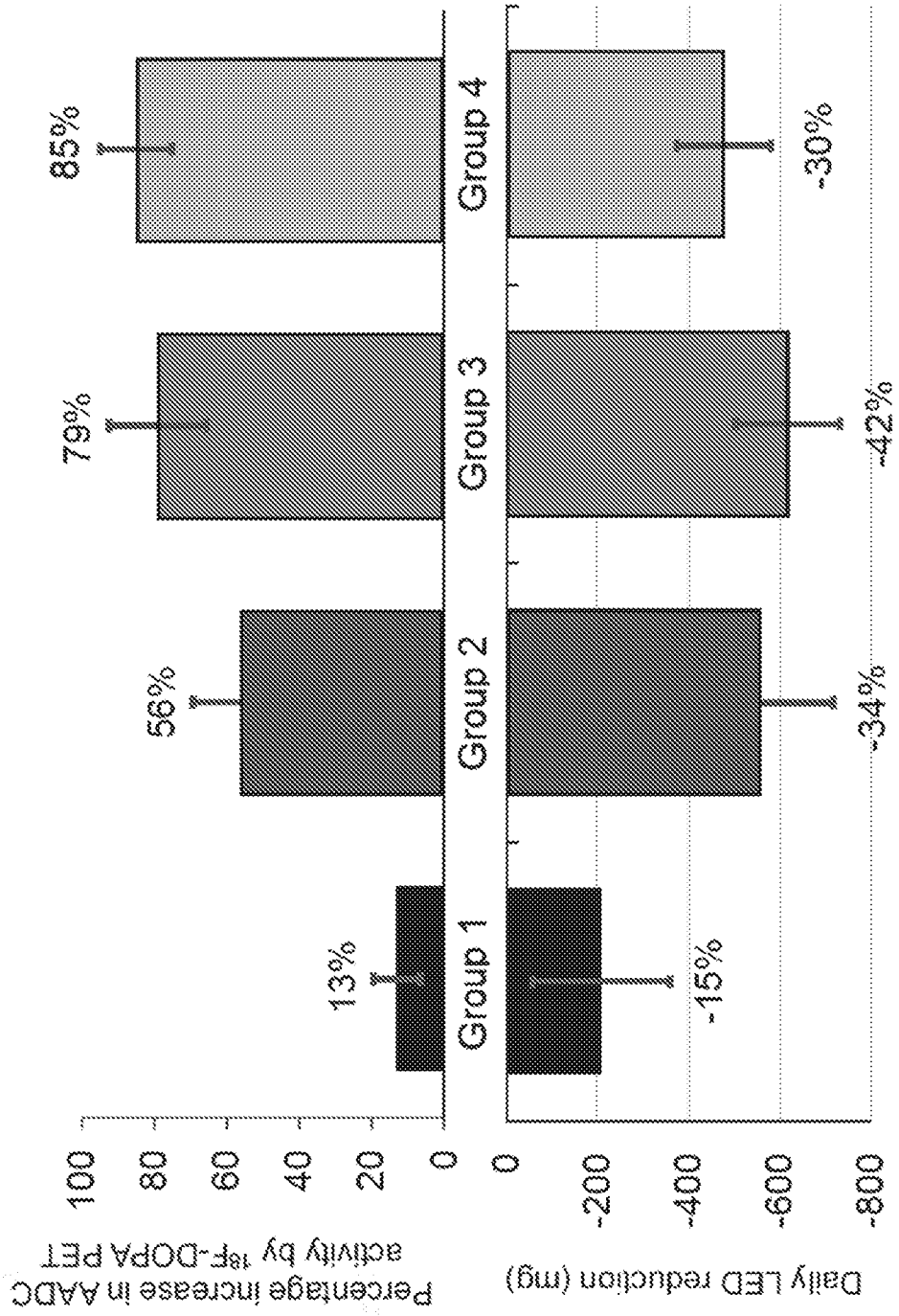

Percentage increase in AADC activity by 18F-DOPA PET
Daily LED reduction (mg)
100
80
60
40
20
0
0
-200
-400
-600
-800
13%
56%
79%
85%
-15%
-34%
-42%
-30%
Group 1
Group 2
Group 3
Group 4

FIG. 5

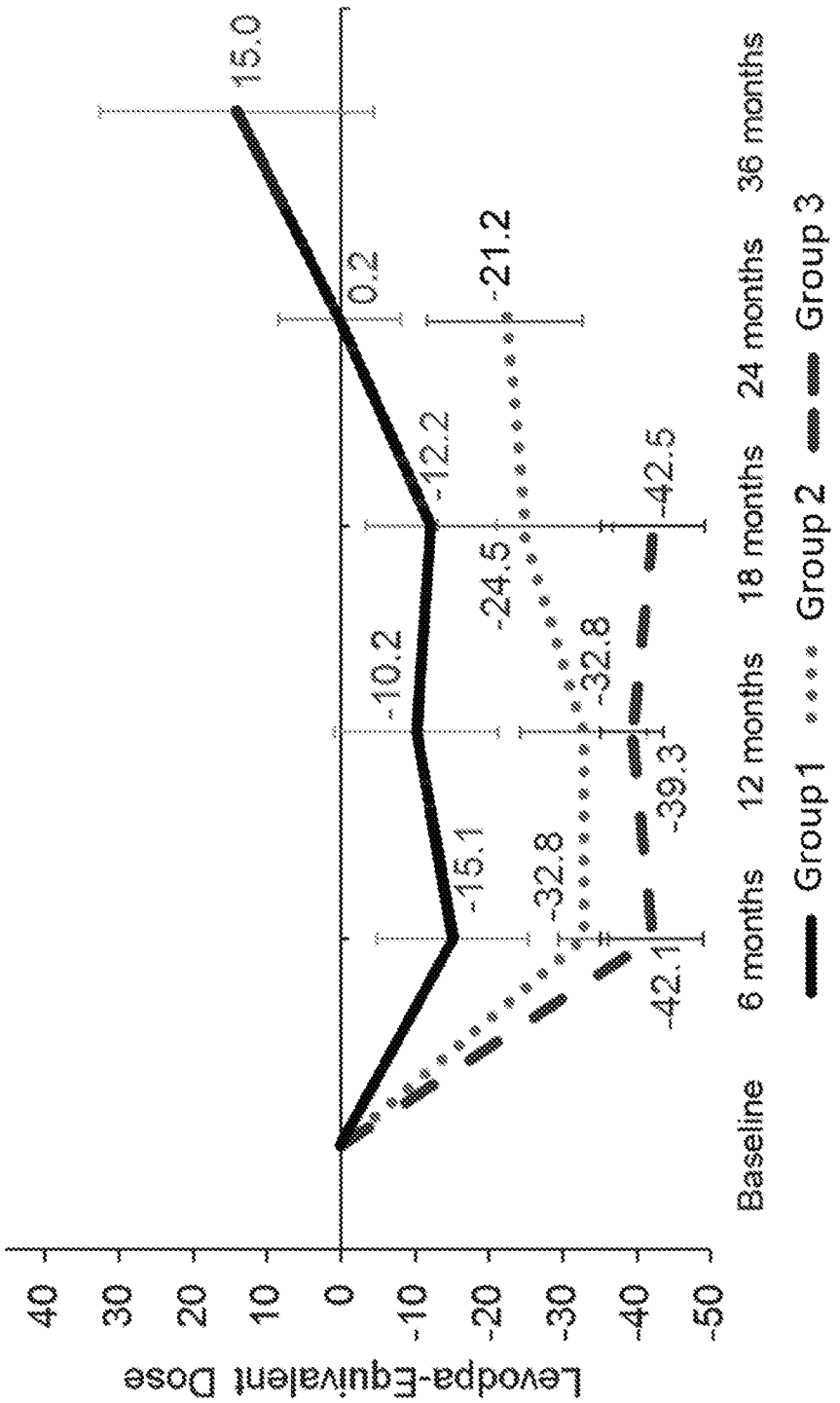

Levodpa-Equivalent Dose
40
30
20
10
0
-10
-20
-30
-40
-50
Baseline
6 months
12 months
18 months
24 months
36 months
15.0
0.2
-10.2
-15.1
-12.2
-21.2
-24.5
-32.8
-32.8
-39.3
-42.5
-42.1
Group 1
Group 2
Group 3

FIG. 6

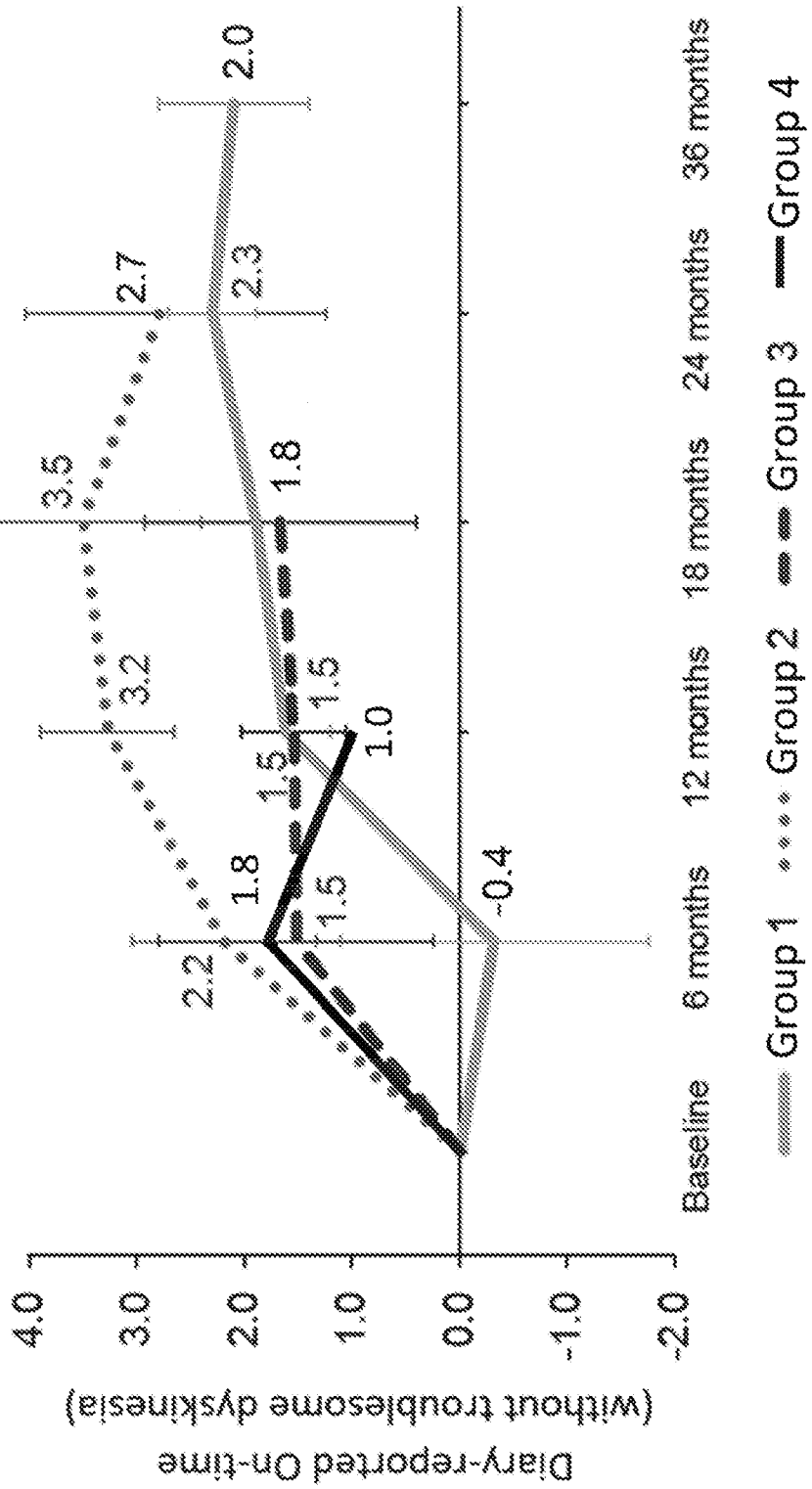

Diary-reported On-time
(without troublesome dyskinesia)
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
Baseline
6 months
12 months
18 months
24 months
36 months
2.2
1.8
1.5
3.2
1.5
1.5
3.5
1.8
2.7
2.3
2.0
1.0
-0.4
Group 1
Group 2
Group 3
Group 4

FIG. 7

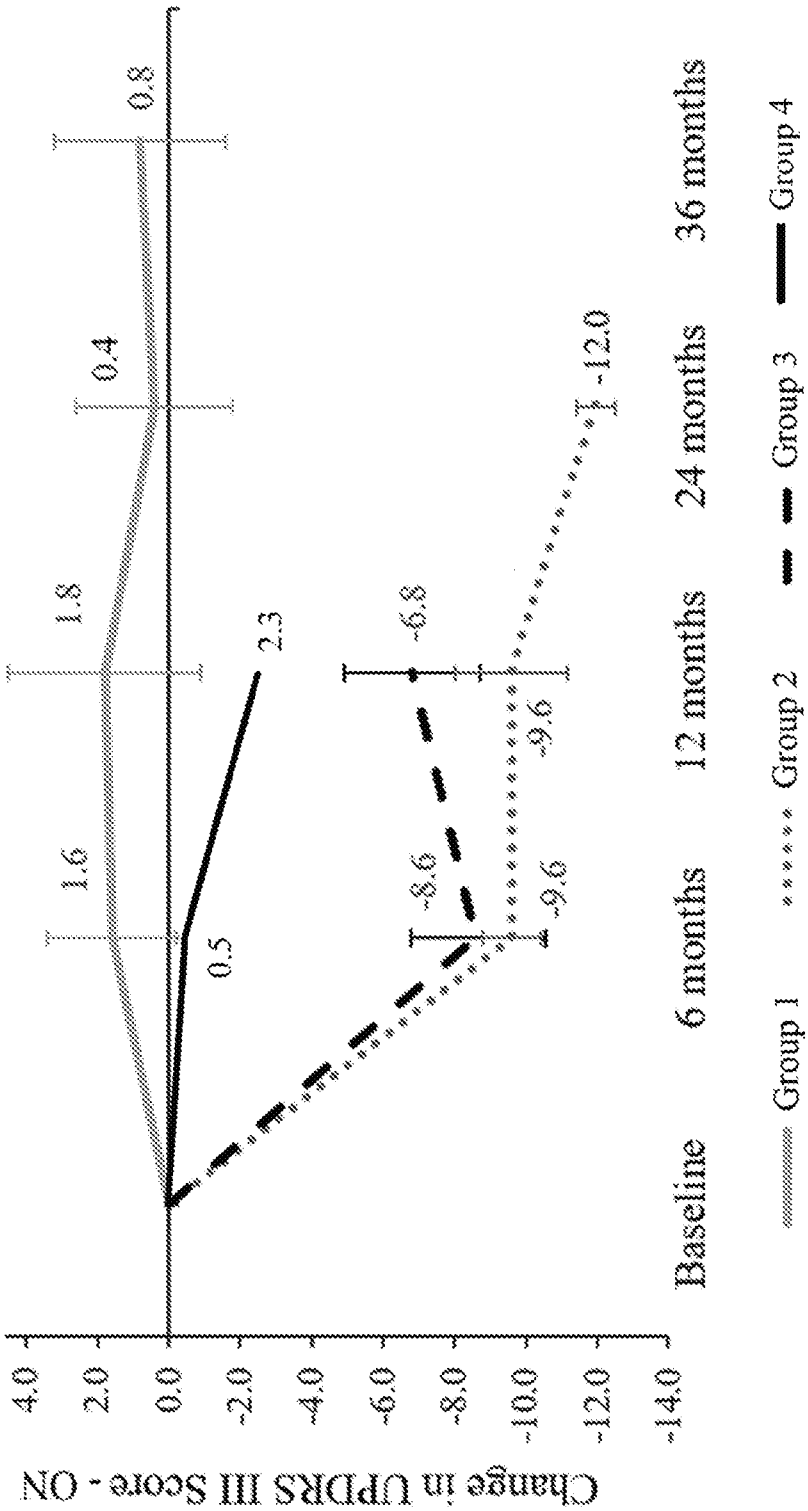

Change in UPDRS III Score - ON
4.0
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
-14.0
Baseline
6 months
12 months
24 months
36 months
Group 1
Group 2
Group 3
Group 4
1.6
0.5
1.8
2.3
0.4
-6.6
-9.6
-6.8
-9.6
-12.0
0.8

FIG. 8

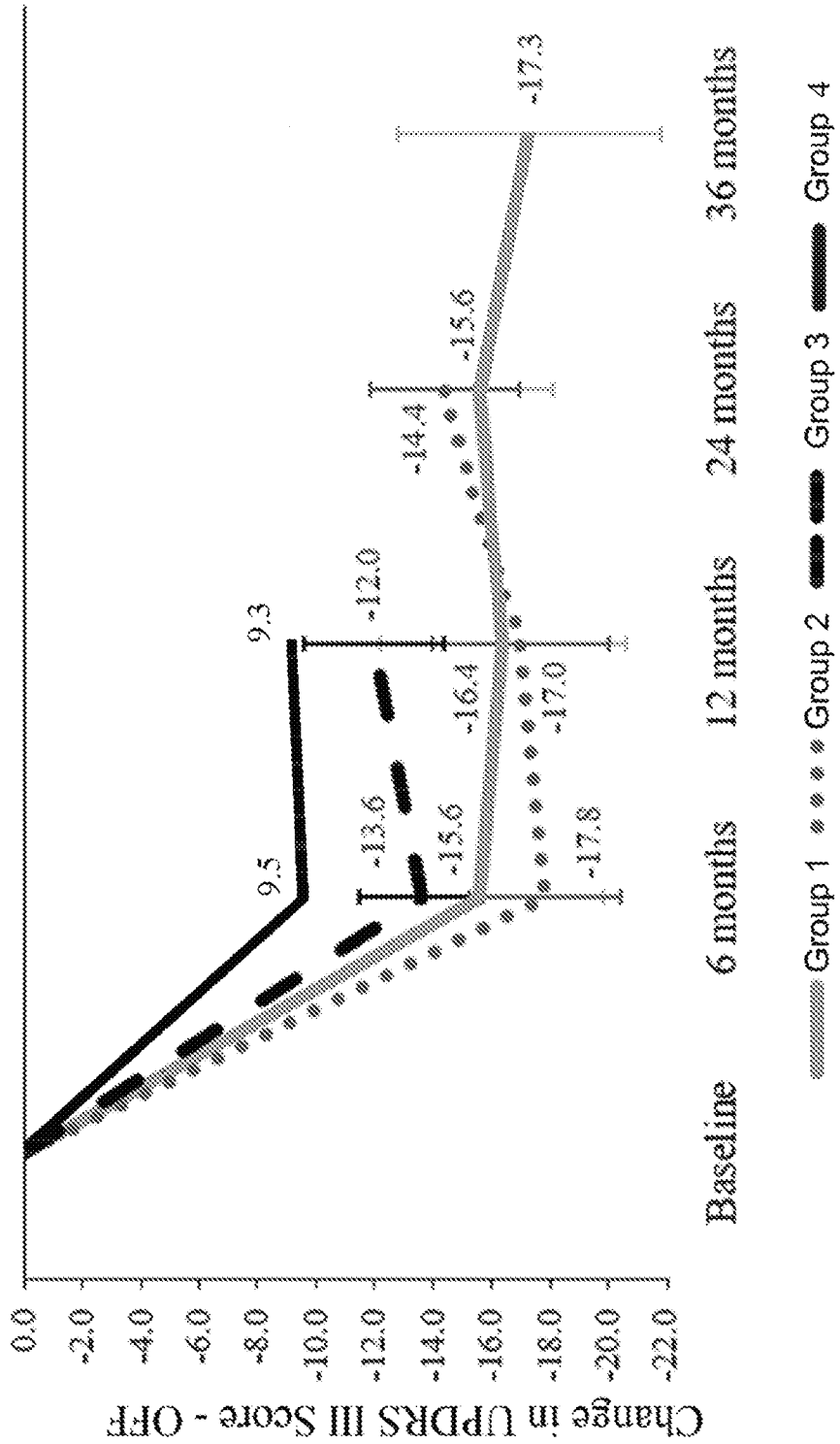

Change in UPDRS III Score - OFF
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
-14.0
-16.0
-18.0
-20.0
-22.0
Baseline
6 months
12 months
24 months
36 months
9.5
9.3
-13.6
-15.6
-12.0
-16.4
-14.4
-17.0
-15.6
-17.8
-17.3
Group 1
Group 2
Group 3
Group 4

FIG. 9

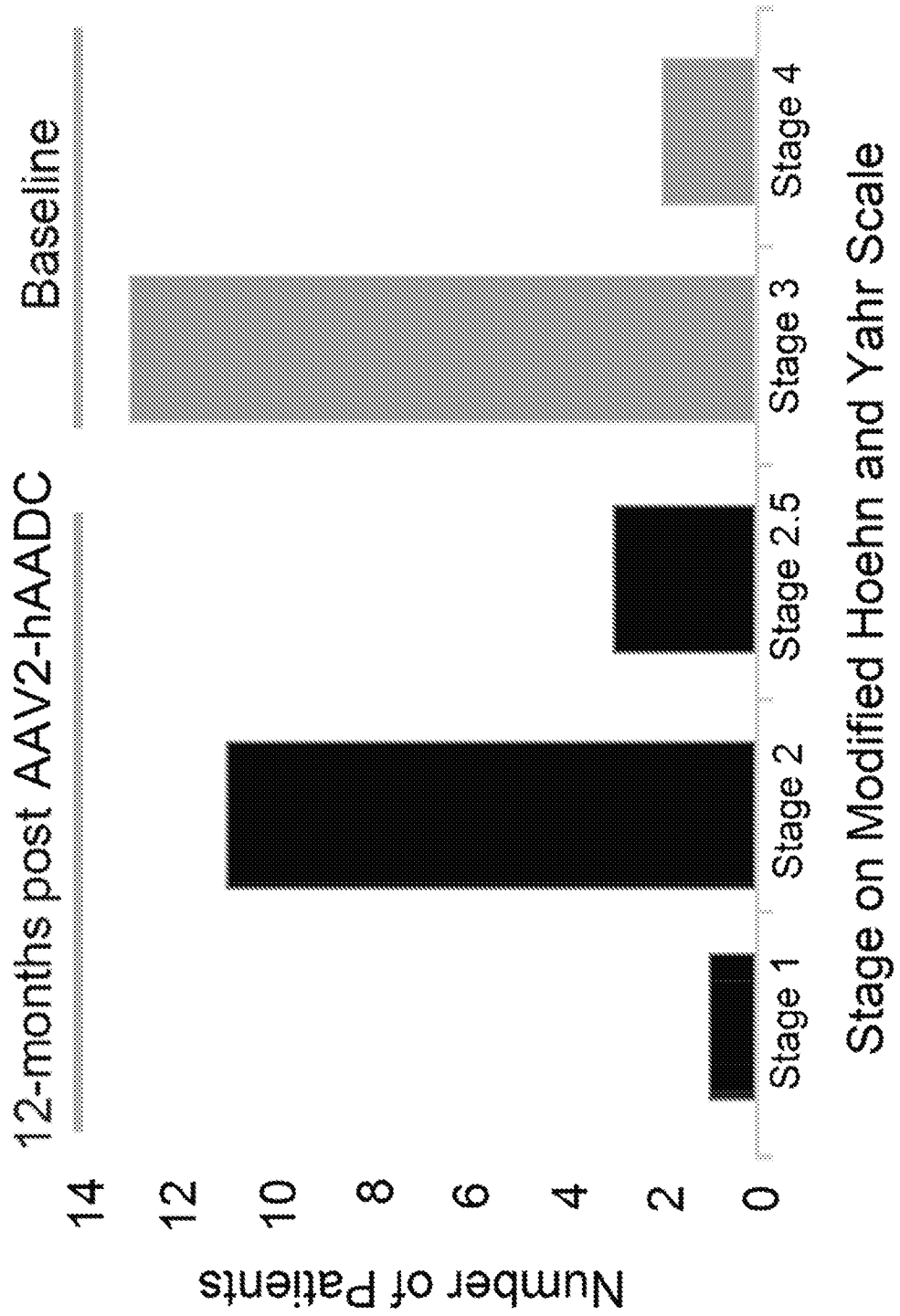

12-months post AAV2-hAADC
Baseline
Number of Patients
0
2
4
6
8
10
12
14
Stage 1
Stage 2
Stage 2.5
Stage 3
Stage 4
Stage on Modified Hoehn and Yahr Scale

FIG. 10

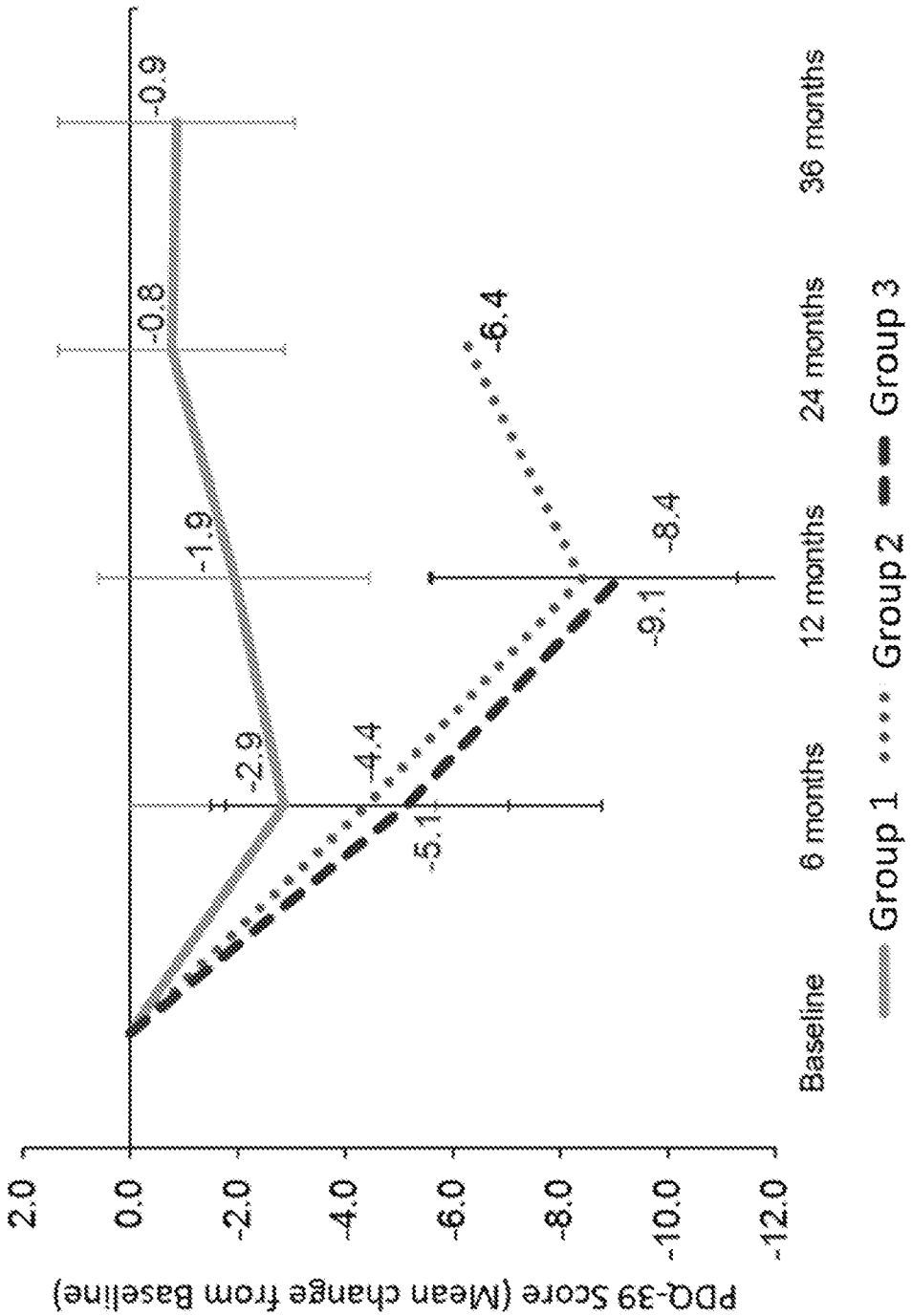

PDQ-39 Score (Mean change from Baseline)
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
Baseline
6 months
12 months
24 months
36 months
-0.9
-0.8
-1.9
-2.9
-4.4
-5.1
-6.4
-8.4
-9.1
Group 1
Group 2
Group 3

FIG. 11a

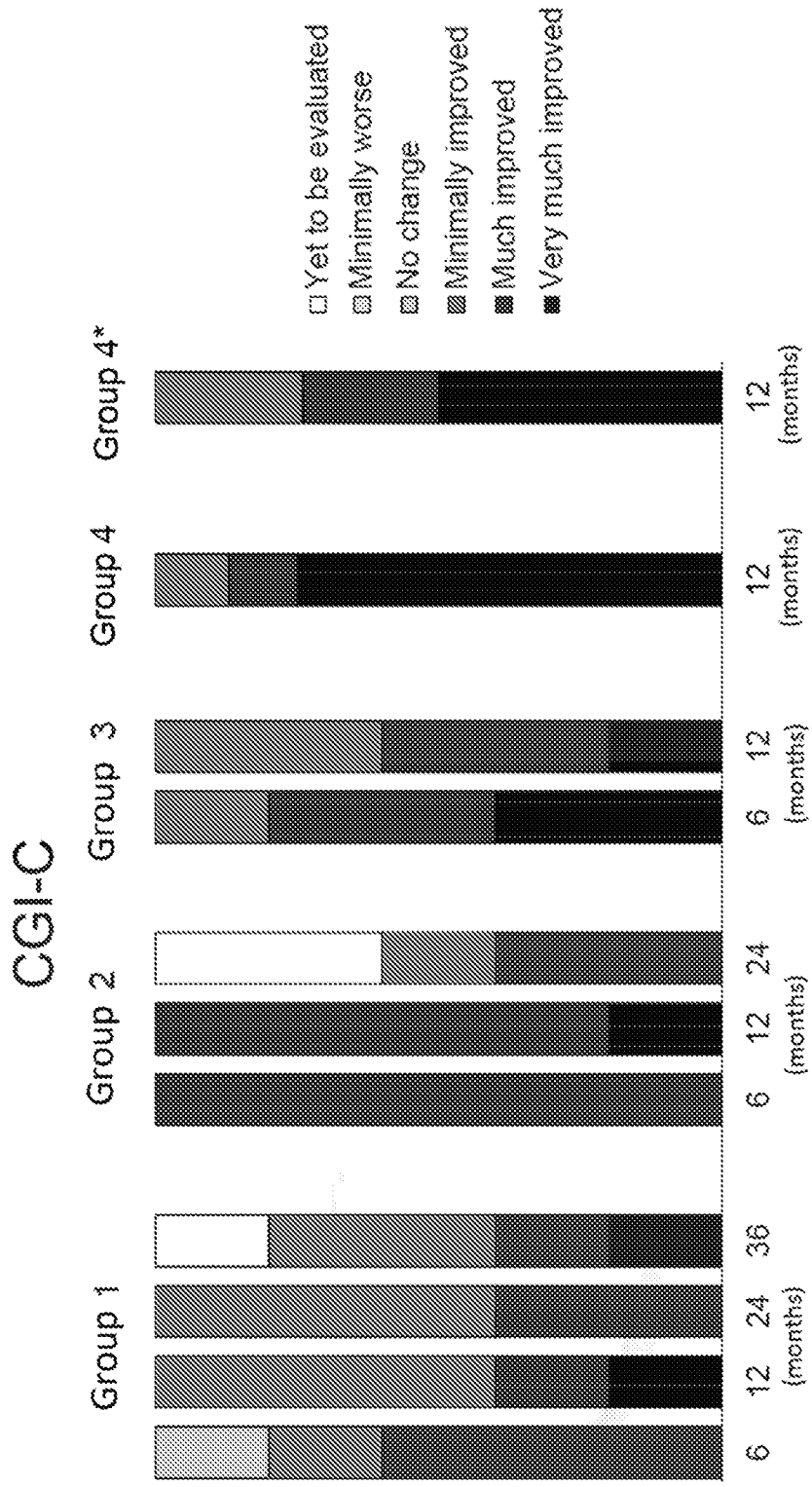

CGI-C
Yet to be evaluated
Minimally worse
No change
Minimally improved
Much improved
Very much improved
Group 1
Group 2
Group 3
Group 4
Group 4*
6 12 24 36 (months)
6 12 24 (months)
6 12 (months)
12 (months)
12 (months)

FIG. 11b

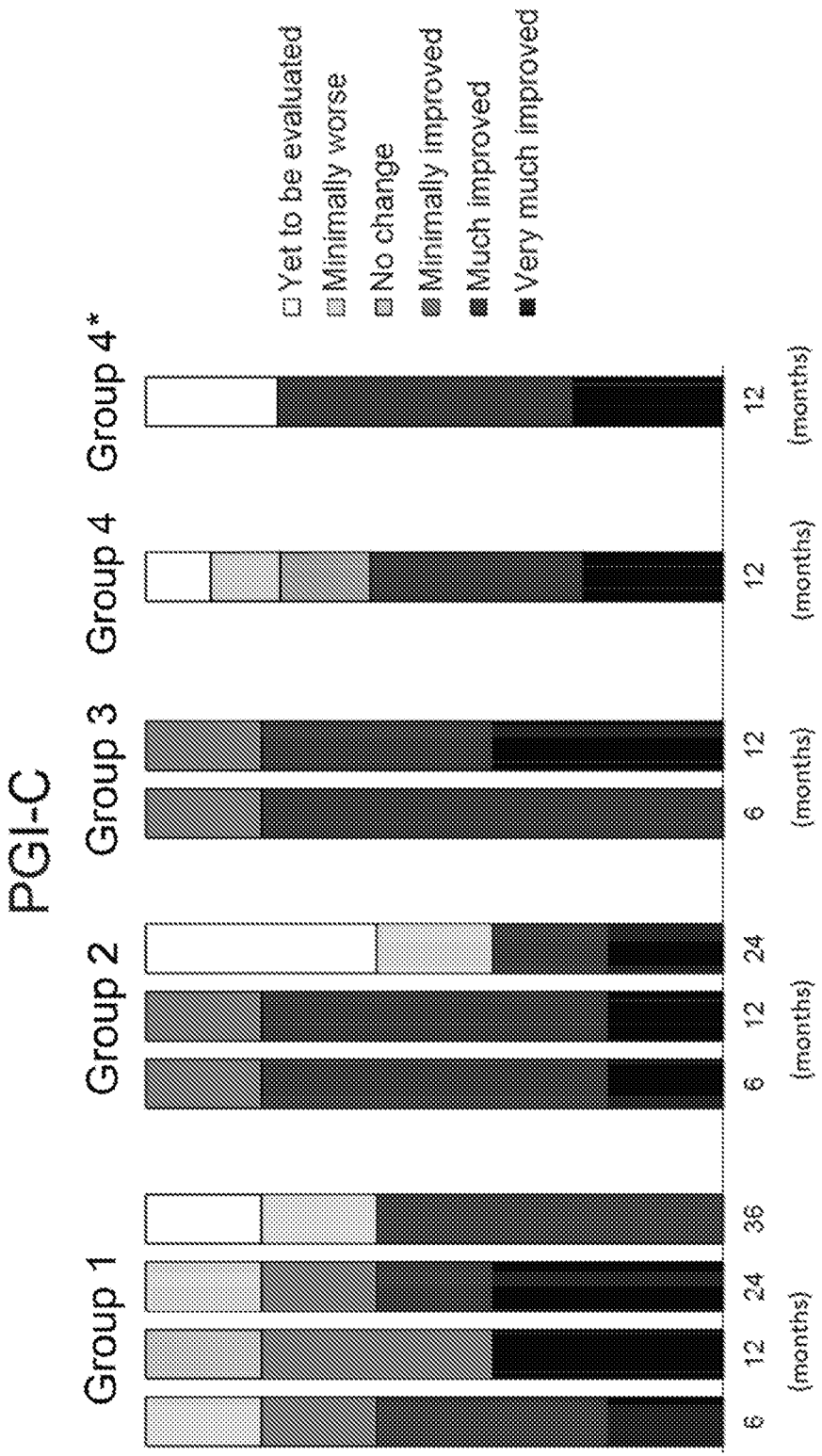

PGI-C
Group 1
Group 2
Group 3
Group 4
Group 4*
Yet to be evaluated
Minimally worse
No change
Minimally improved
Much improved
Very much improved
6
12
24
36
(months)

FIG. 12a

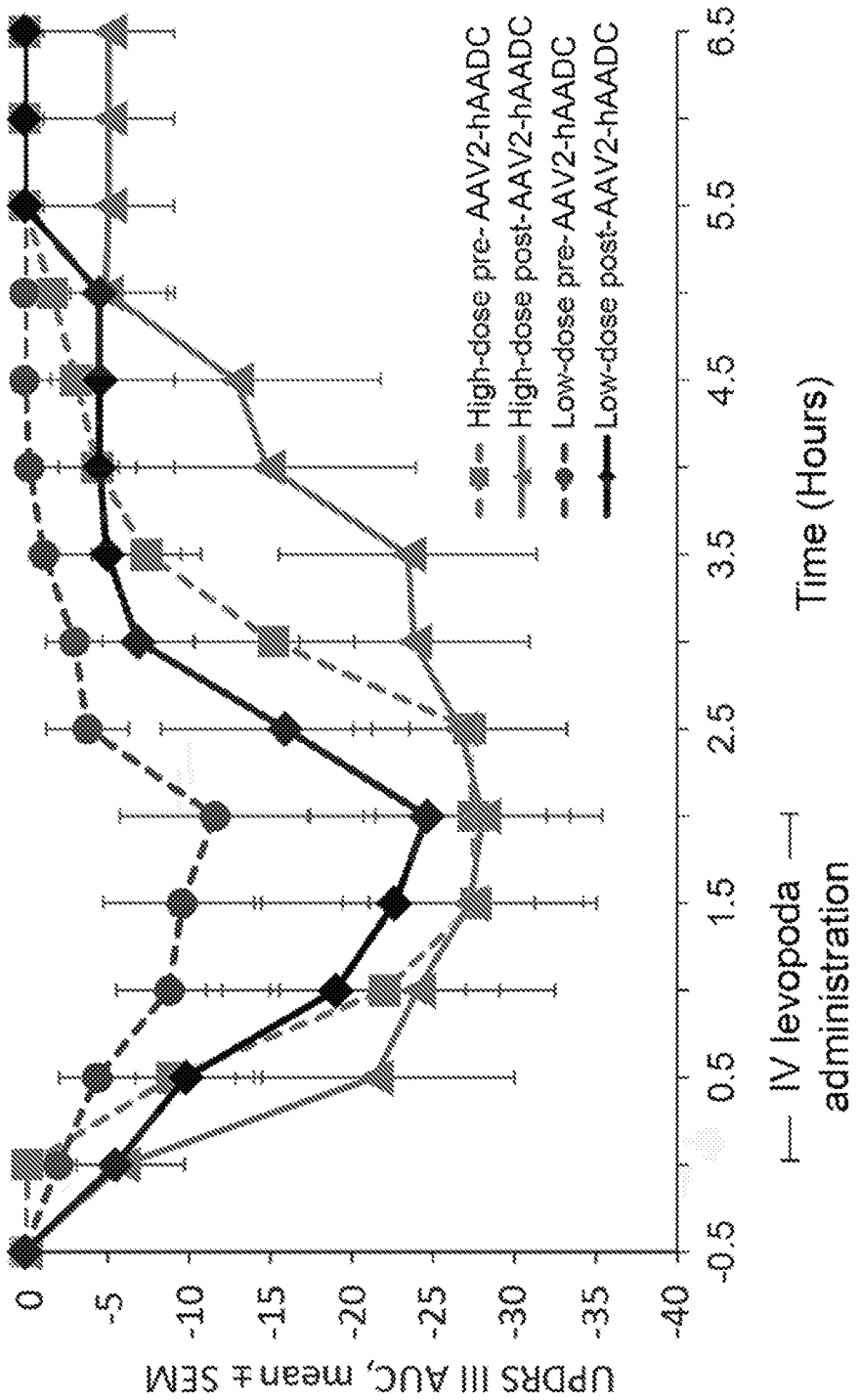

UPDRS III AUC, mean ± SEM
0
-5
-10
-15
-20
-25
-30
-35
-40
-0.5
0.5
1.5
2.5
3.5
4.5
5.5
6.5
Time (Hours)
IV levopoda administration
High-dose pre- AAV2-hAADC
High-dose post-AAV2-hAADC
Low-dose pre-AAV2-hAADC
Low-dose post-AAV2-hAADC

FIG. 12b

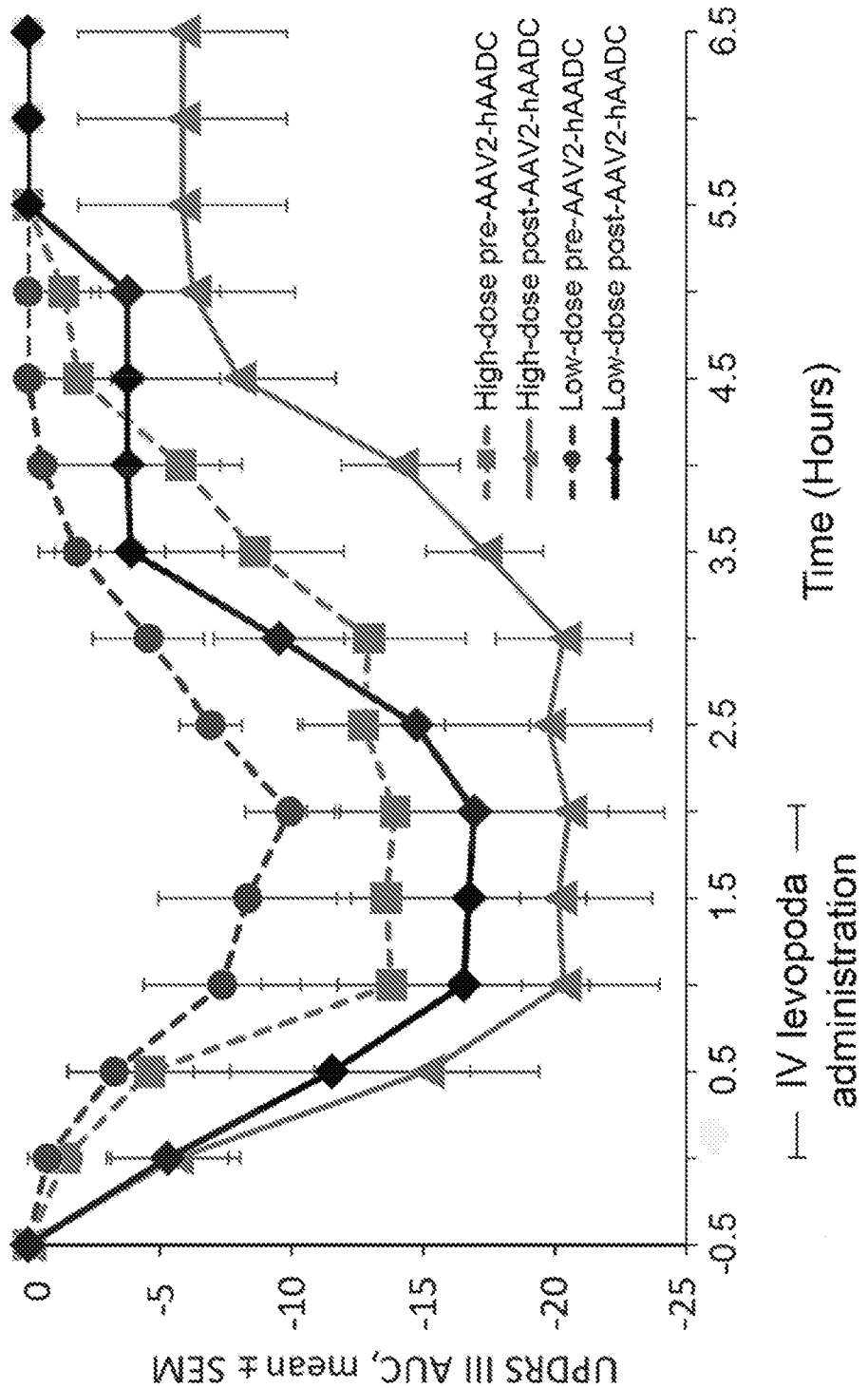

UPDRS III AUC, mean ± SEM
0
-5
-10
-15
-20
-25
-0.5
0.5
1.5
2.5
3.5
4.5
5.5
6.5
Time (Hours)
IV levopoda administration
High-dose pre-AAV2-hAADC
High-dose post-AAV2-hAADC
Low-dose pre-AAV2-hAADC
Low-dose post-AAV2-hAADC

FIG. 12c

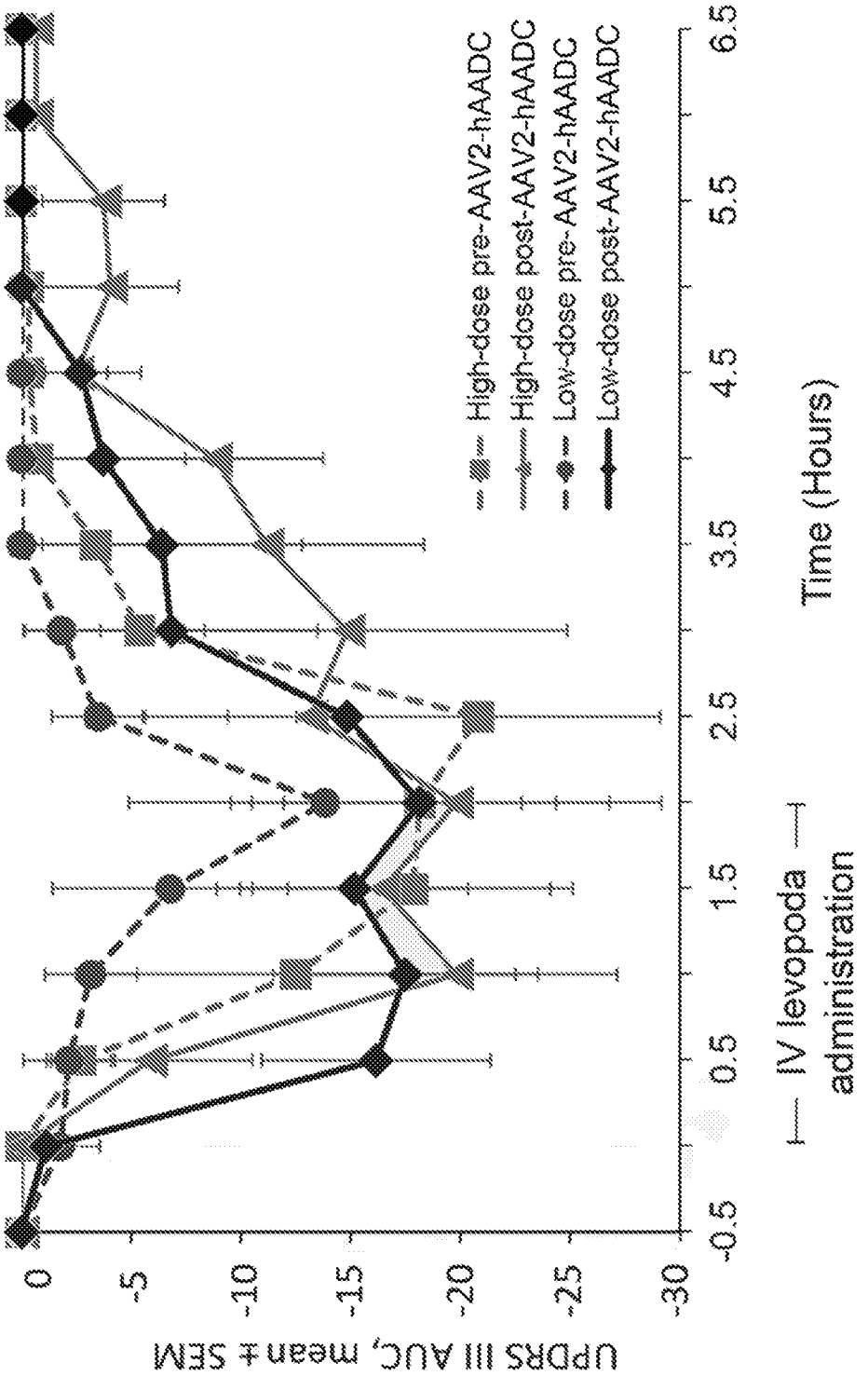

UPDRS III AUC, mean ± SEM
0
-5
-10
-15
-20
-25
-30
-0.5
0.5
1.5
2.5
3.5
4.5
5.5
6.5
Time (Hours)
IV levopoda administration
High-dose pre-AAV2-hAADC
High-dose post-AAV2-hAADC
Low-dose pre-AAV2-hAADC
Low-dose post-AAV2-hAADC

FIG. 13

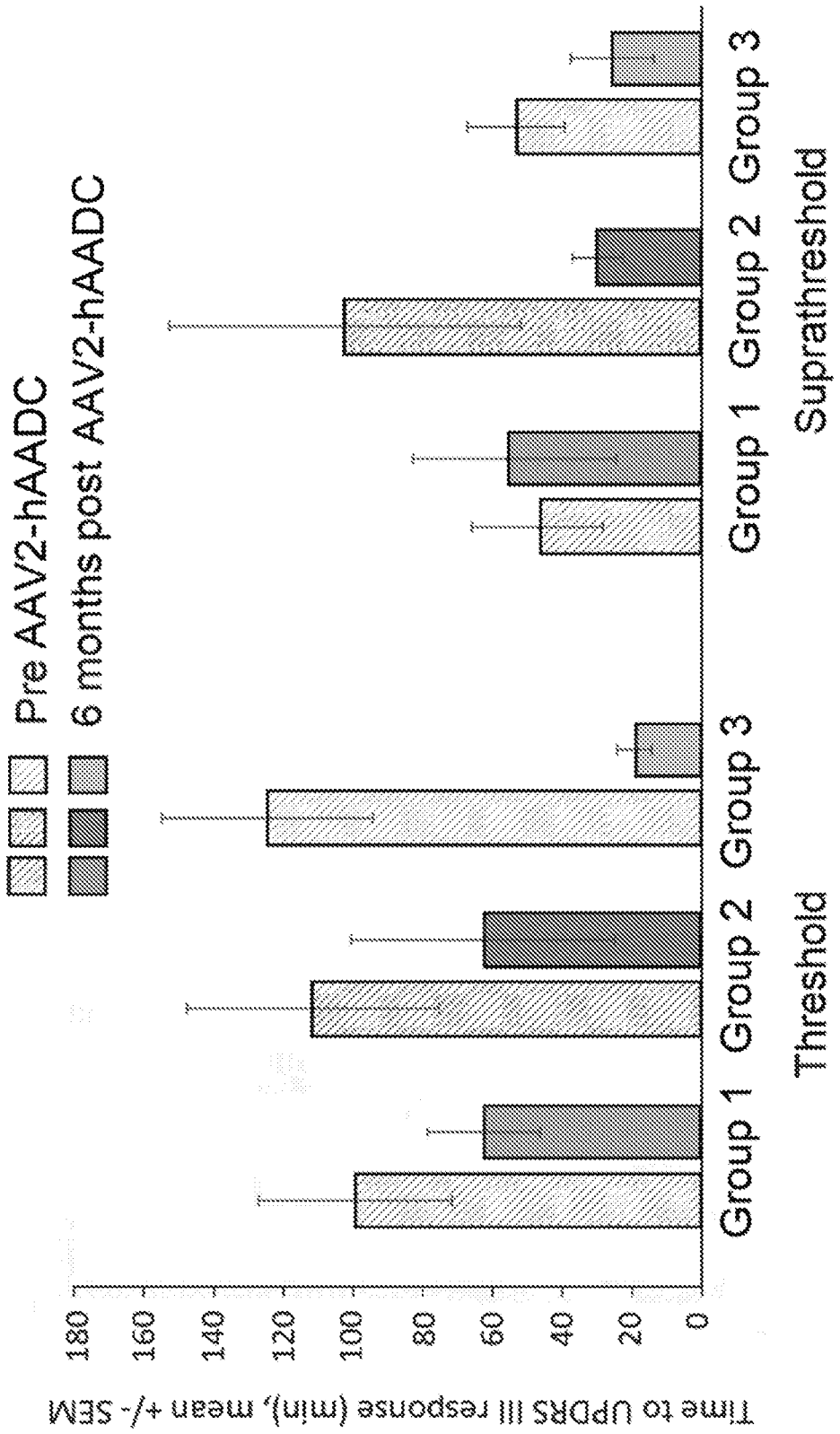

Pre AAV2-hAADC
6 months post AAV2-hAADC
Time to UPDRS III response (min), mean +/- SEM
180
160
140
120
100
80
60
40
20
0
Group 1
Group 2
Group 3
Threshold
Group 1
Group 2
Group 3
Suprathreshold

FIG. 14

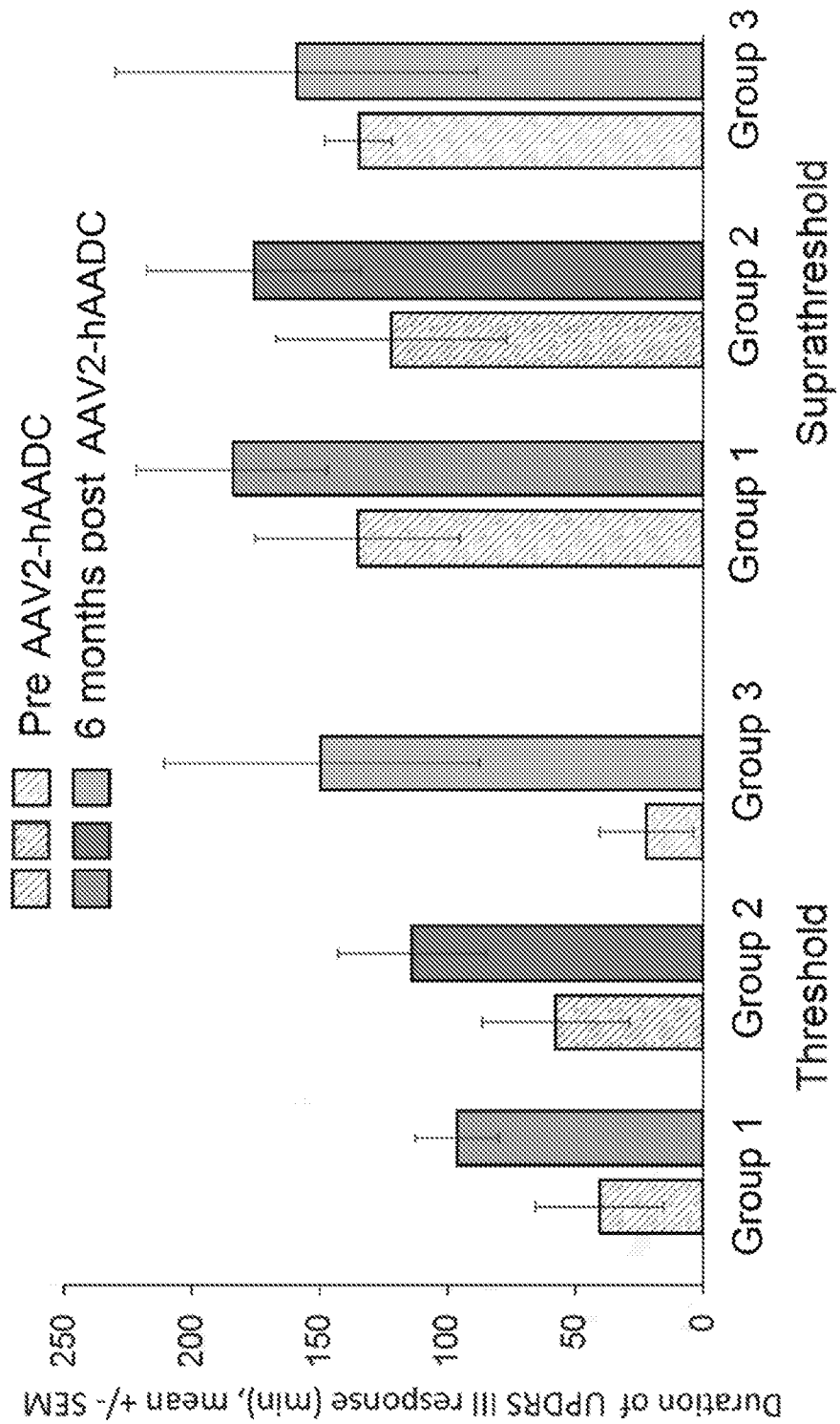

Pre AAV2-hAADC
6 months post AAV2-hAADC
Duration of UPDRS III response (min), mean +/- SEM
250
200
150
100
50
0
Group 1
Group 2
Group 3
Threshold
Group 1
Group 2
Group 3
Suprathreshold

FIG. 15

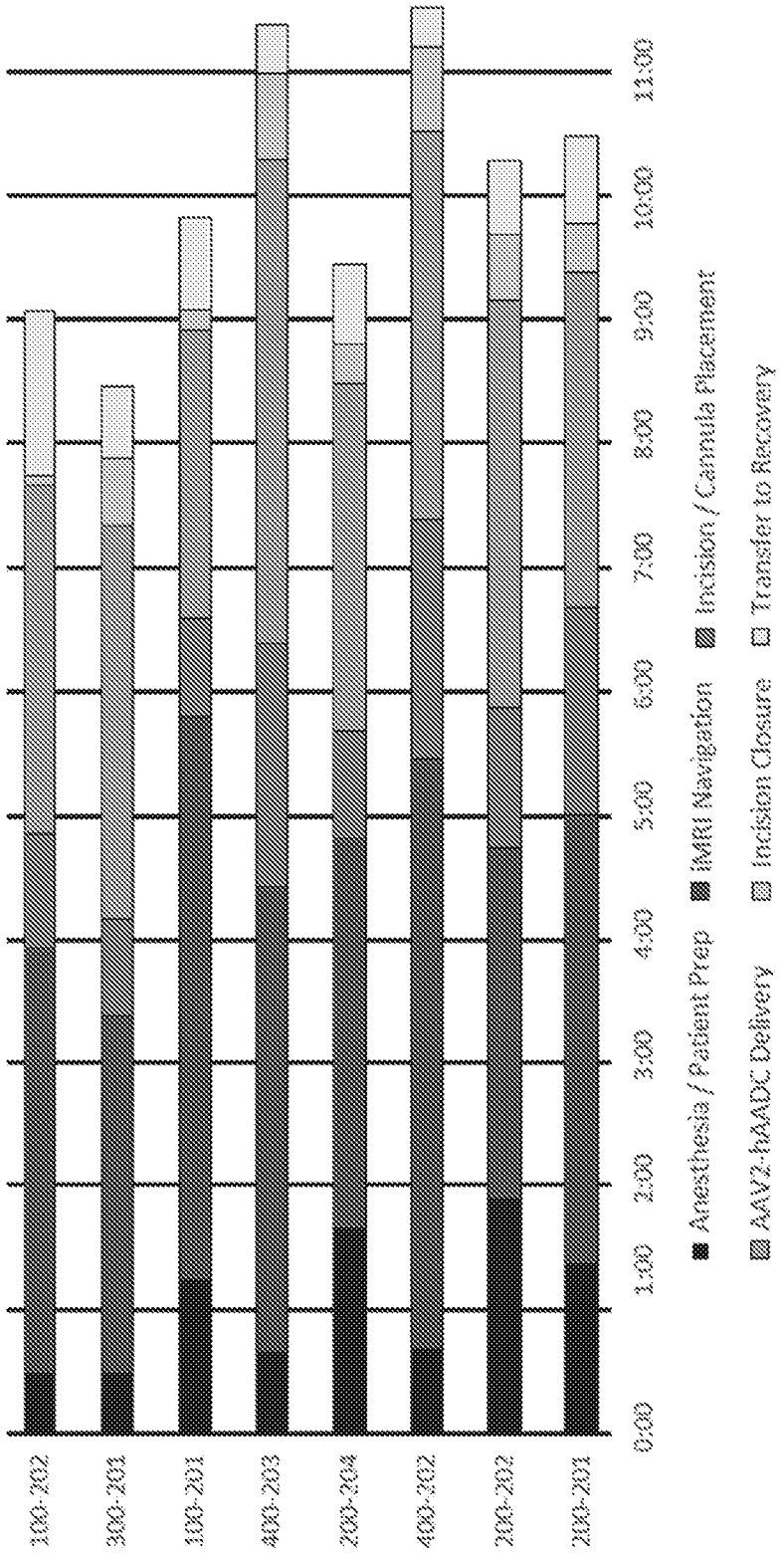
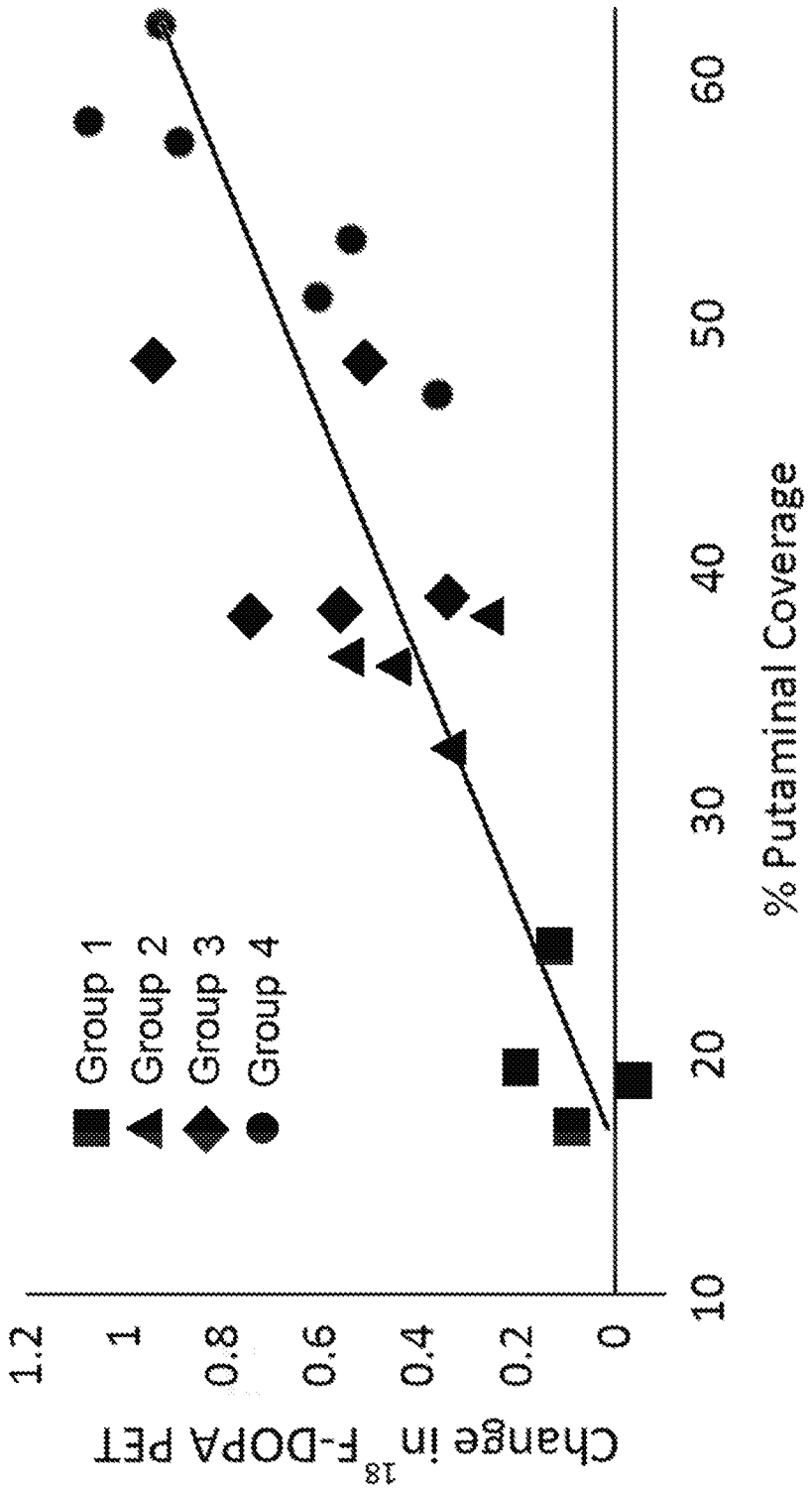

0:00
1:00
2:00
3:00
4:00
5:00
6:00
7:00
8:00
9:00
10:00
11:00
300-202
300-201
100-201
400-203
200-204
400-202
200-202
200-201
Anesthesia / Patient Prep
iMRI Navigation
Incision / Cannula Placement
AAV2-hAADC Delivery
Incision Closure
Transfer to Recovery

FIG. 16


Change in ^{18}F-DOPA PET
1.2
1
0.8
0.6
0.4
0.2
0
10
20
30
40
50
60
% Putaminal Coverage
Group 1
Group 2
Group 3
Group 4