COMPOSITIONS AND METHODS OF TREATING HUNTINGTON'S DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/501,786, filed May 5, 2017, entitled Compositions and Methods of Treating Huntington's Disease, U.S. Provisional Patent Application No. 62/507,921, filed May 18, 2017, entitled Compositions and Methods of Treating Huntington's Disease, and U.S. Provisional Patent Application No. 62/520,086, filed June 15, 2017, the contents of each of which is incorporated herein by reference in its entirety.

REFERENCE TO THE SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 14482_0152_228_SEQ_LISTING.txt, created on May 1, 2018, which is 6,780,111 bytes in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present invention relates to compositions, methods and processes for the design, preparation, manufacture, use and/or formulation of AAV particles comprising modulatory polynucleotides, e.g., polynucleotides encoding small interfering RNA (siRNA) molecules which target the Huntingtin (HTT) gene (e.g., the wild-type or the mutated CAG-expanded HTT gene). Targeting of the mutated HTT gene may interfere with the HTT gene expression and the resultant HTT protein production. The AAV particles comprising modulatory polynucleotides encoding the siRNA molecules may be inserted into recombinant adeno-associated virus (AAV) vectors. Methods for using the AAV particles to inhibit the HTT gene expression in a subject with a neurodegenerative disease (e.g., Huntington's Disease (HD)) are also disclosed.

BACKGROUND OF THE INVENTION

[0004] Huntington's Disease (HD) is a monogenic fatal neurodegenerative disease characterized by progressive chorea, neuropsychiatric and cognitive dysfunction. Huntington's Disease is known to be caused by an autosomal dominant triplet (CAG) repeat expansion which encodes poly-glutamine in the N-terminus of the huntingtin (HTT) protein. This repeat expansion results in a toxic gain of function of HTT and ultimately leads to striatal neurodegeneration which progresses to widespread brain atrophy. Symptoms typically appear between the ages of 35-44 and life expectancy subsequent to onset is 10-25 years. Interestingly, the length of the HTT expansion correlates with both age of onset and rate of disease progression, with longer expansions linked to greater severity of disease. In a small percentage

of the HD population (~6%), disease onset occurs from 2-20 years of age with appearance of an akinetic-rigid syndrome. These cases tend to progress faster than those of the later onset variety and have been classified as juvenile or Westphal variant HD. It is estimated that approximately 35,000-70,000 patients are currently suffering from HD in the US and Europe. Currently, only symptomatic relief and supportive therapies are available for treatment of HD, with a cure yet to be identified. Ultimately, individuals with HD succumb to other diseases (e.g., pneumonia, heart failure), choking, suffocation or other complications such as physical injury from falls.

[0005] The mechanisms by which CAG-expanded HTT results in neurotoxicity are not well understood. Huntingtin protein is expressed in all cells, though its concentration is highest in the brain. The normal function of HTT is unknown, but in the brains of HD patients, HTT aggregates into abnormal nuclear inclusions. It is now believed that it is this process of misfolding and aggregating along with the associated protein intermediates (i.e. the soluble species and toxic N-terminal fragments) that result in neurotoxicity.

[0006] Studies in animal models of HD have suggested that phenotypic reversal is feasible, for example, subsequent to gene shut off in regulated-expression models. Further, animal models in which silencing of HTT was tested, demonstrated promising results with the therapy being both well tolerated and showing potential therapeutic benefit. These findings indicate that HTT silencing may serve as a potential therapeutic target for treatment of HD.

[0007] The adeno-associated virus (AAV) is a member of the parvovirus family and has emerged as an attractive vector for gene therapy in large part because this virus is apparently non-pathogenic; in fact, AAV has not been associated with any human disease. Further appeal is due to its ability to transduce dividing and non-diving cells (including efficient transduction of neurons), diminished proinflammatory and immune responses in humans, its inability to autonomously replicate without a helper virus (AAV is a helper-dependent DNA parvovirus which belongs to the genus *Dependovirus*), and its long-term gene expression. Although over 10 recombinant AAV serotypes (rAAV) have been engineered into vectors, rAAV2 is the most frequently employed serotype for gene therapy trials. Additional rAAV serotypes have been developed and tested in animal models that are more efficient at neuronal transduction.

[0008] The present invention develops an AAV particle comprising modulatory polynucleotides encoding novel double stranded RNA (dsRNA) constructs and siRNA constructs and methods of their design, to inhibit or prevent the expression of CAG-expanded HTT in HD patients for treatment of the disease.

SUMMARY OF THE INVENTION

[0009] Described herein are methods, processes, compositions kits and devices for the administration of AAV particles comprising modulatory polynucleotides encoding siRNA molecules for the treatment, prophylaxis, palliation and/or amelioration of Huntington's Disease (HD) related symptoms and disorders.

[0010] The present invention provides viral genomes comprising modulatory polynucleotides encoding siRNA molecules to target HTT and reduce the expression of HTT in a cell and/or subject.

[0011] In some embodiments the viral genome comprises a 5' inverted terminal repeat (ITR) sequence region such as, but not limited to, SEQ ID NO: 1380 and 1381, an enhancer sequence region such as, but not limited to, SEQ ID NO: 1408 and 1409, a promoter sequence region such as, but not limited to, SEQ ID NO: 1410-1411 and the sequence GTTG, at least one intron sequence region such as, but not limited to, SEQ ID NO: 1417-1419, a modulatory polynucleotide sequence region such as, but not limited to, SEQ ID NO: 1183-1279 and 1346-1347, a polyadenylation (polyA) signal sequence region such as, but not limited to, SEQ ID NO: 1420-1423, and a 3' ITR sequence region such as, but not limited to, SEQ ID NO: 1382 and 1383.

[0012] In some embodiments, the viral genome may comprise at least one more sequence region.

[0013] In one embodiment, the viral genome comprises at least one multiple cloning site (MCS) sequence region such as, but not limited to, SEQ ID NO: 384-1390 and the sequence TCGAG. In one embodiment, the viral genome comprises one MCS sequence region. In one embodiment, the viral genome comprises two MCS sequence regions.

[0014] In one embodiment, the viral genome comprises at least one filler sequence region such as, but not limited to, SEQ ID NO: 1390-1407. In one embodiment, the AAV viral genome comprises one filler sequence region. In one embodiment, the AAV viral genome comprises two filler sequence regions.

[0015] In one embodiment, the viral genome comprises at least one exon sequence region such as, but not limited to, SEQ ID NO: 1415 and 1416.

[0016] In one embodiment, the viral genome comprises one intron sequence region.

[0017] In one embodiment, the viral genome comprises two intron sequence regions.

[0018] In one embodiment, the viral genome comprises a 5' inverted terminal repeat (ITR) sequence region, an enhancer sequence region, a promoter sequence region, at least one intron

sequence region, a modulatory polynucleotide sequence region, a polyadenylation (polyA) signal sequence region, and a 3' ITR sequence region. As a non-limiting example, the AAV viral genome comprises a sequence such as SEQ ID NO: 1352-1379 or a fragment or variant thereof.

[0019] In one embodiment, the viral genome such as, but not limited to, any of SEQ ID NO: 1352-1379 or variants having at least 95% identity thereto.

[0020] In one embodiment, an AAV particle may comprise a viral genome such as, but not limited to, any of SEQ ID NO: 1352-1379 or variants having at least 95% identity thereto. The AAV particle may comprise a serotype such as, but not limited to, any of the serotypes listed in Table 1.

[0021] Provided herein are also pharmaceutical compositions of AAV particles. The AAV particle may comprise a viral genome such as, but not limited to, any of SEQ ID NO: 1352-1379 or variants having at least 95% identity thereto. The AAV particle may comprise a serotype such as, but not limited to, any of the serotypes listed in Table 1.

[0022] In some embodiments, the present invention provides methods for inhibiting/silencing HTT gene expression in a cell. The cell may be a neuron (e.g., medium spiny neurons of the putamen, caudate or striatum, and cortical neurons in the cerebral cortex), an astrocyte (e.g., astrocyte in the striatum, cortical astrocytes in the cerebral cortex) and/or oligodendrocytes. As a non-limiting example, the inhibition (or lowering) of the HTT gene expression in the putamen, caudate and cortex reduces the effect of Huntington's Disease in a subject. As another non-limiting example, the inhibition (or lowering) of the HTT gene expression in the medium spiny neurons in the striatum reduces the effect of Huntington's Disease in a subject. As yet another non-limiting example, the inhibition (or lowering) of the HTT gene expression in the astrocytes in the striatum reduces the effect of Huntington's Disease in a subject. In some aspects, the inhibition of the HTT gene expression refers to an inhibition or lowering by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%. Accordingly, the protein product of the targeted gene may be inhibited by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%.

[0023] In one embodiment, the present invention provides methods for inhibiting/silencing HTT gene expression by at least about 40% in a cell using the viral genomes comprising the modulatory polynucleotides encoding the siRNA molecules. The cell may be a neuron (e.g., medium spiny neurons of the putamen or striatum, and cortical neurons in the cerebral cortex), an astrocyte (e.g., astrocyte in the striatum, cortical astrocytes in the cerebral cortex) and/or oligodendrocytes. As a non-limiting example, the at least 40% inhibition (or lowering) of the

HTT gene expression in the putamen and cortex reduces the effect of Huntington's Disease in a subject. As another non-limiting example, the at least 40% inhibition (or lowering) of the HTT gene expression in the medium spiny neurons in the striatum reduces the effect of Huntington's Disease in a subject. As yet another non-limiting example, the at least 40% inhibition (or lowering) of the HTT gene expression in the astrocytes in the striatum reduces the effect of Huntington's Disease in a subject.

[0024] In some embodiments, the present invention provides methods for treating, or ameliorating Huntington's Disease associated with the HTT gene (e.g., CAG-expanded HTT gene) and the resultant HTT protein (e.g., poly-Q protein) in a subject in need of treatment, the method comprising administering to the subject a pharmaceutically effective amount a pharmaceutical composition comprising the AAV particles described herein, and ameliorating symptoms of HD in the subject.

[0025] In some embodiments, an AAV particle comprising the nucleic acid sequence encoding at least one siRNA duplex targeting the HTT gene is administered to the subject in need for treating and/or ameliorating HD. The AAV vector serotype may be any of the serotypes listed in Table 1.

[0026] In some embodiments, the AAV particles may be introduced directly into the central nervous system of the subject, for example, by intracranial injection.

[0027] In some embodiments, the pharmaceutical composition of the present invention is used as a solo therapy. In other embodiments, the pharmaceutical composition of the present invention is used in combination therapy. The combination therapy may be in combination with one or more neuroprotective agents such as small molecule compounds, growth factors and hormones which have been tested for their neuroprotective effect on neuron degeneration.

[0028] In some embodiments, the present invention provides methods for treating, or ameliorating Huntington's Disease by administering to a subject in need thereof a therapeutically effective amount of a plasmid or AAV vector described herein.

[0029] In some embodiments, the present invention provides a method for inhibiting the expression of the HTT gene in a region of the central nervous system of a subject by administering to the subject a composition with at least one AAV particle which comprises a modulatory polynucleotide encoding an siRNA molecule that, when expressed, inhibits or suppresses the expression of HTT in the subject. The expression may be reduced in a region of the subject such as, but not limited to, the forebrain of a subject or a region of the forebrain such as, but not limited to, the putamen. The expression of HTT in the forebrain or region of the

forebrain (e.g., putamen) may be reduced by 40-70%, 40-60%, 50-70%, 50-60%, or it may be reduced by 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%.

[0030] In some embodiments, the present invention provides a method for treating Huntington's Disease (HD) in a subject in need of treatment. The method may inhibit the expression of the HTT gene in a region of the central nervous system of a subject comprising administering to the subject a composition comprising at least one AAV particle which comprises a modulatory polynucleotide encoding an siRNA molecule that, when expressed, inhibits or suppresses the expression of HTT in the subject. The expression may be reduced in a region of the subject such as, but not limited to, the forebrain of a subject or a region of the forebrain such as, but not limited to, the putamen. The expression of HTT in the forebrain or region of the forebrain (e.g., putamen) may be reduced by 40-70%, 40-60%, 50-70%, 50-60%, or it may be reduced by 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, 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 invention.

[0032] FIG. 1 is a schematic of a viral genome of the invention.

[0033] FIG. 2 is a schematic of a viral genome of the invention.

[0034] FIG. 3 is a schematic of a viral genome of the invention.

[0035] FIG. 4 is a schematic of a viral genome of the invention.

[0036] FIG. 5 is a schematic of a viral genome of the invention.

[0037] FIG. 6 is a schematic of a viral genome of the invention.

[0038] FIG. 7 is a schematic of a viral genome of the invention.

[0039] FIG. 8 is a schematic of a viral genome of the invention.

[0040] FIG. 9 is a schematic of a viral genome of the invention.

[0041] The details of one or more embodiments of the invention are set forth in the accompanying description below. Although any materials and methods similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred materials and methods are now described. Other features, objects and advantages of the invention will be apparent from the description. In the description, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by

one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present description will control.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOSITIONS OF THE INVENTION

[0042] According to the present invention, compositions for delivering modulatory polynucleotides and/or modulatory polynucleotide-based compositions by adeno-associated viruses (AAVs) are provided. AAV particles of the invention may be provided via any of several routes of administration, to a cell, tissue, organ, or organism, *in vivo*, *ex vivo* or *in vitro*.

[0043] As used herein, an "AAV particle" is a virus which comprises a viral genome with at least one payload region and at least one inverted terminal repeat (ITR) region.

[0044] As used herein, "viral genome" or "vector genome" or "viral vector" refers to the nucleic acid sequence(s) encapsulated in an AAV particle. Viral genomes comprise at least one payload region encoding polypeptides or fragments thereof.

[0045] As used herein, a "payload" or "payload region" is any nucleic acid molecule which encodes one or more polypeptides of the invention. At a minimum, a payload region comprises nucleic acid sequences that encode a sense and antisense sequence, an siRNA-based composition, or a fragment thereof, but may also optionally comprise one or more functional or regulatory elements to facilitate transcriptional expression and/or polypeptide translation.

[0046] The nucleic acid sequences and polypeptides disclosed herein may be engineered to contain modular elements and/or sequence motifs assembled to enable expression of the modulatory polynucleotides and/or modulatory polynucleotide-based compositions of the invention. In some embodiments, the nucleic acid sequence comprising the payload region may comprise one or more of a promoter region, an intron, a Kozak sequence, an enhancer or a polyadenylation sequence. Payload regions of the invention typically encode at least one sense and antisense sequence, an siRNA-based compositions, or fragments of the foregoing in combination with each other or in combination with other polypeptide moieties.

[0047] The payload regions of the invention may be delivered to one or more target cells, tissues, organs or organisms within the viral genome of an AAV particle.

Adeno-associated viruses (AAVs) and AAV particles

[0048] 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.

[0049] 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.

[0050] 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.

[0051] The AAV viral 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 AAV viral 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.

[0052] In addition to the encoded heterologous payload, AAV vectors 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.

[0053] In one embodiment, AAV particles of the present invention are recombinant AAV vectors which are replication defective, lacking sequences encoding functional Rep and Cap proteins within their viral genome. These defective AAV vectors 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.

[0054] In one embodiment, the viral genome of the AAV particles of the present invention 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.

[0055] According to the present invention, 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.

[0056] AAV vectors of the present invention 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.

[0057] In addition to single stranded AAV viral genomes (e.g., ssAAVs), the present invention also provides for self-complementary AAV (scAAVs) viral genomes. scAAV viral genomes contain DNA strands which anneal together to form double stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the cell.

[0058] In one embodiment, the AAV particle of the present invention is an scAAV.

[0059] In one embodiment, the AAV particle of the present invention is an ssAAV.

[0060] Methods for producing and/or modifying AAV particles are disclosed in the art such as pseudotyped AAV vectors (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).

[0061] 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.

[0062] In one embodiment, the AAV particles comprising a payload region encoding the polypeptides of the invention may be introduced into mammalian cells.

AAV serotypes

[0063] AAV particles of the present invention may comprise or be derived from any natural or recombinant AAV serotype. According to the present invention, the AAV particles may utilize or be based on a serotype selected from any of the following 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, AAV-PHP.B (PHP.B), AAV-PHP.A (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.

[0064] 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.

[0065] 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).

[0066] 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 one embodiment, 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 one embodiment, the tyrosine residue at position 446 of AAV9 (SEQ ID NO: 6 US 20130224836) is substituted with a phenylalanine residue.

[0067] 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 one embodiment, the amino acid sequence of any AAV may comprise a V708K mutation.

[0068] 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.

[0069] 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.

[0070] 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).

[0071] 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.

[0072] 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.

[0073] 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.

[0074] In some embodiments, the serotype may be AAVDJ (or AAV-DJ) 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). As a non-limiting example, 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). As another non-limiting example, 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).

[0075] 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).

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] According to the present invention, AAV capsid serotype selection or use may be from a variety of species. In one embodiment, 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.

[0088] In one embodiment, 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.

[0089] In one embodiment, 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.

[0090] In other embodiments the AAV may be engineered as a hybrid AAV from two or more parental serotypes. In one embodiment, 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.

[0091] In one embodiment, 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).

[0092] 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.

[0093] 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: 37 and 111 of US8734809), AAV CLv-R9 (SEQ ID NO: 38 and 112 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.

[0094] 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.

[0095] In one embodiment, the AAV may be a serotype selected from any of those found in Table 1.

[0096] In one embodiment, the AAV may comprise a sequence, fragment or variant thereof, of the sequences in Table 1.

[0097] In one embodiment, 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
AAV1	1	US20150159173 SEQ ID NO: 11, US20150315612 SEQ ID NO: 202
AAV1	2	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	3	US20030138772 SEQ ID NO: 6
AAV1.3	4	US20030138772 SEQ ID NO: 14
AAV10	5	US20030138772 SEQ ID NO: 117
AAV10	6	WO2015121501 SEQ ID NO: 9
AAV10	7	WO2015121501 SEQ ID NO: 8
AAV11	8	US20030138772 SEQ ID NO: 118
AAV12	9	US20030138772 SEQ ID NO: 119
AAV2	10	US20150159173 SEQ ID NO: 7, US20150315612 SEQ ID NO: 211
AAV2	11	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	12	US6156303 SEQ ID NO: 8
AAV2	13	US20030138772 SEQ ID NO: 7
AAV2	14	US6156303 SEQ ID NO: 3
AAV2.5T	15	US9233131 SEQ ID NO: 42
AAV223.10	16	US20030138772 SEQ ID NO: 75
AAV223.2	17	US20030138772 SEQ ID NO: 49
AAV223.2	18	US20030138772 SEQ ID NO: 76
AAV223.4	19	US20030138772 SEQ ID NO: 50

AAV223.4	20	US20030138772 SEQ ID NO: 73
AAV223.5	21	US20030138772 SEQ ID NO: 51
AAV223.5	22	US20030138772 SEQ ID NO: 74
AAV223.6	23	US20030138772 SEQ ID NO: 52
AAV223.6	24	US20030138772 SEQ ID NO: 78
AAV223.7	25	US20030138772 SEQ ID NO: 53
AAV223.7	26	US20030138772 SEQ ID NO: 77
AAV29.3	27	US20030138772 SEQ ID NO: 82
AAV29.4	28	US20030138772 SEQ ID NO: 12
AAV29.5	29	US20030138772 SEQ ID NO: 83
AAV29.5 (AAVbb.2)	30	US20030138772 SEQ ID NO: 13
AAV3	31	US20150159173 SEQ ID NO: 12
AAV3	32	US20030138772 SEQ ID NO: 71, US20150159173 SEQ ID NO: 28, US20160017295 SEQ ID NO: 3, US7198951 SEQ ID NO: 6
AAV3	33	US20030138772 SEQ ID NO: 8
AAV3.3b	34	US20030138772 SEQ ID NO: 72
AAV3-3	35	US20150315612 SEQ ID NO: 200
AAV3-3	36	US20150315612 SEQ ID NO: 217
AAV3a	37	US6156303 SEQ ID NO: 5
AAV3a	38	US6156303 SEQ ID NO: 9
AAV3b	39	US6156303 SEQ ID NO: 6
AAV3b	40	US6156303 SEQ ID NO: 10
AAV3b	41	US6156303 SEQ ID NO: 1
AAV4	42	US20140348794 SEQ ID NO: 17
AAV4	43	US20140348794 SEQ ID NO: 5
AAV4	44	US20140348794 SEQ ID NO: 3
AAV4	45	US20140348794 SEQ ID NO: 14
AAV4	46	US20140348794 SEQ ID NO: 15
AAV4	47	US20140348794 SEQ ID NO: 19
AAV4	48	US20140348794 SEQ ID NO: 12
AAV4	49	US20140348794 SEQ ID NO: 13
AAV4	50	US20140348794 SEQ ID NO: 7
AAV4	51	US20140348794 SEQ ID NO: 8
AAV4	52	US20140348794 SEQ ID NO: 9
AAV4	53	US20140348794 SEQ ID NO: 2
AAV4	54	US20140348794 SEQ ID NO: 10
AAV4	55	US20140348794 SEQ ID NO: 11
AAV4	56	US20140348794 SEQ ID NO: 18
AAV4	57	US20030138772 SEQ ID NO: 63, US20160017295 SEQ ID NO: 4, US20140348794 SEQ ID NO: 4
AAV4	58	US20140348794 SEQ ID NO: 16
AAV4	59	US20140348794 SEQ ID NO: 20
AAV4	60	US20140348794 SEQ ID NO: 6
AAV4	61	US20140348794 SEQ ID NO: 1

AAV42.2	62	US20030138772 SEQ ID NO: 9
AAV42.2	63	US20030138772 SEQ ID NO: 102
AAV42.3b	64	US20030138772 SEQ ID NO: 36
AAV42.3B	65	US20030138772 SEQ ID NO: 107
AAV42.4	66	US20030138772 SEQ ID NO: 33
AAV42.4	67	US20030138772 SEQ ID NO: 88
AAV42.8	68	US20030138772 SEQ ID NO: 27
AAV42.8	69	US20030138772 SEQ ID NO: 85
AAV43.1	70	US20030138772 SEQ ID NO: 39
AAV43.1	71	US20030138772 SEQ ID NO: 92
AAV43.12	72	US20030138772 SEQ ID NO: 41
AAV43.12	73	US20030138772 SEQ ID NO: 93
AAV43.20	74	US20030138772 SEQ ID NO: 42
AAV43.20	75	US20030138772 SEQ ID NO: 99
AAV43.21	76	US20030138772 SEQ ID NO: 43
AAV43.21	77	US20030138772 SEQ ID NO: 96
AAV43.23	78	US20030138772 SEQ ID NO: 44
AAV43.23	79	US20030138772 SEQ ID NO: 98
AAV43.25	80	US20030138772 SEQ ID NO: 45
AAV43.25	81	US20030138772 SEQ ID NO: 97
AAV43.5	82	US20030138772 SEQ ID NO: 40
AAV43.5	83	US20030138772 SEQ ID NO: 94
AAV4-4	84	US20150315612 SEQ ID NO: 201
AAV4-4	85	US20150315612 SEQ ID NO: 218
AAV44.1	86	US20030138772 SEQ ID NO: 46
AAV44.1	87	US20030138772 SEQ ID NO: 79
AAV44.5	88	US20030138772 SEQ ID NO: 47
AAV44.5	89	US20030138772 SEQ ID NO: 80
AAV4407	90	US20150315612 SEQ ID NO: 90
AAV5	91	US7427396 SEQ ID NO: 1
AAV5	92	US20030138772 SEQ ID NO: 114
AAV5	93	US20160017295 SEQ ID NO: 5, US7427396 SEQ ID NO: 2, US20150315612 SEQ ID NO: 216
AAV5	94	US20150315612 SEQ ID NO: 199
AAV6	95	US20150159173 SEQ ID NO: 13
AAV6	96	US20030138772 SEQ ID NO: 65, US20150159173 SEQ ID NO: 29, US20160017295 SEQ ID NO: 6, US6156303 SEQ ID NO: 7
AAV6	97	US6156303 SEQ ID NO: 11
AAV6	98	US6156303 SEQ ID NO: 2
AAV6	99	US20150315612 SEQ ID NO: 203
AAV6	100	US20150315612 SEQ ID NO: 220
AAV6.1	101	US20150159173
AAV6.12	102	US20150159173
AAV6.2	103	US20150159173
AAV7	104	US20150159173 SEQ ID NO: 14

AAV7	105	US20150315612 SEQ ID NO: 183
AAV7	106	US20030138772 SEQ ID NO: 2, US20150159173 SEQ ID NO: 30, US20150315612 SEQ ID NO: 181, US20160017295 SEQ ID NO: 7
AAV7	107	US20030138772 SEQ ID NO: 3
AAV7	108	US20030138772 SEQ ID NO: 1, US20150315612 SEQ ID NO: 180
AAV7	109	US20150315612 SEQ ID NO: 213
AAV7	110	US20150315612 SEQ ID NO: 222
AAV8	111	US20150159173 SEQ ID NO: 15
AAV8	112	US20150376240 SEQ ID NO: 7
AAV8	113	US20030138772 SEQ ID NO: 4, US20150315612 SEQ ID NO: 182
AAV8	114	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	115	US20150376240 SEQ ID NO: 8
AAV8	116	US20150315612 SEQ ID NO: 214
AAV-8b	117	US20150376240 SEQ ID NO: 5
AAV-8b	118	US20150376240 SEQ ID NO: 3
AAV-8h	119	US20150376240 SEQ ID NO: 6
AAV-8h	120	US20150376240 SEQ ID NO: 4
AAV9	121	US20030138772 SEQ ID NO: 5
AAV9	122	US7198951 SEQ ID NO: 1
AAV9	123	US20160017295 SEQ ID NO: 9
AAV9	124	US20030138772 SEQ ID NO: 100, US7198951 SEQ ID NO: 2
AAV9	125	US7198951 SEQ ID NO: 3
AAV9 (AAVhu.14)	126	US7906111 SEQ ID NO: 3; WO2015038958 SEQ ID NO: 11
AAV9 (AAVhu.14)	127	US7906111 SEQ ID NO: 123; WO2015038958 SEQ ID NO: 2
AAVA3.1	128	US20030138772 SEQ ID NO: 120
AAVA3.3	129	US20030138772 SEQ ID NO: 57
AAVA3.3	130	US20030138772 SEQ ID NO: 66
AAVA3.4	131	US20030138772 SEQ ID NO: 54
AAVA3.4	132	US20030138772 SEQ ID NO: 68
AAVA3.5	133	US20030138772 SEQ ID NO: 55
AAVA3.5	134	US20030138772 SEQ ID NO: 69
AAVA3.7	135	US20030138772 SEQ ID NO: 56
AAVA3.7	136	US20030138772 SEQ ID NO: 67
AAV29.3 (AAVbb.1)	137	US20030138772 SEQ ID NO: 11
AAVC2	138	US20030138772 SEQ ID NO: 61
AAVCh.5	139	US20150159173 SEQ ID NO: 46, US20150315612 SEQ ID NO: 234
AAVcy.2 (AAV13.3)	140	US20030138772 SEQ ID NO: 15
AAV24.1	141	US20030138772 SEQ ID NO: 101
AAVcy.3 (AAV24.1)	142	US20030138772 SEQ ID NO: 16
AAV27.3	143	US20030138772 SEQ ID NO: 104

AAVcy.4 (AAV27.3)	144	US20030138772 SEQ ID NO: 17
AAVcy.5	145	US20150315612 SEQ ID NO: 227
AAV7.2	146	US20030138772 SEQ ID NO: 103
AAVcy.5 (AAV7.2)	147	US20030138772 SEQ ID NO: 18
AAV16.3	148	US20030138772 SEQ ID NO: 105
AAVcy.6 (AAV16.3)	149	US20030138772 SEQ ID NO: 10
AAVcy.5	150	US20150159173 SEQ ID NO: 8
AAVcy.5	151	US20150159173 SEQ ID NO: 24
AAVCy.5R1	152	US20150159173
AAVCy.5R2	153	US20150159173
AAVCy.5R3	154	US20150159173
AAVCy.5R4	155	US20150159173
AAVDJ	156	US20140359799 SEQ ID NO: 3, US7588772 SEQ ID NO: 2
AAVDJ	157	US20140359799 SEQ ID NO: 2, US7588772 SEQ ID NO: 1
AAVDJ-8	158	US7588772; Grimm et al 2008
AAVDJ-8	159	US7588772; Grimm et al 2008
AAVF5	160	US20030138772 SEQ ID NO: 110
AAVH2	161	US20030138772 SEQ ID NO: 26
AAVH6	162	US20030138772 SEQ ID NO: 25
AAVhE1.1	163	US9233131 SEQ ID NO: 44
AAVhEr1.14	164	US9233131 SEQ ID NO: 46
AAVhEr1.16	165	US9233131 SEQ ID NO: 48
AAVhEr1.18	166	US9233131 SEQ ID NO: 49
AAVhEr1.23 (AAVhEr2.29)	167	US9233131 SEQ ID NO: 53
AAVhEr1.35	168	US9233131 SEQ ID NO: 50
AAVhEr1.36	169	US9233131 SEQ ID NO: 52
AAVhEr1.5	170	US9233131 SEQ ID NO: 45
AAVhEr1.7	171	US9233131 SEQ ID NO: 51
AAVhEr1.8	172	US9233131 SEQ ID NO: 47
AAVhEr2.16	173	US9233131 SEQ ID NO: 55
AAVhEr2.30	174	US9233131 SEQ ID NO: 56
AAVhEr2.31	175	US9233131 SEQ ID NO: 58
AAVhEr2.36	176	US9233131 SEQ ID NO: 57
AAVhEr2.4	177	US9233131 SEQ ID NO: 54
AAVhEr3.1	178	US9233131 SEQ ID NO: 59
AAVhu.1	179	US20150315612 SEQ ID NO: 46
AAVhu.1	180	US20150315612 SEQ ID NO: 144
AAVhu.10 (AAV16.8)	181	US20150315612 SEQ ID NO: 56
AAVhu.10 (AAV16.8)	182	US20150315612 SEQ ID NO: 156
AAVhu.11 (AAV16.12)	183	US20150315612 SEQ ID NO: 57

AAVhu.11 (AAV16.12)	184	US20150315612 SEQ ID NO: 153
AAVhu.12	185	US20150315612 SEQ ID NO: 59
AAVhu.12	186	US20150315612 SEQ ID NO: 154
AAVhu.13	187	US20150159173 SEQ ID NO: 16, US20150315612 SEQ ID NO: 71
AAVhu.13	188	US20150159173 SEQ ID NO: 32, US20150315612 SEQ ID NO: 129
AAVhu.136.1	189	US20150315612 SEQ ID NO: 165
AAVhu.140.1	190	US20150315612 SEQ ID NO: 166
AAVhu.140.2	191	US20150315612 SEQ ID NO: 167
AAVhu.145.6	192	US20150315612 SEQ ID No: 178
AAVhu.15	193	US20150315612 SEQ ID NO: 147
AAVhu.15 (AAV33.4)	194	US20150315612 SEQ ID NO: 50
AAVhu.156.1	195	US20150315612 SEQ ID No: 179
AAVhu.16	196	US20150315612 SEQ ID NO: 148
AAVhu.16 (AAV33.8)	197	US20150315612 SEQ ID NO: 51
AAVhu.17	198	US20150315612 SEQ ID NO: 83
AAVhu.17 (AAV33.12)	199	US20150315612 SEQ ID NO: 4
AAVhu.172.1	200	US20150315612 SEQ ID NO: 171
AAVhu.172.2	201	US20150315612 SEQ ID NO: 172
AAVhu.173.4	202	US20150315612 SEQ ID NO: 173
AAVhu.173.8	203	US20150315612 SEQ ID NO: 175
AAVhu.18	204	US20150315612 SEQ ID NO: 52
AAVhu.18	205	US20150315612 SEQ ID NO: 149
AAVhu.19	206	US20150315612 SEQ ID NO: 62
AAVhu.19	207	US20150315612 SEQ ID NO: 133
AAVhu.2	208	US20150315612 SEQ ID NO: 48
AAVhu.2	209	US20150315612 SEQ ID NO: 143
AAVhu.20	210	US20150315612 SEQ ID NO: 63
AAVhu.20	211	US20150315612 SEQ ID NO: 134
AAVhu.21	212	US20150315612 SEQ ID NO: 65
AAVhu.21	213	US20150315612 SEQ ID NO: 135
AAVhu.22	214	US20150315612 SEQ ID NO: 67
AAVhu.22	215	US20150315612 SEQ ID NO: 138
AAVhu.23	216	US20150315612 SEQ ID NO: 60
AAVhu.23.2	217	US20150315612 SEQ ID NO: 137
AAVhu.24	218	US20150315612 SEQ ID NO: 66
AAVhu.24	219	US20150315612 SEQ ID NO: 136
AAVhu.25	220	US20150315612 SEQ ID NO: 49

AAVhu.25	221	US20150315612 SEQ ID NO: 146
AAVhu.26	222	US20150159173 SEQ ID NO: 17, US20150315612 SEQ ID NO: 61
AAVhu.26	223	US20150159173 SEQ ID NO: 33, US20150315612 SEQ ID NO: 139
AAVhu.27	224	US20150315612 SEQ ID NO: 64
AAVhu.27	225	US20150315612 SEQ ID NO: 140
AAVhu.28	226	US20150315612 SEQ ID NO: 68
AAVhu.28	227	US20150315612 SEQ ID NO: 130
AAVhu.29	228	US20150315612 SEQ ID NO: 69
AAVhu.29	229	US20150159173 SEQ ID NO: 42, US20150315612 SEQ ID NO: 132
AAVhu.29	230	US20150315612 SEQ ID NO: 225
AAVhu.29R	231	US20150159173
AAVhu.3	232	US20150315612 SEQ ID NO: 44
AAVhu.3	233	US20150315612 SEQ ID NO: 145
AAVhu.30	234	US20150315612 SEQ ID NO: 70
AAVhu.30	235	US20150315612 SEQ ID NO: 131
AAVhu.31	236	US20150315612 SEQ ID NO: 1
AAVhu.31	237	US20150315612 SEQ ID NO: 121
AAVhu.32	238	US20150315612 SEQ ID NO: 2
AAVhu.32	239	US20150315612 SEQ ID NO: 122
AAVhu.33	240	US20150315612 SEQ ID NO: 75
AAVhu.33	241	US20150315612 SEQ ID NO: 124
AAVhu.34	242	US20150315612 SEQ ID NO: 72
AAVhu.34	243	US20150315612 SEQ ID NO: 125
AAVhu.35	244	US20150315612 SEQ ID NO: 73
AAVhu.35	245	US20150315612 SEQ ID NO: 164
AAVhu.36	246	US20150315612 SEQ ID NO: 74
AAVhu.36	247	US20150315612 SEQ ID NO: 126
AAVhu.37	248	US20150159173 SEQ ID NO: 34, US20150315612 SEQ ID NO: 88
AAVhu.37 (AAV106.1)	249	US20150315612 SEQ ID NO: 10, US20150159173 SEQ ID NO: 18
AAVhu.38	250	US20150315612 SEQ ID NO: 161
AAVhu.39	251	US20150315612 SEQ ID NO: 102
AAVhu.39 (AAVLG-9)	252	US20150315612 SEQ ID NO: 24
AAVhu.4	253	US20150315612 SEQ ID NO: 47
AAVhu.4	254	US20150315612 SEQ ID NO: 141
AAVhu.40	255	US20150315612 SEQ ID NO: 87
AAVhu.40 (AAV114.3)	256	US20150315612 SEQ ID No: 11
AAVhu.41	257	US20150315612 SEQ ID NO: 91
AAVhu.41 (AAV127.2)	258	US20150315612 SEQ ID NO: 6
AAVhu.42	259	US20150315612 SEQ ID NO: 85
AAVhu.42 (AAV127.5)	260	US20150315612 SEQ ID NO: 8
AAVhu.43	261	US20150315612 SEQ ID NO: 160

AAVhu.43	262	US20150315612 SEQ ID NO: 236
AAVhu.43 (AAV128.1)	263	US20150315612 SEQ ID NO: 80
AAVhu.44	264	US20150159173 SEQ ID NO: 45, US20150315612 SEQ ID NO: 158
AAVhu.44 (AAV128.3)	265	US20150315612 SEQ ID NO: 81
AAVhu.44R1	266	US20150159173
AAVhu.44R2	267	US20150159173
AAVhu.44R3	268	US20150159173
AAVhu.45	269	US20150315612 SEQ ID NO: 76
AAVhu.45	270	US20150315612 SEQ ID NO: 127
AAVhu.46	271	US20150315612 SEQ ID NO: 82
AAVhu.46	272	US20150315612 SEQ ID NO: 159
AAVhu.46	273	US20150315612 SEQ ID NO: 224
AAVhu.47	274	US20150315612 SEQ ID NO: 77
AAVhu.47	275	US20150315612 SEQ ID NO: 128
AAVhu.48	276	US20150159173 SEQ ID NO: 38
AAVhu.48	277	US20150315612 SEQ ID NO: 157
AAVhu.48 (AAV130.4)	278	US20150315612 SEQ ID NO: 78
AAVhu.48R1	279	US20150159173
AAVhu.48R2	280	US20150159173
AAVhu.48R3	281	US20150159173
AAVhu.49	282	US20150315612 SEQ ID NO: 209
AAVhu.49	283	US20150315612 SEQ ID NO: 189
AAVhu.5	284	US20150315612 SEQ ID NO: 45
AAVhu.5	285	US20150315612 SEQ ID NO: 142
AAVhu.51	286	US20150315612 SEQ ID NO: 208
AAVhu.51	287	US20150315612 SEQ ID NO: 190
AAVhu.52	288	US20150315612 SEQ ID NO: 210
AAVhu.52	289	US20150315612 SEQ ID NO: 191
AAVhu.53	290	US20150159173 SEQ ID NO: 19
AAVhu.53	291	US20150159173 SEQ ID NO: 35
AAVhu.53 (AAV145.1)	292	US20150315612 SEQ ID NO: 176
AAVhu.54	293	US20150315612 SEQ ID NO: 188
AAVhu.54 (AAV145.5)	294	US20150315612 SEQ ID No: 177
AAVhu.55	295	US20150315612 SEQ ID NO: 187
AAVhu.56	296	US20150315612 SEQ ID NO: 205
AAVhu.56 (AAV145.6)	297	US20150315612 SEQ ID NO: 168
AAVhu.56 (AAV145.6)	298	US20150315612 SEQ ID NO: 192
AAVhu.57	299	US20150315612 SEQ ID NO: 206
AAVhu.57	300	US20150315612 SEQ ID NO: 169
AAVhu.57	301	US20150315612 SEQ ID NO: 193

AAVhu.58	302	US20150315612 SEQ ID NO: 207
AAVhu.58	303	US20150315612 SEQ ID NO: 194
AAVhu.6 (AAV3.1)	304	US20150315612 SEQ ID NO: 5
AAVhu.6 (AAV3.1)	305	US20150315612 SEQ ID NO: 84
AAVhu.60	306	US20150315612 SEQ ID NO: 184
AAVhu.60 (AAV161.10)	307	US20150315612 SEQ ID NO: 170
AAVhu.61	308	US20150315612 SEQ ID NO: 185
AAVhu.61 (AAV161.6)	309	US20150315612 SEQ ID NO: 174
AAVhu.63	310	US20150315612 SEQ ID NO: 204
AAVhu.63	311	US20150315612 SEQ ID NO: 195
AAVhu.64	312	US20150315612 SEQ ID NO: 212
AAVhu.64	313	US20150315612 SEQ ID NO: 196
AAVhu.66	314	US20150315612 SEQ ID NO: 197
AAVhu.67	315	US20150315612 SEQ ID NO: 215
AAVhu.67	316	US20150315612 SEQ ID NO: 198
AAVhu.7	317	US20150315612 SEQ ID NO: 226
AAVhu.7	318	US20150315612 SEQ ID NO: 150
AAVhu.7 (AAV7.3)	319	US20150315612 SEQ ID NO: 55
AAVhu.71	320	US20150315612 SEQ ID NO: 79
AAVhu.8	321	US20150315612 SEQ ID NO: 53
AAVhu.8	322	US20150315612 SEQ ID NO: 12
AAVhu.8	323	US20150315612 SEQ ID NO: 151
AAVhu.9 (AAV3.1)	324	US20150315612 SEQ ID NO: 58
AAVhu.9 (AAV3.1)	325	US20150315612 SEQ ID NO: 155
AAV-LK01	326	US20150376607 SEQ ID NO: 2
AAV-LK01	327	US20150376607 SEQ ID NO: 29
AAV-LK02	328	US20150376607 SEQ ID NO: 3
AAV-LK02	329	US20150376607 SEQ ID NO: 30
AAV-LK03	330	US20150376607 SEQ ID NO: 4
AAV-LK03	331	WO2015121501 SEQ ID NO: 12, US20150376607 SEQ ID NO: 31
AAV-LK04	332	US20150376607 SEQ ID NO: 5
AAV-LK04	333	US20150376607 SEQ ID NO: 32
AAV-LK05	334	US20150376607 SEQ ID NO: 6
AAV-LK05	335	US20150376607 SEQ ID NO: 33
AAV-LK06	336	US20150376607 SEQ ID NO: 7
AAV-LK06	337	US20150376607 SEQ ID NO: 34
AAV-LK07	338	US20150376607 SEQ ID NO: 8
AAV-LK07	339	US20150376607 SEQ ID NO: 35
AAV-LK08	340	US20150376607 SEQ ID NO: 9
AAV-LK08	341	US20150376607 SEQ ID NO: 36

AAV-LK09	342	US20150376607 SEQ ID NO: 10
AAV-LK09	343	US20150376607 SEQ ID NO: 37
AAV-LK10	344	US20150376607 SEQ ID NO: 11
AAV-LK10	345	US20150376607 SEQ ID NO: 38
AAV-LK11	346	US20150376607 SEQ ID NO: 12
AAV-LK11	347	US20150376607 SEQ ID NO: 39
AAV-LK12	348	US20150376607 SEQ ID NO: 13
AAV-LK12	349	US20150376607 SEQ ID NO: 40
AAV-LK13	350	US20150376607 SEQ ID NO: 14
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AAV-LK15	354	US20150376607 SEQ ID NO: 16
AAV-LK15	355	US20150376607 SEQ ID NO: 43
AAV-LK16	356	US20150376607 SEQ ID NO: 17
AAV-LK16	357	US20150376607 SEQ ID NO: 44
AAV-LK17	358	US20150376607 SEQ ID NO: 18
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AAV-PAEC11	367	US20150376607 SEQ ID NO: 54
AAV-PAEC12	368	US20150376607 SEQ ID NO: 27
AAV-PAEC12	369	US20150376607 SEQ ID NO: 51
AAV-PAEC13	370	US20150376607 SEQ ID NO: 28
AAV-PAEC13	371	US20150376607 SEQ ID NO: 49
AAV-PAEC2	372	US20150376607 SEQ ID NO: 21
AAV-PAEC2	373	US20150376607 SEQ ID NO: 56
AAV-PAEC4	374	US20150376607 SEQ ID NO: 22
AAV-PAEC4	375	US20150376607 SEQ ID NO: 55
AAV-PAEC6	376	US20150376607 SEQ ID NO: 23
AAV-PAEC6	377	US20150376607 SEQ ID NO: 52
AAV-PAEC7	378	US20150376607 SEQ ID NO: 24
AAV-PAEC7	379	US20150376607 SEQ ID NO: 53
AAV-PAEC8	380	US20150376607 SEQ ID NO: 25
AAV-PAEC8	381	US20150376607 SEQ ID NO: 50
AAVpi.1	382	US20150315612 SEQ ID NO: 28

AAVpi.1	383	US20150315612 SEQ ID NO: 93
AAVpi.2	384	US20150315612 SEQ ID NO: 30
AAVpi.2	385	US20150315612 SEQ ID NO: 95
AAVpi.3	386	US20150315612 SEQ ID NO: 29
AAVpi.3	387	US20150315612 SEQ ID NO: 94
AAVrh.10	388	US20150159173 SEQ ID NO: 9
AAVrh.10	389	US20150159173 SEQ ID NO: 25
AAV44.2	390	US20030138772 SEQ ID NO: 59
AAVrh.10 (AAV44.2)	391	US20030138772 SEQ ID NO: 81
AAV42.1B	392	US20030138772 SEQ ID NO: 90
AAVrh.12 (AAV42.1b)	393	US20030138772 SEQ ID NO: 30
AAVrh.13	394	US20150159173 SEQ ID NO: 10
AAVrh.13	395	US20150159173 SEQ ID NO: 26
AAVrh.13	396	US20150315612 SEQ ID NO: 228
AAVrh.13R	397	US20150159173
AAV42.3A	398	US20030138772 SEQ ID NO: 87
AAVrh.14 (AAV42.3a)	399	US20030138772 SEQ ID NO: 32
AAV42.5A	400	US20030138772 SEQ ID NO: 89
AAVrh.17 (AAV42.5a)	401	US20030138772 SEQ ID NO: 34
AAV42.5B	402	US20030138772 SEQ ID NO: 91
AAVrh.18 (AAV42.5b)	403	US20030138772 SEQ ID NO: 29
AAV42.6B	404	US20030138772 SEQ ID NO: 112
AAVrh.19 (AAV42.6b)	405	US20030138772 SEQ ID NO: 38
AAVrh.2	406	US20150159173 SEQ ID NO: 39
AAVrh.2	407	US20150315612 SEQ ID NO: 231
AAVrh.20	408	US20150159173 SEQ ID NO: 1
AAV42.10	409	US20030138772 SEQ ID NO: 106
AAVrh.21 (AAV42.10)	410	US20030138772 SEQ ID NO: 35
AAV42.11	411	US20030138772 SEQ ID NO: 108
AAVrh.22 (AAV42.11)	412	US20030138772 SEQ ID NO: 37
AAV42.12	413	US20030138772 SEQ ID NO: 113
AAVrh.23 (AAV42.12)	414	US20030138772 SEQ ID NO: 58
AAV42.13	415	US20030138772 SEQ ID NO: 86
AAVrh.24 (AAV42.13)	416	US20030138772 SEQ ID NO: 31
AAV42.15	417	US20030138772 SEQ ID NO: 84
AAVrh.25 (AAV42.15)	418	US20030138772 SEQ ID NO: 28
AAVrh.2R	419	US20150159173
AAVrh.31 (AAV223.1)	420	US20030138772 SEQ ID NO: 48

AAVC1	421	US20030138772 SEQ ID NO: 60
AAVrh.32 (AAVC1)	422	US20030138772 SEQ ID NO: 19
AAVrh.32/33	423	US20150159173 SEQ ID NO: 2
AAVrh.33 (AAVC3)	424	US20030138772 SEQ ID NO: 20
AAVC5	425	US20030138772 SEQ ID NO: 62
AAVrh.34 (AAVC5)	426	US20030138772 SEQ ID NO: 21
AAVF1	427	US20030138772 SEQ ID NO: 109
AAVrh.35 (AAVF1)	428	US20030138772 SEQ ID NO: 22
AAVF3	429	US20030138772 SEQ ID NO: 111
AAVrh.36 (AAVF3)	430	US20030138772 SEQ ID NO: 23
AAVrh.37	431	US20030138772 SEQ ID NO: 24
AAVrh.37	432	US20150159173 SEQ ID NO: 40
AAVrh.37	433	US20150315612 SEQ ID NO: 229
AAVrh.37R2	434	US20150159173
AAVrh.38 (AAVLG-4)	435	US20150315612 SEQ ID NO: 7
AAVrh.38 (AAVLG-4)	436	US20150315612 SEQ ID NO: 86
AAVrh.39	437	US20150159173 SEQ ID NO: 20, US20150315612 SEQ ID NO: 13
AAVrh.39	438	US20150159173 SEQ ID NO: 3, US20150159173 SEQ ID NO: 36, US20150315612 SEQ ID NO: 89
AAVrh.40	439	US20150315612 SEQ ID NO: 92
AAVrh.40 (AAVLG-10)	440	US20150315612 SEQ ID No: 14
AAVrh.43 (AAVN721-8)	441	US20150315612 SEQ ID NO: 43, US20150159173 SEQ ID NO: 21
AAVrh.43 (AAVN721-8)	442	US20150315612 SEQ ID NO: 163, US20150159173 SEQ ID NO: 37
AAVrh.44	443	US20150315612 SEQ ID NO: 34
AAVrh.44	444	US20150315612 SEQ ID NO: 111
AAVrh.45	445	US20150315612 SEQ ID NO: 41
AAVrh.45	446	US20150315612 SEQ ID NO: 109
AAVrh.46	447	US20150159173 SEQ ID NO: 22, US20150315612 SEQ ID NO: 19
AAVrh.46	448	US20150159173 SEQ ID NO: 4, US20150315612 SEQ ID NO: 101
AAVrh.47	449	US20150315612 SEQ ID NO: 38
AAVrh.47	450	US20150315612 SEQ ID NO: 118
AAVrh.48	451	US20150159173 SEQ ID NO: 44, US20150315612 SEQ ID NO: 115
AAVrh.48.1	452	US20150159173
AAVrh.48.1.2	453	US20150159173
AAVrh.48.2	454	US20150159173
AAVrh.48 (AAV1-7)	455	US20150315612 SEQ ID NO: 32

AAVrh.49 (AAV1-8)	456	US20150315612 SEQ ID NO: 25
AAVrh.49 (AAV1-8)	457	US20150315612 SEQ ID NO: 103
AAVrh.50 (AAV2-4)	458	US20150315612 SEQ ID NO: 23
AAVrh.50 (AAV2-4)	459	US20150315612 SEQ ID NO: 108
AAVrh.51 (AAV2-5)	460	US20150315612 SEQ ID No: 22
AAVrh.51 (AAV2-5)	461	US20150315612 SEQ ID NO: 104
AAVrh.52 (AAV3-9)	462	US20150315612 SEQ ID NO: 18
AAVrh.52 (AAV3-9)	463	US20150315612 SEQ ID NO: 96
AAVrh.53	464	US20150315612 SEQ ID NO: 97
AAVrh.53 (AAV3-11)	465	US20150315612 SEQ ID NO: 17
AAVrh.53 (AAV3-11)	466	US20150315612 SEQ ID NO: 186
AAVrh.54	467	US20150315612 SEQ ID NO: 40
AAVrh.54	468	US20150159173 SEQ ID NO: 49, US20150315612 SEQ ID NO: 116
AAVrh.55	469	US20150315612 SEQ ID NO: 37
AAVrh.55 (AAV4-19)	470	US20150315612 SEQ ID NO: 117
AAVrh.56	471	US20150315612 SEQ ID NO: 54
AAVrh.56	472	US20150315612 SEQ ID NO: 152
AAVrh.57	473	US20150315612 SEQ ID NO: 26
AAVrh.57	474	US20150315612 SEQ ID NO: 105
AAVrh.58	475	US20150315612 SEQ ID NO: 27
AAVrh.58	476	US20150159173 SEQ ID NO: 48, US20150315612 SEQ ID NO: 106
AAVrh.58	477	US20150315612 SEQ ID NO: 232
AAVrh.59	478	US20150315612 SEQ ID NO: 42
AAVrh.59	479	US20150315612 SEQ ID NO: 110
AAVrh.60	480	US20150315612 SEQ ID NO: 31
AAVrh.60	481	US20150315612 SEQ ID NO: 120
AAVrh.61	482	US20150315612 SEQ ID NO: 107
AAVrh.61 (AAV2-3)	483	US20150315612 SEQ ID NO: 21
AAVrh.62 (AAV2-15)	484	US20150315612 SEQ ID No: 33
AAVrh.62 (AAV2-15)	485	US20150315612 SEQ ID NO: 114
AAVrh.64	486	US20150315612 SEQ ID No: 15
AAVrh.64	487	US20150159173 SEQ ID NO: 43, US20150315612 SEQ ID NO: 99
AAVrh.64	488	US20150315612 SEQ ID NO: 233
AAVRh.64R1	489	US20150159173
AAVRh.64R2	490	US20150159173
AAVrh.65	491	US20150315612 SEQ ID NO: 35

AAVrh.65	492	US20150315612 SEQ ID NO: 112
AAVrh.67	493	US20150315612 SEQ ID NO: 36
AAVrh.67	494	US20150315612 SEQ ID NO: 230
AAVrh.67	495	US20150159173 SEQ ID NO: 47, US20150315612 SEQ ID NO: 113
AAVrh.68	496	US20150315612 SEQ ID NO: 16
AAVrh.68	497	US20150315612 SEQ ID NO: 100
AAVrh.69	498	US20150315612 SEQ ID NO: 39
AAVrh.69	499	US20150315612 SEQ ID NO: 119
AAVrh.70	500	US20150315612 SEQ ID NO: 20
AAVrh.70	501	US20150315612 SEQ ID NO: 98
AAVrh.71	502	US20150315612 SEQ ID NO: 162
AAVrh.72	503	US20150315612 SEQ ID NO: 9
AAVrh.73	504	US20150159173 SEQ ID NO: 5
AAVrh.74	505	US20150159173 SEQ ID NO: 6
AAVrh.8	506	US20150159173 SEQ ID NO: 41
AAVrh.8	507	US20150315612 SEQ ID NO: 235
AAVrh.8R	508	US20150159173, WO2015168666 SEQ ID NO: 9
AAVrh.8R A586R mutant	509	WO2015168666 SEQ ID NO: 10
AAVrh.8R R533A mutant	510	WO2015168666 SEQ ID NO: 11
BAAV (bovine AAV)	511	US9193769 SEQ ID NO: 8
BAAV (bovine AAV)	512	US9193769 SEQ ID NO: 10
BAAV (bovine AAV)	513	US9193769 SEQ ID NO: 4
BAAV (bovine AAV)	514	US9193769 SEQ ID NO: 2
BAAV (bovine AAV)	515	US9193769 SEQ ID NO: 6
BAAV (bovine AAV)	516	US9193769 SEQ ID NO: 1
BAAV (bovine AAV)	517	US9193769 SEQ ID NO: 5
BAAV (bovine AAV)	518	US9193769 SEQ ID NO: 3
BAAV (bovine AAV)	519	US9193769 SEQ ID NO: 11
BAAV (bovine AAV)	520	US7427396 SEQ ID NO: 5

BAAV (bovine AAV)	521	US7427396 SEQ ID NO: 6
BAAV (bovine AAV)	522	US9193769 SEQ ID NO: 7
BAAV (bovine AAV)	523	US9193769 SEQ ID NO: 9
BNP61 AAV	524	US20150238550 SEQ ID NO: 1
BNP61 AAV	525	US20150238550 SEQ ID NO: 2
BNP62 AAV	526	US20150238550 SEQ ID NO: 3
BNP63 AAV	527	US20150238550 SEQ ID NO: 4
caprine AAV	528	US7427396 SEQ ID NO: 3
caprine AAV	529	US7427396 SEQ ID NO: 4
true type AAV (ttAAV)	530	WO2015121501 SEQ ID NO: 2
AAAV (Avian AAV)	531	US9238800 SEQ ID NO: 12
AAAV (Avian AAV)	532	US9238800 SEQ ID NO: 2
AAAV (Avian AAV)	533	US9238800 SEQ ID NO: 6
AAAV (Avian AAV)	534	US9238800 SEQ ID NO: 4
AAAV (Avian AAV)	535	US9238800 SEQ ID NO: 8
AAAV (Avian AAV)	536	US9238800 SEQ ID NO: 14
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AAAV (Avian AAV)	542	US9238800 SEQ ID NO: 7
AAAV (Avian AAV)	543	US9238800 SEQ ID NO: 11
AAAV (Avian AAV)	544	US9238800 SEQ ID NO: 13
AAAV (Avian AAV)	545	US9238800 SEQ ID NO: 1
AAV Shuffle 100-1	546	US20160017295 SEQ ID NO: 23
AAV Shuffle 100-1	547	US20160017295 SEQ ID NO: 11
AAV Shuffle 100-2	548	US20160017295 SEQ ID NO: 37
AAV Shuffle 100-2	549	US20160017295 SEQ ID NO: 29

AAV Shuffle 100-3	550	US20160017295 SEQ ID NO: 24
AAV Shuffle 100-3	551	US20160017295 SEQ ID NO: 12
AAV Shuffle 100-7	552	US20160017295 SEQ ID NO: 25
AAV Shuffle 100-7	553	US20160017295 SEQ ID NO: 13
AAV Shuffle 10-2	554	US20160017295 SEQ ID NO: 34
AAV Shuffle 10-2	555	US20160017295 SEQ ID NO: 26
AAV Shuffle 10-6	556	US20160017295 SEQ ID NO: 35
AAV Shuffle 10-6	557	US20160017295 SEQ ID NO: 27
AAV Shuffle 10-8	558	US20160017295 SEQ ID NO: 36
AAV Shuffle 10-8	559	US20160017295 SEQ ID NO: 28
AAV SM 100-10	560	US20160017295 SEQ ID NO: 41
AAV SM 100-10	561	US20160017295 SEQ ID NO: 33
AAV SM 100-3	562	US20160017295 SEQ ID NO: 40
AAV SM 100-3	563	US20160017295 SEQ ID NO: 32
AAV SM 10-1	564	US20160017295 SEQ ID NO: 38
AAV SM 10-1	565	US20160017295 SEQ ID NO: 30
AAV SM 10-2	566	US20160017295 SEQ ID NO: 10
AAV SM 10-2	567	US20160017295 SEQ ID NO: 22
AAV SM 10-8	568	US20160017295 SEQ ID NO: 39
AAV SM 10-8	569	US20160017295 SEQ ID NO: 31
AAV SM 100-10	560	US20160017295 SEQ ID NO: 41
AAV SM 100-10	561	US20160017295 SEQ ID NO: 33
AAV SM 100-3	562	US20160017295 SEQ ID NO: 40
AAV SM 100-3	563	US20160017295 SEQ ID NO: 32
AAV SM 10-1	564	US20160017295 SEQ ID NO: 38
AAV SM 10-1	565	US20160017295 SEQ ID NO: 30
AAV SM 10-2	566	US20160017295 SEQ ID NO: 10
AAV SM 10-2	567	US20160017295 SEQ ID NO: 22
AAV SM 10-8	568	US20160017295 SEQ ID NO: 39

AAV SM 10-8	569	US20160017295 SEQ ID NO: 31
AAVF1/HSC1	570	WO2016049230 SEQ ID NO: 20
AAVF2/HSC2	571	WO2016049230 SEQ ID NO: 21
AAVF3/HSC3	572	WO2016049230 SEQ ID NO: 22
AAVF4/HSC4	573	WO2016049230 SEQ ID NO: 23
AAVF5/HSC5	574	WO2016049230 SEQ ID NO: 25
AAVF6/HSC6	575	WO2016049230 SEQ ID NO: 24
AAVF7/HSC7	576	WO2016049230 SEQ ID NO: 27
AAVF8/HSC8	577	WO2016049230 SEQ ID NO: 28
AAVF9/HSC9	578	WO2016049230 SEQ ID NO: 29
AAVF11/HSC11	579	WO2016049230 SEQ ID NO: 26
AAVF12/HSC12	580	WO2016049230 SEQ ID NO: 30
AAVF13/HSC13	581	WO2016049230 SEQ ID NO: 31
AAVF14/HSC14	582	WO2016049230 SEQ ID NO: 32
AAVF15/HSC15	583	WO2016049230 SEQ ID NO: 33
AAVF16/HSC16	584	WO2016049230 SEQ ID NO: 34
AAVF17/HSC17	585	WO2016049230 SEQ ID NO: 35
AAVF1/HSC1	586	WO2016049230 SEQ ID NO: 2
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AAVF11/HSC11	595	WO2016049230 SEQ ID NO: 4
AAVF12/HSC12	596	WO2016049230 SEQ ID NO: 12
AAVF13/HSC13	597	WO2016049230 SEQ ID NO: 14

AAVF14/HSC14	598	WO2016049230 SEQ ID NO: 15
AAVF15/HSC15	599	WO2016049230 SEQ ID NO: 16
AAVF16/HSC16	600	WO2016049230 SEQ ID NO: 17
AAVF17/HSC17	601	WO2016049230 SEQ ID NO: 13
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AAV CBr-E2	603	US8734809 SEQ ID NO: 14
AAV CBr-E3	604	US8734809 SEQ ID NO: 15
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AAV CBr-E5	606	US8734809 SEQ ID NO: 17
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AAV CBr-E6	608	US8734809 SEQ ID NO: 19
AAV CBr-E7	609	US8734809 SEQ ID NO: 20
AAV CBr-E8	610	US8734809 SEQ ID NO: 21
AAV CLv-D1	611	US8734809 SEQ ID NO: 22
AAV CLv-D2	612	US8734809 SEQ ID NO: 23
AAV CLv-D3	613	US8734809 SEQ ID NO: 24
AAV CLv-D4	614	US8734809 SEQ ID NO: 25
AAV CLv-D5	615	US8734809 SEQ ID NO: 26
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AAV CLv-D7	617	US8734809 SEQ ID NO: 28
AAV CLv-D8	618	US8734809 SEQ ID NO: 29
AAV CLv-E1	619	US8734809 SEQ ID NO: 13
AAV CLv-R1	620	US8734809 SEQ ID NO: 30
AAV CLv-R2	621	US8734809 SEQ ID NO: 31
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AAV CLv-R6	625	US8734809 SEQ ID NO: 35
AAV CLv-R7	626	US8734809 SEQ ID NO: 36
AAV CLv-R8	627	US8734809 SEQ ID NO: 37
AAV CLv-R9	628	US8734809 SEQ ID NO: 38
AAV CLg-F1	629	US8734809 SEQ ID NO: 39
AAV CLg-F2	630	US8734809 SEQ ID NO: 40

AAV CLg-F3	631	US8734809 SEQ ID NO: 41
AAV CLg-F4	632	US8734809 SEQ ID NO: 42
AAV CLg-F5	633	US8734809 SEQ ID NO: 43
AAV CLg-F6	634	US8734809 SEQ ID NO: 43
AAV CLg-F7	635	US8734809 SEQ ID NO: 44
AAV CLg-F8	636	US8734809 SEQ ID NO: 43
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AAV CSp-11	639	US8734809 SEQ ID NO: 47
AAV CSp-2	640	US8734809 SEQ ID NO: 48
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AAV CSp-6	643	US8734809 SEQ ID NO: 51
AAV CSp-7	644	US8734809 SEQ ID NO: 52
AAV CSp-8	645	US8734809 SEQ ID NO: 53
AAV CSp-9	646	US8734809 SEQ ID NO: 54
AAV CHt-2	647	US8734809 SEQ ID NO: 55
AAV CHt-3	648	US8734809 SEQ ID NO: 56
AAV CKd-1	649	US8734809 SEQ ID NO: 57
AAV CKd-10	650	US8734809 SEQ ID NO: 58
AAV CKd-2	651	US8734809 SEQ ID NO: 59
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AAV CLv-13	659	US8734809 SEQ ID NO: 67
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AAV CLv-3	661	US8734809 SEQ ID NO: 69
AAV CLv-4	662	US8734809 SEQ ID NO: 70
AAV CLv-6	663	US8734809 SEQ ID NO: 71
AAV CLv-8	664	US8734809 SEQ ID NO: 72
AAV CKd-B1	665	US8734809 SEQ ID NO: 73
AAV CKd-B2	666	US8734809 SEQ ID NO: 74
AAV CKd-B3	667	US8734809 SEQ ID NO: 75
AAV CKd-B4	668	US8734809 SEQ ID NO: 76
AAV CKd-B5	669	US8734809 SEQ ID NO: 77
AAV CKd-B6	670	US8734809 SEQ ID NO: 78

AAV CKd-B7	671	US8734809 SEQ ID NO: 79
AAV CKd-B8	672	US8734809 SEQ ID NO: 80
AAV CKd-H1	673	US8734809 SEQ ID NO: 81
AAV CKd-H2	674	US8734809 SEQ ID NO: 82
AAV CKd-H3	675	US8734809 SEQ ID NO: 83
AAV CKd-H4	676	US8734809 SEQ ID NO: 84
AAV CKd-H5	677	US8734809 SEQ ID NO: 85
AAV CKd-H6	678	US8734809 SEQ ID NO: 77
AAV CHt-1	679	US8734809 SEQ ID NO: 86
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AAV CLv1-2	681	US8734809 SEQ ID NO: 172
AAV CLv1-3	682	US8734809 SEQ ID NO: 173
AAV CLv1-4	683	US8734809 SEQ ID NO: 174
AAV Clv1-7	684	US8734809 SEQ ID NO: 175
AAV Clv1-8	685	US8734809 SEQ ID NO: 176
AAV Clv1-9	686	US8734809 SEQ ID NO: 177
AAV Clv1-10	687	US8734809 SEQ ID NO: 178
AAV.VR-355	688	US8734809 SEQ ID NO: 181
AAV.hu.48R3	689	US8734809 SEQ ID NO: 183
AAV CBr-E1	690	US8734809 SEQ ID NO: 87
AAV CBr-E2	691	US8734809 SEQ ID NO: 88
AAV CBr-E3	692	US8734809 SEQ ID NO: 89
AAV CBr-E4	693	US8734809 SEQ ID NO: 90
AAV CBr-E5	694	US8734809 SEQ ID NO: 91
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AAV CBr-E7	697	US8734809 SEQ ID NO: 94
AAV CBr-E8	698	US8734809 SEQ ID NO: 95
AAV CLv-D1	699	US8734809 SEQ ID NO: 96
AAV CLv-D2	700	US8734809 SEQ ID NO: 97
AAV CLv-D3	701	US8734809 SEQ ID NO: 98
AAV CLv-D4	702	US8734809 SEQ ID NO: 99
AAV CLv-D5	703	US8734809 SEQ ID NO: 100
AAV CLv-D6	704	US8734809 SEQ ID NO: 101
AAV CLv-D7	705	US8734809 SEQ ID NO: 102

AAV CLv-D8	706	US8734809 SEQ ID NO: 103
AAV CLv-E1	707	US8734809 SEQ ID NO: 87
AAV CLv-R1	708	US8734809 SEQ ID NO: 104
AAV CLv-R2	709	US8734809 SEQ ID NO: 105
AAV CLv-R3	710	US8734809 SEQ ID NO: 106
AAV CLv-R4	711	US8734809 SEQ ID NO: 107
AAV CLv-R5	712	US8734809 SEQ ID NO: 108
AAV CLv-R6	713	US8734809 SEQ ID NO: 109
AAV CLv-R7	714	US8734809 SEQ ID NO: 110
AAV CLv-R8	715	US8734809 SEQ ID NO: 111
AAV CLv-R9	716	US8734809 SEQ ID NO: 112
AAV CLg-F1	717	US8734809 SEQ ID NO: 113
AAV CLg-F2	718	US8734809 SEQ ID NO: 114
AAV CLg-F3	719	US8734809 SEQ ID NO: 115
AAV CLg-F4	720	US8734809 SEQ ID NO: 116
AAV CLg-F5	721	US8734809 SEQ ID NO: 117
AAV CLg-F6	722	US8734809 SEQ ID NO: 117
AAV CLg-F7	723	US8734809 SEQ ID NO: 118
AAV CLg-F8	724	US8734809 SEQ ID NO: 117
AAV CSp-1	725	US8734809 SEQ ID NO: 119
AAV CSp-10	726	US8734809 SEQ ID NO: 120
AAV CSp-11	727	US8734809 SEQ ID NO: 121
AAV CSp-2	728	US8734809 SEQ ID NO: 122
AAV CSp-3	729	US8734809 SEQ ID NO: 123
AAV CSp-4	730	US8734809 SEQ ID NO: 124
AAV CSp-6	731	US8734809 SEQ ID NO: 125
AAV CSp-7	732	US8734809 SEQ ID NO: 126
AAV CSp-8	733	US8734809 SEQ ID NO: 127
AAV CSp-9	734	US8734809 SEQ ID NO: 128
AAV CHt-2	735	US8734809 SEQ ID NO: 129
AAV CHt-3	736	US8734809 SEQ ID NO: 130
AAV CKd-1	737	US8734809 SEQ ID NO: 131
AAV CKd-10	738	US8734809 SEQ ID NO: 132
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AAV CKd-3	740	US8734809 SEQ ID NO: 134
AAV CKd-4	741	US8734809 SEQ ID NO: 135
AAV CKd-6	742	US8734809 SEQ ID NO: 136
AAV CKd-7	743	US8734809 SEQ ID NO: 137
AAV CKd-8	744	US8734809 SEQ ID NO: 138

AAV CLv-1	745	US8734809 SEQ ID NO: 139
AAV CLv-12	746	US8734809 SEQ ID NO: 140
AAV CLv-13	747	US8734809 SEQ ID NO: 141
AAV CLv-2	748	US8734809 SEQ ID NO: 142
AAV CLv-3	749	US8734809 SEQ ID NO: 143
AAV CLv-4	750	US8734809 SEQ ID NO: 144
AAV CLv-6	751	US8734809 SEQ ID NO: 145
AAV CLv-8	752	US8734809 SEQ ID NO: 146
AAV CKd-B1	753	US8734809 SEQ ID NO: 147
AAV CKd-B2	754	US8734809 SEQ ID NO: 148
AAV CKd-B3	755	US8734809 SEQ ID NO: 149
AAV CKd-B4	756	US8734809 SEQ ID NO: 150
AAV CKd-B5	757	US8734809 SEQ ID NO: 151
AAV CKd-B6	758	US8734809 SEQ ID NO: 152
AAV CKd-B7	759	US8734809 SEQ ID NO: 153
AAV CKd-B8	760	US8734809 SEQ ID NO: 154
AAV CKd-H1	761	US8734809 SEQ ID NO: 155
AAV CKd-H2	762	US8734809 SEQ ID NO: 156
AAV CKd-H3	763	US8734809 SEQ ID NO: 157
AAV CKd-H4	764	US8734809 SEQ ID NO: 158
AAV CKd-H5	765	US8734809 SEQ ID NO: 159
AAV CKd-H6	766	US8734809 SEQ ID NO: 151
AAV CHt-1	767	US8734809 SEQ ID NO: 160
AAV CHt-P2	768	WO2016065001 SEQ ID NO: 1
AAV CHt-P5	769	WO2016065001 SEQ ID NO: 2
AAV CHt-P9	770	WO2016065001 SEQ ID NO: 3
AAV CBr-7.1	771	WO2016065001 SEQ ID NO: 4
AAV CBr-7.2	772	WO2016065001 SEQ ID NO: 5
AAV CBr-7.3	773	WO2016065001 SEQ ID NO: 6
AAV CBr-7.4	774	WO2016065001 SEQ ID NO: 7
AAV CBr-7.5	775	WO2016065001 SEQ ID NO: 8
AAV CBr-7.7	776	WO2016065001 SEQ ID NO: 9
AAV CBr-7.8	777	WO2016065001 SEQ ID NO: 10

AAV CBr-7.10	778	WO2016065001 SEQ ID NO: 11
AAV CKd-N3	779	WO2016065001 SEQ ID NO: 12
AAV CKd-N4	780	WO2016065001 SEQ ID NO: 13
AAV CKd-N9	781	WO2016065001 SEQ ID NO: 14
AAV CLv-L4	782	WO2016065001 SEQ ID NO: 15
AAV CLv-L5	783	WO2016065001 SEQ ID NO: 16
AAV CLv-L6	784	WO2016065001 SEQ ID NO: 17
AAV CLv-K1	785	WO2016065001 SEQ ID NO: 18
AAV CLv-K3	786	WO2016065001 SEQ ID NO: 19
AAV CLv-K6	787	WO2016065001 SEQ ID NO: 20
AAV CLv-M1	788	WO2016065001 SEQ ID NO: 21
AAV CLv-M11	789	WO2016065001 SEQ ID NO: 22
AAV CLv-M2	790	WO2016065001 SEQ ID NO: 23
AAV CLv-M5	791	WO2016065001 SEQ ID NO: 24
AAV CLv-M6	792	WO2016065001 SEQ ID NO: 25
AAV CLv-M7	793	WO2016065001 SEQ ID NO: 26
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AAV CHt-P8	798	WO2016065001 SEQ ID NO: 31
AAV CHt-6.1	799	WO2016065001 SEQ ID NO: 32
AAV CHt-6.10	800	WO2016065001 SEQ ID NO: 33
AAV CHt-6.5	801	WO2016065001 SEQ ID NO: 34
AAV CHt-6.6	802	WO2016065001 SEQ ID NO: 35
AAV CHt-6.7	803	WO2016065001 SEQ ID NO: 36
AAV CHt-6.8	804	WO2016065001 SEQ ID NO: 37
AAV CSp-8.10	805	WO2016065001 SEQ ID NO: 38
AAV CSp-8.2	806	WO2016065001 SEQ ID NO: 39
AAV CSp-8.4	807	WO2016065001 SEQ ID NO: 40
AAV CSp-8.5	808	WO2016065001 SEQ ID NO: 41

AAV CSp-8.6	809	WO2016065001 SEQ ID NO: 42
AAV CSp-8.7	810	WO2016065001 SEQ ID NO: 43
AAV CSp-8.8	811	WO2016065001 SEQ ID NO: 44
AAV CSp-8.9	812	WO2016065001 SEQ ID NO: 45
AAV CBr-B7.3	813	WO2016065001 SEQ ID NO: 46
AAV CBr-B7.4	814	WO2016065001 SEQ ID NO: 47
AAV3B	815	WO2016065001 SEQ ID NO: 48
AAV4	816	WO2016065001 SEQ ID NO: 49
AAV5	817	WO2016065001 SEQ ID NO: 50
AAV CHt-P2	818	WO2016065001 SEQ ID NO: 51
AAV CHt-P5	819	WO2016065001 SEQ ID NO: 52
AAV CHt-P9	820	WO2016065001 SEQ ID NO: 53
AAV CBr-7.1	821	WO2016065001 SEQ ID NO: 54
AAV CBr-7.2	822	WO2016065001 SEQ ID NO: 55
AAV CBr-7.3	823	WO2016065001 SEQ ID NO: 56
AAV CBr-7.4	824	WO2016065001 SEQ ID NO: 57
AAV CBr-7.5	825	WO2016065001 SEQ ID NO: 58
AAV CBr-7.7	826	WO2016065001 SEQ ID NO: 59
AAV CBr-7.8	827	WO2016065001 SEQ ID NO: 60
AAV CBr-7.10	828	WO2016065001 SEQ ID NO: 61
AAV CKd-N3	829	WO2016065001 SEQ ID NO: 62
AAV CKd-N4	830	WO2016065001 SEQ ID NO: 63
AAV CKd-N9	831	WO2016065001 SEQ ID NO: 64
AAV CLv-L4	832	WO2016065001 SEQ ID NO: 65
AAV CLv-L5	833	WO2016065001 SEQ ID NO: 66
AAV CLv-L6	834	WO2016065001 SEQ ID NO: 67
AAV CLv-K1	835	WO2016065001 SEQ ID NO: 68
AAV CLv-K3	836	WO2016065001 SEQ ID NO: 69
AAV CLv-K6	837	WO2016065001 SEQ ID NO: 70
AAV CLv-M1	838	WO2016065001 SEQ ID NO: 71
AAV CLv-M11	839	WO2016065001 SEQ ID NO: 72
AAV CLv-M2	840	WO2016065001 SEQ ID NO: 73

AAV CLv-M5	841	WO2016065001 SEQ ID NO: 74
AAV CLv-M6	842	WO2016065001 SEQ ID NO: 75
AAV CLv-M7	843	WO2016065001 SEQ ID NO: 76
AAV CLv-M8	844	WO2016065001 SEQ ID NO: 77
AAV CLv-M9	845	WO2016065001 SEQ ID NO: 78
AAV CHt-P1	846	WO2016065001 SEQ ID NO: 79
AAV CHt-P6	847	WO2016065001 SEQ ID NO: 80
AAV CHt-P8	848	WO2016065001 SEQ ID NO: 81
AAV CHt-6.1	849	WO2016065001 SEQ ID NO: 82
AAV CHt-6.10	850	WO2016065001 SEQ ID NO: 83
AAV CHt-6.5	851	WO2016065001 SEQ ID NO: 84
AAV CHt-6.6	852	WO2016065001 SEQ ID NO: 85
AAV CHt-6.7	853	WO2016065001 SEQ ID NO: 86
AAV CHt-6.8	854	WO2016065001 SEQ ID NO: 87
AAV CSp-8.10	855	WO2016065001 SEQ ID NO: 88
AAV CSp-8.2	856	WO2016065001 SEQ ID NO: 89
AAV CSp-8.4	857	WO2016065001 SEQ ID NO: 90
AAV CSp-8.5	858	WO2016065001 SEQ ID NO: 91
AAV CSp-8.6	859	WO2016065001 SEQ ID NO: 92
AAV CSp-8.7	860	WO2016065001 SEQ ID NO: 93
AAV CSp-8.8	861	WO2016065001 SEQ ID NO: 94
AAV CSp-8.9	862	WO2016065001 SEQ ID NO: 95
AAV CBr-B7.3	863	WO2016065001 SEQ ID NO: 96
AAV CBr-B7.4	864	WO2016065001 SEQ ID NO: 97
AAV3B	865	WO2016065001 SEQ ID NO: 98
AAV4	866	WO2016065001 SEQ ID NO: 99
AAV5	867	WO2016065001 SEQ ID NO: 100
AAVPHP.B or G2B-26	868	WO2015038958 SEQ ID NO: 8 and 13; GenBankALU85156.1
AAVPHP.B	869	WO2015038958 SEQ ID NO: 9
AAVG2B-13	870	WO2015038958 SEQ ID NO: 12
AAVTH1.1-32	871	WO2015038958 SEQ ID NO: 14
AAVTH1.1-35	872	WO2015038958 SEQ ID NO: 15

PHP.N/PHP.B-DGT	1439	WO2017100671 SEQ ID NO: 46
PHP.S/G2A12	1440	WO2017100671 SEQ ID NO: 47
AAV9/hu.14 K449R	1441	WO2017100671 SEQ ID NO: 45
GPV	1518	US9624274B2 SEQ ID NO: 192
B19	1519	US9624274B2 SEQ ID NO: 193
MVM	1520	US9624274B2 SEQ ID NO: 194
FPV	1521	US9624274B2 SEQ ID NO: 195
CPV	1522	US9624274B2 SEQ ID NO: 196
AAV6	1523	US9546112B2 SEQ ID NO: 5
AAV6	1524	US9457103B2 SEQ ID NO: 1
AAV2	1525	US9457103B2 SEQ ID NO: 2
ShH10	1526	US9457103B2 SEQ ID NO: 3
ShH13	1527	US9457103B2 SEQ ID NO: 4
ShH10	1528	US9457103B2 SEQ ID NO: 5
ShH10	1529	US9457103B2 SEQ ID NO: 6
ShH10	1530	US9457103B2 SEQ ID NO: 7
ShH10	1531	US9457103B2 SEQ ID NO: 8
ShH10	1532	US9457103B2 SEQ ID NO: 9
rh74	1533	US9434928B2 SEQ ID NO: 1, US2015023924A1 SEQ ID NO: 2
rh74	1534	US9434928B2 SEQ ID NO: 2, US2015023924A1 SEQ ID NO: 1
AAV8	1535	US9434928B2 SEQ ID NO: 4
rh74	1536	US9434928B2 SEQ ID NO: 5
rh74 (RHM4-1)	1537	US2015023924A1 SEQ ID NO: 5, US20160375110A1 SEQ ID NO: 4
rh74 (RHM15-1)	1538	US2015023924A1 SEQ ID NO: 6, US20160375110A1 SEQ ID NO: 5
rh74 (RHM15-2)	1539	US2015023924A1 SEQ ID NO: 7, US20160375110A1 SEQ ID NO: 6
rh74 (RHM15-3/RHM15-5)	1540	US2015023924A1 SEQ ID NO: 8, US20160375110A1 SEQ ID NO: 7
rh74 (RHM15-4)	1541	US2015023924A1 SEQ ID NO: 9, US20160375110A1 SEQ ID NO: 8
rh74 (RHM15-6)	1542	US2015023924A1 SEQ ID NO: 10, US20160375110A1 SEQ ID NO: 9
rh74 (RHM4-1)	1543	US2015023924A1 SEQ ID NO: 11
rh74 (RHM15-1)	1544	US2015023924A1 SEQ ID NO: 12
rh74 (RHM15-2)	1545	US2015023924A1 SEQ ID NO: 13
rh74 (RHM15-3/RHM15-5)	1546	US2015023924A1 SEQ ID NO: 14
rh74 (RHM15-4)	1547	US2015023924A1 SEQ ID NO: 15
rh74 (RHM15-6)	1548	US2015023924A1 SEQ ID NO: 16

AAV2 (comprising lung specific polypeptide)	1549	US20160175389A1 SEQ ID NO: 9
AAV2 (comprising lung specific polypeptide)	1550	US20160175389A1 SEQ ID NO: 10
Anc80	1551	US20170051257A1 SEQ ID NO: 1
Anc80	1552	US20170051257A1 SEQ ID NO: 2
Anc81	1553	US20170051257A1 SEQ ID NO: 3
Anc80	1554	US20170051257A1 SEQ ID NO: 4
Anc82	1555	US20170051257A1 SEQ ID NO: 5
Anc82	1556	US20170051257A1 SEQ ID NO: 6
Anc83	1557	US20170051257A1 SEQ ID NO: 7
Anc83	1558	US20170051257A1 SEQ ID NO: 8
Anc84	1559	US20170051257A1 SEQ ID NO: 9
Anc84	1560	US20170051257A1 SEQ ID NO: 10
Anc94	1561	US20170051257A1 SEQ ID NO: 11
Anc94	1562	US20170051257A1 SEQ ID NO: 12
Anc113	1563	US20170051257A1 SEQ ID NO: 13
Anc113	1564	US20170051257A1 SEQ ID NO: 14
Anc126	1565	US20170051257A1 SEQ ID NO: 15
Anc126	1566	US20170051257A1 SEQ ID NO: 16
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Anc127	1568	US20170051257A1 SEQ ID NO: 18
Anc80L27	1569	US20170051257A1 SEQ ID NO: 19
Anc80L59	1570	US20170051257A1 SEQ ID NO: 20
Anc80L60	1571	US20170051257A1 SEQ ID NO: 21
Anc80L62	1572	US20170051257A1 SEQ ID NO: 22
Anc80L65	1573	US20170051257A1 SEQ ID NO: 23
Anc80L33	1574	US20170051257A1 SEQ ID NO: 24
Anc80L36	1575	US20170051257A1 SEQ ID NO: 25
Anc80L44	1576	US20170051257A1 SEQ ID NO: 26
Anc80L1	1577	US20170051257A1 SEQ ID NO: 35
Anc80L1	1578	US20170051257A1 SEQ ID NO: 36
AAV-X1	1579	US8283151B2 SEQ ID NO: 11
AAV-X1b	1580	US8283151B2 SEQ ID NO: 12
AAV-X5	1581	US8283151B2 SEQ ID NO: 13
AAV-X19	1582	US8283151B2 SEQ ID NO: 14
AAV-X21	1583	US8283151B2 SEQ ID NO: 15
AAV-X22	1584	US8283151B2 SEQ ID NO: 16
AAV-X23	1585	US8283151B2 SEQ ID NO: 17
AAV-X24	1586	US8283151B2 SEQ ID NO: 18
AAV-X25	1587	US8283151B2 SEQ ID NO: 19
AAV-X26	1588	US8283151B2 SEQ ID NO: 20

AAV-X1	1589	US8283151B2 SEQ ID NO: 21
AAV-X1b	1590	US8283151B2 SEQ ID NO: 22
AAV-X5	1591	US8283151B2 SEQ ID NO: 23
AAV-X19	1592	US8283151B2 SEQ ID NO: 24
AAV-X21	1593	US8283151B2 SEQ ID NO: 25
AAV-X22	1594	US8283151B2 SEQ ID NO: 26
AAV-X23	1595	US8283151B2 SEQ ID NO: 27
AAV-X24	1596	US8283151B2 SEQ ID NO: 28
AAV-X25	1597	US8283151B2 SEQ ID NO: 29
AAV-X26	1598	US8283151B2 SEQ ID NO: 30
AAVrh8	1599	WO2016054554A1 SEQ ID NO: 8
AAVrh8VP2 FC5	1600	WO2016054554A1 SEQ ID NO: 9
AAVrh8VP2 FC44	1601	WO2016054554A1 SEQ ID NO: 10
AAVrh8VP2 ApoB100	1602	WO2016054554A1 SEQ ID NO: 11
AAVrh8VP2 RVG	1603	WO2016054554A1 SEQ ID NO: 12
AAVrh8VP2 Angiopep-2 VP2	1604	WO2016054554A1 SEQ ID NO: 13
AAV9.47VP 1.3	1605	WO2016054554A1 SEQ ID NO: 14
AAV9.47VP 2ICAMg3	1606	WO2016054554A1 SEQ ID NO: 15
AAV9.47VP 2RVG	1607	WO2016054554A1 SEQ ID NO: 16
AAV9.47VP 2Angiopep-2	1608	WO2016054554A1 SEQ ID NO: 17
AAV9.47VP 2A-string	1609	WO2016054554A1 SEQ ID NO: 18
AAVrh8VP2 FC5 VP2	1610	WO2016054554A1 SEQ ID NO: 19
AAVrh8VP2 FC44 VP2	1611	WO2016054554A1 SEQ ID NO: 20
AAVrh8VP2 ApoB100 VP2	1612	WO2016054554A1 SEQ ID NO: 21
AAVrh8VP2 RVG VP2	1613	WO2016054554A1 SEQ ID NO: 22
AAVrh8VP2 Angiopep-2 VP2	1614	WO2016054554A1 SEQ ID NO: 23
AAV9.47VP 2ICAMg3 VP2	1615	WO2016054554A1 SEQ ID NO: 24
AAV9.47VP 2RVG VP2	1616	WO2016054554A1 SEQ ID NO: 25
AAV9.47VP 2Angiopep-2 VP2	1617	WO2016054554A1 SEQ ID NO: 26
AAV9.47VP 2A-string VP2	1618	WO2016054554A1 SEQ ID NO: 27

rAAV-B1	1619	WO2016054557A1 SEQ ID NO: 1
rAAV-B2	1620	WO2016054557A1 SEQ ID NO: 2
rAAV-B3	1621	WO2016054557A1 SEQ ID NO: 3
rAAV-B4	1622	WO2016054557A1 SEQ ID NO: 4
rAAV-B1	1623	WO2016054557A1 SEQ ID NO: 5
rAAV-B2	1624	WO2016054557A1 SEQ ID NO: 6
rAAV-B3	1625	WO2016054557A1 SEQ ID NO: 7
rAAV-B4	1626	WO2016054557A1 SEQ ID NO: 8
rAAV-L1	1627	WO2016054557A1 SEQ ID NO: 9
rAAV-L2	1628	WO2016054557A1 SEQ ID NO: 10
rAAV-L3	1629	WO2016054557A1 SEQ ID NO: 11
rAAV-L4	1630	WO2016054557A1 SEQ ID NO: 12
rAAV-L1	1631	WO2016054557A1 SEQ ID NO: 13
rAAV-L2	1632	WO2016054557A1 SEQ ID NO: 14
rAAV-L3	1633	WO2016054557A1 SEQ ID NO: 15
rAAV-L4	1634	WO2016054557A1 SEQ ID NO: 16
AAV9	1635	WO2016073739A1 SEQ ID NO: 3
rAAV	1636	WO2016081811A1 SEQ ID NO: 1
rAAV	1637	WO2016081811A1 SEQ ID NO: 2
rAAV	1638	WO2016081811A1 SEQ ID NO: 3
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rAAV	1671	WO2016081811A1 SEQ ID NO: 36
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rAAV	1704	WO2016081811A1 SEQ ID NO: 69
rAAV	1705	WO2016081811A1 SEQ ID NO: 70
rAAV	1706	WO2016081811A1 SEQ ID NO: 71

rAAV	1707	WO2016081811A1 SEQ ID NO: 72
rAAV	1708	WO2016081811A1 SEQ ID NO: 73
rAAV	1709	WO2016081811A1 SEQ ID NO: 74
rAAV	1710	WO2016081811A1 SEQ ID NO: 75
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rAAV	1748	WO2016081811A1 SEQ ID NO: 113
rAAV	1749	WO2016081811A1 SEQ ID NO: 114
rAAV	1750	WO2016081811A1 SEQ ID NO: 115

rAAV	1751	WO2016081811A1 SEQ ID NO: 116
rAAV	1752	WO2016081811A1 SEQ ID NO: 117
rAAV	1753	WO2016081811A1 SEQ ID NO: 118
rAAV	1754	WO2016081811A1 SEQ ID NO: 119
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rAAV	1761	WO2016081811A1 SEQ ID NO: 126
rAAV	1762	WO2016081811A1 SEQ ID NO: 127
rAAV	1763	WO2016081811A1 SEQ ID NO: 128
AAV8 E532K	1764	WO2016081811A1 SEQ ID NO: 133
AAV8 E532K	1765	WO2016081811A1 SEQ ID NO: 134
rAAV4	1766	WO2016115382A1 SEQ ID NO: 2
rAAV4	1767	WO2016115382A1 SEQ ID NO: 3
rAAV4	1768	WO2016115382A1 SEQ ID NO: 4
rAAV4	1769	WO2016115382A1 SEQ ID NO: 5
rAAV4	1770	WO2016115382A1 SEQ ID NO: 6
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rAAV4	1776	WO2016115382A1 SEQ ID NO: 12
rAAV4	1777	WO2016115382A1 SEQ ID NO: 13
rAAV4	1778	WO2016115382A1 SEQ ID NO: 14
rAAV4	1779	WO2016115382A1 SEQ ID NO: 15
rAAV4	1780	WO2016115382A1 SEQ ID NO: 16
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rAAV4	1785	WO2016115382A1 SEQ ID NO: 21
AAV11	1786	WO2016115382A1 SEQ ID NO: 22
AAV12	1787	WO2016115382A1 SEQ ID NO: 23
rh32	1788	WO2016115382A1 SEQ ID NO: 25
rh33	1789	WO2016115382A1 SEQ ID NO: 26
rh34	1790	WO2016115382A1 SEQ ID NO: 27
rAAV4	1791	WO2016115382A1 SEQ ID NO: 28
rAAV4	1792	WO2016115382A1 SEQ ID NO: 29
rAAV4	1793	WO2016115382A1 SEQ ID NO: 30

rAAV4	1794	WO2016115382A1 SEQ ID NO: 31
rAAV4	1795	WO2016115382A1 SEQ ID NO: 32
rAAV4	1796	WO2016115382A1 SEQ ID NO: 33
AAV2/8	1797	WO2016131981A1 SEQ ID NO: 47
AAV2/8	1798	WO2016131981A1 SEQ ID NO: 48
ancestral AAV	1799	WO2016154344A1 SEQ ID NO: 7
ancestral AAV variant C4	1800	WO2016154344A1 SEQ ID NO: 13
ancestral AAV variant C7	1801	WO2016154344A1 SEQ ID NO: 14
ancestral AAV variant G4	1802	WO2016154344A1 SEQ ID NO: 15
consensus amino acid sequence of ancestral AAV variants, C4, C7 and G4	1803	WO2016154344A1 SEQ ID NO: 16
consensus amino acid sequence of ancestral AAV variants, C4 and C7	1804	WO2016154344A1 SEQ ID NO: 17
AAV8 (with a AAV2 phospholipase domain)	1805	WO2016150403A1 SEQ ID NO: 13
AAV VR-942n	1806	US20160289275A1 SEQ ID NO: 10
AAV5-A (M569V)	1807	US20160289275A1 SEQ ID NO: 13
AAV5-A (M569V)	1808	US20160289275A1 SEQ ID NO: 14
AAV5-A (Y585V)	1809	US20160289275A1 SEQ ID NO: 16
AAV5-A (Y585V)	1810	US20160289275A1 SEQ ID NO: 17
AAV5-A (L587T)	1811	US20160289275A1 SEQ ID NO: 19
AAV5-A (L587T)	1812	US20160289275A1 SEQ ID NO: 20
AAV5-A (Y585V/L587T)	1813	US20160289275A1 SEQ ID NO: 22
AAV5-A (Y585V/L587T)	1814	US20160289275A1 SEQ ID NO: 23
AAV5-B (D652A)	1815	US20160289275A1 SEQ ID NO: 25

AAV5-B (D652A)	1816	US20160289275A1 SEQ ID NO: 26
AAV5-B (T362M)	1817	US20160289275A1 SEQ ID NO: 28
AAV5-B (T362M)	1818	US20160289275A1 SEQ ID NO: 29
AAV5-B (Q359D)	1819	US20160289275A1 SEQ ID NO: 31
AAV5-B (Q359D)	1820	US20160289275A1 SEQ ID NO: 32
AAV5-B (E350Q)	1821	US20160289275A1 SEQ ID NO: 34
AAV5-B (E350Q)	1822	US20160289275A1 SEQ ID NO: 35
AAV5-B (P533S)	1823	US20160289275A1 SEQ ID NO: 37
AAV5-B (P533S)	1824	US20160289275A1 SEQ ID NO: 38
AAV5-B (P533G)	1825	US20160289275A1 SEQ ID NO: 40
AAV5-B (P533G)	1826	US20160289275A1 SEQ ID NO: 41
AAV5-mutation in loop VII	1827	US20160289275A1 SEQ ID NO: 43
AAV5-mutation in loop VII	1828	US20160289275A1 SEQ ID NO: 44
AAV8	1829	US20160289275A1 SEQ ID NO: 47
Mut A (LK03/AAV8)	1830	WO2016181123A1 SEQ ID NO: 1
Mut B (LK03/AAV5)	1831	WO2016181123A1 SEQ ID NO: 2
Mut C (AAV8/AAV 3B)	1832	WO2016181123A1 SEQ ID NO: 3
Mut D (AAV5/AAV 3B)	1833	WO2016181123A1 SEQ ID NO: 4
Mut E (AAV8/AAV 3B)	1834	WO2016181123A1 SEQ ID NO: 5
Mut F (AAV3B/AA V8)	1835	WO2016181123A1 SEQ ID NO: 6
AAV44.9	1836	WO2016183297A1 SEQ ID NO: 4
AAV44.9	1837	WO2016183297A1 SEQ ID NO: 5
AAVrh8	1838	WO2016183297A1 SEQ ID NO: 6
AAV44.9 (S470N)	1839	WO2016183297A1 SEQ ID NO: 9
rh74 VP1	1840	US20160375110A1 SEQ ID NO: 1
AAV-LK03 (L125I)	1841	WO2017015102A1 SEQ ID NO: 5

AAV3B (S663V+T492V)	1842	WO2017015102A1 SEQ ID NO: 6
Anc80	1843	WO2017019994A2 SEQ ID NO: 1
Anc80	1844	WO2017019994A2 SEQ ID NO: 2
Anc81	1845	WO2017019994A2 SEQ ID NO: 3
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Anc82	1847	WO2017019994A2 SEQ ID NO: 5
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Anc80L27	1861	WO2017019994A2 SEQ ID NO: 19
Anc80L59	1862	WO2017019994A2 SEQ ID NO: 20
Anc80L60	1863	WO2017019994A2 SEQ ID NO: 21
Anc80L62	1864	WO2017019994A2 SEQ ID NO: 22
Anc80L65	1865	WO2017019994A2 SEQ ID NO: 23
Anc80L33	1866	WO2017019994A2 SEQ ID NO: 24
Anc80L36	1867	WO2017019994A2 SEQ ID NO: 25
Anc80L44	1868	WO2017019994A2 SEQ ID NO: 26
Anc80L1	1869	WO2017019994A2 SEQ ID NO: 35
Anc80L1	1870	WO2017019994A2 SEQ ID NO: 36
AAVrh10	1871	WO2017019994A2 SEQ ID NO: 41
Anc110	1872	WO2017019994A2 SEQ ID NO: 42
Anc110	1873	WO2017019994A2 SEQ ID NO: 43
AAVrh32.33	1874	WO2017019994A2 SEQ ID NO: 45
AAVrh74	1875	WO2017049031A1 SEQ ID NO: 1
AAV2	1876	WO2017053629A2 SEQ ID NO: 49
AAV2	1877	WO2017053629A2 SEQ ID NO: 50
AAV2	1878	WO2017053629A2 SEQ ID NO: 82
Parvo-like virus	1879	WO2017070476A2 SEQ ID NO: 1
Parvo-like virus	1880	WO2017070476A2 SEQ ID NO: 2
Parvo-like virus	1881	WO2017070476A2 SEQ ID NO: 3
Parvo-like virus	1882	WO2017070476A2 SEQ ID NO: 4

Parvo-like virus	1883	WO2017070476A2 SEQ ID NO: 5
Parvo-like virus	1884	WO2017070476A2 SEQ ID NO: 6
AAVrh.10	1885	WO2017070516A1 SEQ ID NO: 7
AAVrh.10	1886	WO2017070516A1 SEQ ID NO: 14
AAV2tYF	1887	WO2017070491A1 SEQ ID NO: 1
AAV-SPK	1888	WO2017075619A1 SEQ ID NO:28
AAV2.5	1889	US20170128528A1 SEQ ID NO: 13
AAV1.1	1890	US20170128528A1 SEQ ID NO: 15
AAV6.1	1891	US20170128528A1 SEQ ID NO: 17
AAV6.3.1	1892	US20170128528A1 SEQ ID NO: 18
AAV2i8	1893	US20170128528A1 SEQ ID NO: 28
AAV2i8	1894	US20170128528A1 SEQ ID NO: 29
ttAAV	1895	US20170128528A1 SEQ ID NO: 30
ttAAV-S312N	1896	US20170128528A1 SEQ ID NO: 32
ttAAV-S312N	1897	US20170128528A1 SEQ ID NO: 33
AAV6 (Y705, Y731, and T492)	1898	WO2016134337A1 SEQ ID NO: 24
AAV2	1899	WO2016134375A1 SEQ ID NO: 9
AAV2	1900	WO2016134375A1 SEQ ID NO: 10

[0098] Each of the patents, applications and/or publications listed in Table 1 are hereby incorporated by reference in their entirety.

[0099] In one embodiment, 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: 127 and 126 respectively herein), PHP.B (SEQ ID NO: 8 and 9 of WO2015038958, herein SEQ ID NO: 868 and 869), G2B-13 (SEQ ID NO: 12 of WO2015038958, herein SEQ ID NO: 870), G2B-26 (SEQ ID NO: 13 of WO2015038958, herein SEQ ID NO: 868 and 869), TH1.1-32 (SEQ ID NO: 14 of WO2015038958, herein SEQ ID NO: 871), TH1.1-35 (SEQ ID NO: 15 of WO2015038958, herein SEQ ID NO: 872) 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: 126 for the DNA sequence and SEQ ID NO: 127 for the amino acid sequence). In one embodiment, 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: 873), KFPVALT (SEQ ID NO: 3 of WO2015038958; herein SEQ ID NO: 874), LAVPFK (SEQ ID NO: 31 of WO2015038958; herein SEQ ID NO: 875), AVPFK (SEQ ID NO: 32 of WO2015038958; herein SEQ ID NO: 876), VPFK (SEQ ID NO: 33 of WO2015038958; herein SEQ ID NO: 877), TLAVPF (SEQ ID NO: 34 of WO2015038958; herein SEQ ID NO: 878), TLAVP (SEQ ID NO: 35 of WO2015038958; herein SEQ ID NO: 879), TLAV (SEQ ID NO: 36 of WO2015038958; herein SEQ ID NO: 880), SVSKPFL (SEQ ID NO: 28 of WO2015038958; herein SEQ ID NO: 881), FTLTTPK (SEQ ID NO: 29 of WO2015038958; herein SEQ ID NO: 882), MNATKNV (SEQ ID NO: 30 of WO2015038958; herein SEQ ID NO: 883), QSSQTPR (SEQ ID NO: 54 of WO2015038958; herein SEQ ID NO: 884), ILGTGTS (SEQ ID NO: 55 of WO2015038958; herein SEQ ID NO: 885), TRTNPEA (SEQ ID NO: 56 of WO2015038958; herein SEQ ID NO: 886), NGGTSSS (SEQ ID NO: 58 of WO2015038958; herein SEQ ID NO: 887), or YTLSQGW (SEQ ID NO: 60 of WO2015038958; herein SEQ ID NO: 888). 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: 889), ACTTTGGCGGTGCCTTTTAAG (SEQ ID NO: 24 and 49 of WO2015038958; herein SEQ ID NO: 890), AGTGTGAGTAAGCCTTTTTTG (SEQ ID NO: 25 of WO2015038958; herein SEQ ID NO: 891), TTTACGTTGACGACGCCTAAG (SEQ ID NO: 26 of WO2015038958; herein SEQ ID NO: 892), ATGAATGCTACGAAGAATGTG (SEQ ID NO: 27 of WO2015038958; herein SEQ ID NO: 893), CAGTCGTCGCAGACGCCTAGG (SEQ ID NO: 48 of WO2015038958; herein SEQ ID NO: 894), ATTCTGGGGACTGGTACTTCG (SEQ ID NO: 50 and 52 of WO2015038958; herein SEQ ID NO: 895), ACGCGGACTAATCCTGAGGCT (SEQ ID NO: 51 of WO2015038958; herein SEQ ID NO: 896), AATGGGGGGACTAGTAGTTCT (SEQ ID NO: 53 of WO2015038958; herein SEQ ID NO: 897), or TATACTTTGTCGCAGGGTTGG (SEQ ID NO: 59 of WO2015038958; herein SEQ ID NO: 898).

[00100] In one embodiment, the AAV serotype may be engineered to comprise at least one AAV capsid CD8+ T-cell epitope for AAV2 such as, but not limited to, SADNNNSEY (SEQ ID NO: 899), LIDQYLYYL (SEQ ID NO: 900), VPQYGYLTL (SEQ ID NO: 901), TTSTRTWAL (SEQ ID NO: 902), YHLNGRDSL (SEQ ID NO: 903), SQAVGRSSF (SEQ ID NO: 904), VPANPSTTF (SEQ ID NO: 905), FPQSGVLIF (SEQ ID NO: 906), YFDFNRFHCHFSPRD (SEQ ID NO: 907), VGNSSGNWHCDSTWM (SEQ ID NO: 908), QFSQAGASDIRDQSR

(SEQ ID NO: 909), GASDIRQSRNWLP (SEQ ID NO: 910) and GNRQAATADVNTQGV (SEQ ID NO: 911).

[00101] In one embodiment, the AAV serotype may be engineered to comprise at least one AAV capsid CD8+ T-cell epitope for AAV1 such as, but not limited to, LDRLMNPLI (SEQ ID NO: 912), TTSTRTWAL (SEQ ID NO: 902), and QPAKKRLNF (SEQ ID NO: 913)).

[00102] In one embodiment, peptides for inclusion in an AAV serotype may be identified using the methods described by Hui et al. (Molecular Therapy – Methods & Clinical Development (2015) 2, 15029 doi:10.1038/mtm.2015.29; the contents of which are herein incorporated by reference in its entirety). As a non-limiting example, the procedure includes isolating human splenocytes, restimulating the splenocytes *in vitro* using individual peptides spanning the amino acid sequence of the AAV capsid protein, IFN-gamma ELISpot with the individual peptides used for the *in vitro* restimulation, bioinformatics analysis to determine the HLA restriction of 15-mers identified by IFN-gamma ELISpot, identification of candidate reactive 9-mer epitopes for a given HLA allele, synthesis candidate 9-mers, second IFN-gamma ELISpot screening of splenocytes from subjects carrying the HLA alleles to which identified AAV epitopes are predicted to bind, determine the AAV capsid-reactive CD8+ T cell epitopes and determine the frequency of subjects reacting to a given AAV epitope.

[00103] In one embodiment, 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)), the contents of which are herein incorporated by reference in their entirety. In one embodiment, 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 be PHP.B, PHP.B2, PHP.B3, PHP.A, G2A12, G2A15. In one embodiment, these AAV serotypes may be AAV9 (SEQ ID NO: 126 and 127) derivatives with a 7-amino acid insert between amino acids 588-589. Non-limiting examples of these 7-amino acid inserts include TLAVPFK (SEQ ID NO: 873), SVSKPFL (SEQ ID NO: 1249), FTLTTPK (SEQ ID NO: 882), YTLSQGW (SEQ ID NO: 888), QAVRTSL (SEQ ID NO: 1176) and/or LAKERLS (SEQ ID NO: 1177).

[00104] In one embodiment, 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: 1441), PHP.N (SEQ ID NO: 46 of WO2017100671, herein SEQ ID NO: 1439), PHP.S (SEQ ID NO: 47 of WO2017100671, herein SEQ ID NO: 1440), 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: 122 or SEQ ID NO: 1441). In one embodiment, 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: 1442), AQSVSKPFLAQ (SEQ ID NO: 2 of WO2017100671; herein SEQ ID NO: 1443), AQFTLTTPKAQ (SEQ ID NO: 3 in the sequence listing of WO2017100671; herein SEQ ID NO: 1444), DGTLAVPFKAQ (SEQ ID NO: 4 in the sequence listing of WO2017100671; herein SEQ ID NO: 1445), ESTLAVPFKAQ (SEQ ID NO: 5 of WO2017100671; herein SEQ ID NO: 1446), GGTLAVPFKAQ (SEQ ID NO: 6 of WO2017100671; herein SEQ ID NO: 1447), AQTLATPFKAQ (SEQ ID NO: 7 and 33 of WO2017100671; herein SEQ ID NO: 1448), ATTLATPFKAQ (SEQ ID NO: 8 of WO2017100671; herein SEQ ID NO: 1449), DGTLATPFKAQ (SEQ ID NO: 9 of WO2017100671; herein SEQ ID NO: 1450), GGTLATPFKAQ (SEQ ID NO: 10 of WO2017100671; herein SEQ ID NO: 1451), SGSLAVPFKAQ (SEQ ID NO: 11 of WO2017100671; herein SEQ ID NO: 1452), AQTLAQPFKAQ (SEQ ID NO: 12 of WO2017100671; herein SEQ ID NO: 1453), AQTLQQPFKAQ (SEQ ID NO: 13 of WO2017100671; herein SEQ ID NO: 1454), AQTLSNPFKAQ (SEQ ID NO: 14 of WO2017100671; herein SEQ ID NO: 1455), AQTLAVPFSNP (SEQ ID NO: 15 of WO2017100671; herein SEQ ID NO: 1456), QGTLAVPFKAQ (SEQ ID NO: 16 of WO2017100671; herein SEQ ID NO: 1457), NQTLAVPFKAQ (SEQ ID NO: 17 of WO2017100671; herein SEQ ID NO: 1458), EGSLAVPFKAQ (SEQ ID NO: 18 of WO2017100671; herein SEQ ID NO: 1459), SGNLAVPFKAQ (SEQ ID NO: 19 of WO2017100671; herein SEQ ID NO: 1460), EGTLAVPFKAQ (SEQ ID NO: 20 of WO2017100671; herein SEQ ID NO: 1461), DSTLAVPFKAQ (SEQ ID NO: 21 in Table 1 of WO2017100671; herein SEQ ID NO: 1462), AVTLAVPFKAQ (SEQ ID NO: 22 of WO2017100671; herein SEQ ID NO: 1463), AQTLSTPFKAQ (SEQ ID NO: 23 of WO2017100671; herein SEQ ID NO: 1464), AQTLPQPFKAQ (SEQ ID NO: 24 and 32 of WO2017100671; herein SEQ ID NO: 1465), AQTLSQPFKAQ (SEQ ID NO: 25 of WO2017100671; herein SEQ ID NO: 1466), AQTLQLPFKAQ (SEQ ID NO: 26 of WO2017100671; herein SEQ ID NO: 1467), AQTLTMPFKAQ (SEQ ID NO: 27, and 34 of WO2017100671 and SEQ ID NO: 35 in the

sequence listing of WO2017100671; herein SEQ ID NO: 1468), AQTLTTPFKAQ (SEQ ID NO: 28 of WO2017100671; herein SEQ ID NO: 1469), AQYTLSQGWAQ (SEQ ID NO: 29 of WO2017100671; herein SEQ ID NO: 1470), AQMNATKNVAQ (SEQ ID NO: 30 of WO2017100671; herein SEQ ID NO: 1471), AQVSGGHHSAQ (SEQ ID NO: 31 of WO2017100671; herein SEQ ID NO: 1472), AQTLTAPFKAQ (SEQ ID NO: 35 in Table 1 of WO2017100671; herein SEQ ID NO: 1473), AQTLSKPFKAQ (SEQ ID NO: 36 of WO2017100671; herein SEQ ID NO: 1474), QAVRTSL (SEQ ID NO: 37 of WO2017100671; herein SEQ ID NO: 1475), YTLSQGW (SEQ ID NO: 38 of WO2017100671; herein SEQ ID NO: 888), LAKERLS (SEQ ID NO: 39 of WO2017100671; herein SEQ ID NO: 1476), TLAVPFK (SEQ ID NO: 40 in the sequence listing of WO2017100671; herein SEQ ID NO: 873), SVSKPFL (SEQ ID NO: 41 of WO2017100671; herein SEQ ID NO: 881), FTLTTPK (SEQ ID NO: 42 of WO2017100671; herein SEQ ID NO: 882), MNSTKNV (SEQ ID NO: 43 of WO2017100671; herein SEQ ID NO: 1477), VSGGHHS (SEQ ID NO: 44 of WO2017100671; herein SEQ ID NO: 1478), SAQTLAVPFKAQAQ (SEQ ID NO: 48 of WO2017100671; herein SEQ ID NO: 1479), SXXXLAVPFKAQAQ (SEQ ID NO: 49 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 1480), SAQXXXVPFKAQAQ (SEQ ID NO: 50 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 1481), SAQTLXXXFKAQAQ (SEQ ID NO: 51 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 1482), SAQTLAVXXXAQAQ (SEQ ID NO: 52 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 1483), SAQTLAVPFXXXAQ (SEQ ID NO: 53 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 1484), TNHQSAQ (SEQ ID NO: 65 of WO2017100671; herein SEQ ID NO: 1485), AQAQTGW (SEQ ID NO: 66 of WO2017100671; herein SEQ ID NO: 1486), DGTLATPFK (SEQ ID NO: 67 of WO2017100671; herein SEQ ID NO: 1487), DGTLATPFKXX (SEQ ID NO: 68 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 1488), LAVPFKAQ (SEQ ID NO: 80 of WO2017100671; herein SEQ ID NO: 1489), VPFKAQ (SEQ ID NO: 81 of WO2017100671; herein SEQ ID NO: 1490), FKAQ (SEQ ID NO: 82 of WO2017100671; herein SEQ ID NO: 1491), AQTLAV (SEQ ID NO: 83 of WO2017100671; herein SEQ ID NO: 1492), AQTLAVPF (SEQ ID NO: 84 of WO2017100671; herein SEQ ID NO: 1493), QAVR (SEQ ID NO: 85 of WO2017100671; herein SEQ ID NO: 1494), AVRT (SEQ ID NO: 86 of WO2017100671; herein SEQ ID NO: 1495), VRTS (SEQ ID NO: 87 of WO2017100671; herein SEQ ID NO: 1496), RTSL (SEQ ID NO: 88 of WO2017100671; herein SEQ ID NO: 1497), QAVRT (SEQ ID NO: 89 of WO2017100671; herein SEQ ID NO: 1498), AVRTS (SEQ ID

NO: 90 of WO2017100671; herein SEQ ID NO: 1499), VRTSL (SEQ ID NO: 91 of WO2017100671; herein SEQ ID NO: 1500), QAVRTS (SEQ ID NO: 92 of WO2017100671; herein SEQ ID NO: 1501), or AVRTSL (SEQ ID NO: 93 of WO2017100671; herein SEQ ID NO: 1502).

[00105] 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: 1503), GATGGGACGTTGGCGGTGCCTTTTAAGGCACAG (SEQ ID NO: 55 of WO2017100671; herein SEQ ID NO: 1504), CAGGCGGTTAGGACGTCTTTG (SEQ ID NO: 56 of WO2017100671; herein SEQ ID NO: 1505), CAGGTCTTCACGGACTCAGACTATCAG (SEQ ID NO: 57 and 78 of WO2017100671; herein SEQ ID NO: 1506), CAAGTAAAACCTCTACAAATGTGGTAAAATCG (SEQ ID NO: 58 of WO2017100671; herein SEQ ID NO: 1507), ACTCATCGACCAATACTTGTACTATCTCTCTAGAAC (SEQ ID NO: 59 of WO2017100671; herein SEQ ID NO: 1508), GGAAGTATTCCTTGGTTTTGAACCCA (SEQ ID NO: 60 of WO2017100671; herein SEQ ID NO: 1509), GGTCGCGGTTCTTGTTTGTGGAT (SEQ ID NO: 61 of WO2017100671; herein SEQ ID NO: 1510), CGACCTTGAAGCGCATGAACTCCT (SEQ ID NO: 62 of WO2017100671; herein SEQ ID NO: 1511), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCMNNMNNMNNMNNMNNMNNMNNTTGGGCACTCTGGTGGTTTGTC (SEQ ID NO: 63 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 1512), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCMNNMNNMNNAAAAGGCACCGCCAAAGTTTG (SEQ ID NO: 69 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 1513), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCMNNMNNMNNCACCGCCAAAGTTTGGGCACT (SEQ ID NO: 70 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 1514), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCCTTAAAMNNMNNMNNCAAAGTTTGGGCACTCTGGTGG (SEQ ID NO: 71 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 1515), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCCTTAAAAGGCACMNNMNNNMNNTTGGGCACTCTGGTGGTTTGTG (SEQ ID NO: 72 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 1516), ACTTTGGCGGTGCCTTTTAAG (SEQ ID

NO: 74 of WO2017100671; herein SEQ ID NO: 890), AGTGTGAGTAAGCCTTTTTTG (SEQ ID NO: 75 of WO2017100671; herein SEQ ID NO: 891), TTTACGTTGACGACGCCTAAG (SEQ ID NO: 76 of WO2017100671; herein SEQ ID NO: 892), TATACTTTGTCGCAGGGTTGG (SEQ ID NO: 77 of WO2017100671; herein SEQ ID NO: 898), or CTTGCGAAGGAGCGGCTTTCG (SEQ ID NO: 79 of WO2017100671; herein SEQ ID NO: 1517).

[00106] In one embodiment, 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: 1518), B19 (SEQ ID NO: 193 of US9624274; herein SEQ ID NO: 1519), MVM (SEQ ID NO: 194 of US9624274; herein SEQ ID NO: 1520), FPV (SEQ ID NO: 195 of US9624274; herein SEQ ID NO: 1521), CPV (SEQ ID NO: 196 of US9624274; herein SEQ ID NO: 1522) 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: 1901), EFCINHRGYWVCGD (SEQ ID NO:55 of US9624274; herein SEQ ID NO: 1902), EDGQVMDVDLS (SEQ ID NO: 85 of US9624274; herein SEQ ID NO: 1903), EKQRNGTLT (SEQ ID NO: 86 of US9624274; herein SEQ ID NO: 1904), TYQCRVTHPHLPRALMR (SEQ ID NO: 87 of US9624274; herein SEQ ID NO: 1905), RHSTTQPRKTKGSG (SEQ ID NO: 88 of US9624274; herein SEQ ID NO: 1906), DSNPRGVSAYLSR (SEQ ID NO: 89 of US9624274; herein SEQ ID NO: 1907), TITCLWDLAPSK (SEQ ID NO: 90 of US9624274; herein SEQ ID NO: 1908), KTKGSGFFVF (SEQ ID NO: 91 of US9624274; herein SEQ ID NO: 1909), THPHLPRALMRS (SEQ ID NO: 92 of US9624274; herein SEQ ID NO: 1910), GETYQCRVTHPHLPRALMRSTTK (SEQ ID NO: 93 of US9624274; herein SEQ ID NO: 1911), LPRALMRS (SEQ ID NO: 94 of US9624274; herein SEQ ID NO: 1912), INHRGYWV (SEQ ID NO: 95 of US9624274; herein SEQ ID NO: 1913), CDAGSVRTNAPD (SEQ ID NO: 60 of US9624274; herein SEQ ID NO:

1914), AKAVSNLTESRSESLQS (SEQ ID NO: 96 of US9624274; herein SEQ ID NO: 1915), SLTGDEFKKVLET (SEQ ID NO: 97 of US9624274; herein SEQ ID NO: 1916), REAVAYRFEED (SEQ ID NO: 98 of US9624274; herein SEQ ID NO: 1917), INPEIITLDG (SEQ ID NO: 99 of US9624274; herein SEQ ID NO: 1918), DISVTGAPVITATYL (SEQ ID NO: 100 of US9624274; herein SEQ ID NO: 1919), DISVTGAPVITA (SEQ ID NO: 101 of US9624274; herein SEQ ID NO: 1920), PKTVSNLTESSSESVQS (SEQ ID NO: 102 of US9624274; herein SEQ ID NO: 1921), SLMGDEFKAVLET (SEQ ID NO: 103 of US9624274; herein SEQ ID NO: 1922), QHSVAYTFEED (SEQ ID NO: 104 of US9624274; herein SEQ ID NO: 1923), INPEIITRDG (SEQ ID NO: 105 of US9624274; herein SEQ ID NO: 1924), DISLTGDPVITASYL (SEQ ID NO: 106 of US9624274; herein SEQ ID NO: 1925), DISLTGDPVITA (SEQ ID NO: 107 of US9624274; herein SEQ ID NO: 1926), DQSIDFEIDSA (SEQ ID NO: 108 of US9624274; herein SEQ ID NO: 1927), KNVSEDLPLPTFSPTLLGDS (SEQ ID NO: 109 of US9624274; herein SEQ ID NO: 1928), KNVSEDLPLPT (SEQ ID NO: 110 of US9624274; herein SEQ ID NO: 1929), CDSGRVRTDAPD (SEQ ID NO: 111 of US9624274; herein SEQ ID NO: 1930), FPEHLLVDFLQSLS (SEQ ID NO: 112 of US9624274; herein SEQ ID NO: 1931), DAEFRHDSG (SEQ ID NO: 65 of US9624274; herein SEQ ID NO: 1932), HYAAAQWDFGNTMCQL (SEQ ID NO: 113 of US9624274; herein SEQ ID NO: 1933), YAAQWDFGNTMCQ (SEQ ID NO: 114 of US9624274; herein SEQ ID NO: 1934), RSQKEGLHYT (SEQ ID NO: 115 of US9624274; herein SEQ ID NO: 1935), SSRTPSDKPVAHWANPQAE (SEQ ID NO: 116 of US9624274; herein SEQ ID NO: 1936), SRTPSDKPVAHWANP (SEQ ID NO: 117 of US9624274; herein SEQ ID NO: 1937), SSRTPSDKP (SEQ ID NO: 118 of US9624274; herein SEQ ID NO: 1938), NADGNVDYHMNSVP (SEQ ID NO: 119 of US9624274; herein SEQ ID NO: 1939), DGNVDYHMNSV (SEQ ID NO: 120 of US9624274; herein SEQ ID NO: 1940), RSFKEFLQSSLRALRQ (SEQ ID NO: 121 of US9624274; herein SEQ ID NO: 1941); FKEFLQSSLRA (SEQ ID NO: 122 of US9624274; herein SEQ ID NO: 1942), or QMWAPQWGPD (SEQ ID NO: 123 of US9624274; herein SEQ ID NO: 1943).

[00107] In one embodiment, 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: 1944), SSSTDP (SEQ ID NO: 4 of

US9475845; herein SEQ ID NO: 1945), SSNTAP (SEQ ID NO: 5 of US9475845; herein SEQ ID NO: 1946), SNSNLP (SEQ ID NO: 6 of US9475845; herein SEQ ID NO: 1947), SSTTAP (SEQ ID NO: 7 of US9475845; herein SEQ ID NO: 1948), AANTAA (SEQ ID NO: 8 of US9475845; herein SEQ ID NO: 1949), QQNTAP (SEQ ID NO: 9 of US9475845; herein SEQ ID NO: 1950), SAQAQA (SEQ ID NO: 10 of US9475845; herein SEQ ID NO: 1951), QANTGP (SEQ ID NO: 11 of US9475845; herein SEQ ID NO: 1952), NATTAP (SEQ ID NO: 12 of US9475845; herein SEQ ID NO: 1953), SSTAGP (SEQ ID NO: 13 and 20 of US9475845; herein SEQ ID NO: 1954), QQNTAA (SEQ ID NO: 14 of US9475845; herein SEQ ID NO: 1955), PSTAGP (SEQ ID NO: 15 of US9475845; herein SEQ ID NO: 1956), NQNTAP (SEQ ID NO: 16 of US9475845; herein SEQ ID NO: 1957), QAANAP (SEQ ID NO: 17 of US9475845; herein SEQ ID NO: 1958), SIVGLP (SEQ ID NO: 18 of US9475845; herein SEQ ID NO: 1959), AASTAA (SEQ ID NO: 19, and 27 of US9475845; herein SEQ ID NO: 1960), SQNTTA (SEQ ID NO: 21 of US9475845; herein SEQ ID NO: 1961), QQDTAP (SEQ ID NO: 22 of US9475845; herein SEQ ID NO: 1962), QTNTGP (SEQ ID NO: 23 of US9475845; herein SEQ ID NO: 1963), QTNGAP (SEQ ID NO: 24 of US9475845; herein SEQ ID NO: 1964), QQNAAP (SEQ ID NO: 25 of US9475845; herein SEQ ID NO: 1965), or AANTQA (SEQ ID NO: 26 of US9475845; herein SEQ ID NO: 1966). In one embodiment, 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: 1967), QPEHSST (SEQ ID NO: 39 and 50 of US9475845; herein SEQ ID NO: 1968), VNTANST (SEQ ID NO: 40 of US9475845; herein SEQ ID NO: 1969), HGPMQKS (SEQ ID NO: 41 of US9475845; herein SEQ ID NO: 1970), PHKPPLA (SEQ ID NO: 42 of US9475845; herein SEQ ID NO: 1971), IKNNEMW (SEQ ID NO: 43 of US9475845; herein SEQ ID NO: 1972), RNLDTPM (SEQ ID NO: 44 of US9475845; herein SEQ ID NO: 1973), VDSHRQS (SEQ ID NO: 45 of US9475845; herein SEQ ID NO: 1974), YDSKTKT (SEQ ID NO: 46 of US9475845; herein SEQ ID NO: 1975), SQLPHQK (SEQ ID NO: 47 of US9475845; herein SEQ ID NO: 1976), STMQQNT (SEQ ID NO: 48 of US9475845; herein SEQ ID NO: 1977), TERYMTQ (SEQ ID NO: 49 of US9475845; herein SEQ ID NO: 1978), DASLSTS (SEQ ID NO: 51 of US9475845; herein SEQ ID NO: 1979), DLPNKKT (SEQ ID NO: 52 of US9475845; herein SEQ ID NO: 1980), DLTAARL (SEQ ID NO: 53 of US9475845; herein SEQ ID NO: 1981), EPHQFNY (SEQ ID NO: 54 of US9475845; herein SEQ ID NO: 1982), EPQSNHT (SEQ ID NO: 55 of US9475845;

herein SEQ ID NO: 1983), MSSWPSQ (SEQ ID NO: 56 of US9475845; herein SEQ ID NO: 1984), NPKHNAT (SEQ ID NO: 57 of US9475845; herein SEQ ID NO: 1985), PDGMRTT (SEQ ID NO: 58 of US9475845; herein SEQ ID NO: 1986), PNNNKTT (SEQ ID NO: 59 of US9475845; herein SEQ ID NO: 1987), QSTTHDS (SEQ ID NO: 60 of US9475845; herein SEQ ID NO: 1988), TGSKQKQ (SEQ ID NO: 61 of US9475845; herein SEQ ID NO: 1989), SLKHQAL (SEQ ID NO: 62 of US9475845; herein SEQ ID NO: 1990), SPIDGEQ (SEQ ID NO: 63 of US9475845; herein SEQ ID NO: 1991), WIFPWIQL (SEQ ID NO: 64 and 112 of US9475845; herein SEQ ID NO: 1992), CDCRGDCFC (SEQ ID NO: 65 of US9475845; herein SEQ ID NO: 1993), CNGRC (SEQ ID NO: 66 of US9475845; herein SEQ ID NO: 1994), CPRECES (SEQ ID NO: 67 of US9475845; herein SEQ ID NO: 1995), CTTHWGFTLC (SEQ ID NO: 68 and 123 of US9475845; herein SEQ ID NO: 1996), CGRRAGGSC (SEQ ID NO: 69 of US9475845; herein SEQ ID NO: 1997), CKGGRAKDC (SEQ ID NO: 70 of US9475845; herein SEQ ID NO: 1998), CVPELGHEC (SEQ ID NO: 71 and 115 of US9475845; herein SEQ ID NO: 1999), CRRETAWAK (SEQ ID NO: 72 of US9475845; herein SEQ ID NO: 2000), VSWFSHRYSPFAVS (SEQ ID NO: 73 of US9475845; herein SEQ ID NO: 2001), GYRDGYAGPILYN (SEQ ID NO: 74 of US9475845; herein SEQ ID NO: 2002), XXXYXXX (SEQ ID NO: 75 of US9475845; herein SEQ ID NO: 2003), YXNW (SEQ ID NO: 76 of US9475845; herein SEQ ID NO: 2004), RPLPPLP (SEQ ID NO: 77 of US9475845; herein SEQ ID NO: 2005), APPLPPR (SEQ ID NO: 78 of US9475845; herein SEQ ID NO: 2006), DVFYPYPYASGS (SEQ ID NO: 79 of US9475845; herein SEQ ID NO: 2007), MYWYPY (SEQ ID NO: 80 of US9475845; herein SEQ ID NO: 2008), DITWDQLWDLMK (SEQ ID NO: 81 of US9475845; herein SEQ ID NO: 2009), CWDDXWLC (SEQ ID NO: 82 of US9475845; herein SEQ ID NO: 2010), EWCEYLGGYLRCYA (SEQ ID NO: 83 of US9475845; herein SEQ ID NO: 2011), YXCXXGPXTWXCXP (SEQ ID NO: 84 of US9475845; herein SEQ ID NO: 2012), IEGPTLRQWLAARA (SEQ ID NO: 85 of US9475845; herein SEQ ID NO: 2013), LWXXX (SEQ ID NO: 86 of US9475845; herein SEQ ID NO: 2014), XFXXYLW (SEQ ID NO: 87 of US9475845; herein SEQ ID NO: 2015), SSIISHFRWGLCD (SEQ ID NO: 88 of US9475845; herein SEQ ID NO: 2016), MSRPACPPNDKYE (SEQ ID NO: 89 of US9475845; herein SEQ ID NO: 2017), CLRSGRGC (SEQ ID NO: 90 of US9475845; herein SEQ ID NO: 2018), CHWMFSPWC (SEQ ID NO: 91 of US9475845; herein SEQ ID NO: 2019), WXXF (SEQ ID NO: 92 of US9475845; herein SEQ ID NO: 2020), CSSRLDAC (SEQ ID NO: 93 of US9475845; herein SEQ ID NO: 2021), CLPVASC (SEQ ID NO: 94 of US9475845; herein SEQ ID NO: 2022), CGFECVRQCPERC (SEQ ID NO: 95 of US9475845; herein SEQ ID NO:

2023), CVALCREACGEGC (SEQ ID NO: 96 of US9475845; herein SEQ ID NO: 2024), SWCEPGWCR (SEQ ID NO: 97 of US9475845; herein SEQ ID NO: 2025), YSGKWGW (SEQ ID NO: 98 of US9475845; herein SEQ ID NO: 2026), GLSGGRS (SEQ ID NO: 99 of US9475845; herein SEQ ID NO: 2027), LMLPRAD (SEQ ID NO: 100 of US9475845; herein SEQ ID NO: 2028), CSCFRDVCC (SEQ ID NO: 101 of US9475845; herein SEQ ID NO: 2029), CRDVVSVIC (SEQ ID NO: 102 of US9475845; herein SEQ ID NO: 2030), MARSGL (SEQ ID NO: 103 of US9475845; herein SEQ ID NO: 2031), MARAKE (SEQ ID NO: 104 of US9475845; herein SEQ ID NO: 2032), MSRTMS (SEQ ID NO: 105 of US9475845; herein SEQ ID NO: 2033), KCCYSL (SEQ ID NO: 106 of US9475845; herein SEQ ID NO: 2034), MYWGDSHWLQYWYE (SEQ ID NO: 107 of US9475845; herein SEQ ID NO: 2035), MQLPLAT (SEQ ID NO: 108 of US9475845; herein SEQ ID NO: 2036), EWLS (SEQ ID NO: 109 of US9475845; herein SEQ ID NO: 2037), SNEW (SEQ ID NO: 110 of US9475845; herein SEQ ID NO: 2038), TNYL (SEQ ID NO: 111 of US9475845; herein SEQ ID NO: 2039), WDLAWMFRLPVG (SEQ ID NO: 113 of US9475845; herein SEQ ID NO: 2040), CTVALPGGYVRVC (SEQ ID NO: 114 of US9475845; herein SEQ ID NO: 2041), CVAYCIEHHCWTC (SEQ ID NO: 116 of US9475845; herein SEQ ID NO: 2042), CVFAHNYDYLVC (SEQ ID NO: 117 of US9475845; herein SEQ ID NO: 2043), CVFTSNYAFC (SEQ ID NO: 118 of US9475845; herein SEQ ID NO: 2044), VHSPNKK (SEQ ID NO: 119 of US9475845; herein SEQ ID NO: 2045), CRGDGWC (SEQ ID NO: 120 of US9475845; herein SEQ ID NO: 2046), XRGCDX (SEQ ID NO: 121 of US9475845; herein SEQ ID NO: 2047), PXXX (SEQ ID NO: 122 of US9475845; herein SEQ ID NO: 2048), SGKGPRQITAL (SEQ ID NO: 124 of US9475845; herein SEQ ID NO: 2049), AAAAAAAAAXXXXX (SEQ ID NO: 125 of US9475845; herein SEQ ID NO: 2050), VYMSPF (SEQ ID NO: 126 of US9475845; herein SEQ ID NO: 2051), ATWLPPR (SEQ ID NO: 127 of US9475845; herein SEQ ID NO: 2052), HTMYYHHYQHHL (SEQ ID NO: 128 of US9475845; herein SEQ ID NO: 2053), SEVGCRAGPLQWLCEKYFG (SEQ ID NO: 129 of US9475845; herein SEQ ID NO: 2054), CGLLPVGRPDRNVWRWLC (SEQ ID NO: 130 of US9475845; herein SEQ ID NO: 2055), CKGQCDRFKGLPWEC (SEQ ID NO: 131 of US9475845; herein SEQ ID NO: 2056), SGRSA (SEQ ID NO: 132 of US9475845; herein SEQ ID NO: 2057), WGFP (SEQ ID NO: 133 of US9475845; herein SEQ ID NO: 2058), AEPMPHSLNFSQYLWYT (SEQ ID NO: 134 of US9475845; herein SEQ ID NO: 2059), WAYXSP (SEQ ID NO: 135 of US9475845; herein SEQ ID NO: 2060), IELLQAR (SEQ ID NO: 136 of US9475845; herein SEQ ID NO: 2061), AYTKCSRQWRTCMTTH (SEQ ID NO:

137 of US9475845; herein SEQ ID NO: 2062), PQNSKIPGPTFLDPH (SEQ ID NO: 138 of US9475845; herein SEQ ID NO: 2063), SMEPALPDWWWKMFK (SEQ ID NO: 139 of US9475845; herein SEQ ID NO: 2064), ANTPCGPYTHDCPVKR (SEQ ID NO: 140 of US9475845; herein SEQ ID NO: 2065), TACHQHVRMVRP (SEQ ID NO: 141 of US9475845; herein SEQ ID NO: 2066), VPWMEPAYQRFL (SEQ ID NO: 142 of US9475845; herein SEQ ID NO: 2067), DPRATPGS (SEQ ID NO: 143 of US9475845; herein SEQ ID NO: 2068), FRPNRAQDYNTN (SEQ ID NO: 144 of US9475845; herein SEQ ID NO: 2069), CTKNSYLMC (SEQ ID NO: 145 of US9475845; herein SEQ ID NO: 2070), CXXTXXXGXGC (SEQ ID NO: 146 of US9475845; herein SEQ ID NO: 2071), CPIEDRPMC (SEQ ID NO: 147 of US9475845; herein SEQ ID NO: 2072), HEWSYLAPYPWF (SEQ ID NO: 148 of US9475845; herein SEQ ID NO: 2073), MCPKHPLGC (SEQ ID NO: 149 of US9475845; herein SEQ ID NO: 2074), RMWPSSTVNLSAGRR (SEQ ID NO: 150 of US9475845; herein SEQ ID NO: 2075), SAKTAVSQRVWLPSHRGGEP (SEQ ID NO: 151 of US9475845; herein SEQ ID NO: 2076), KSREHVNNSACPSKRITAAL (SEQ ID NO: 152 of US9475845; herein SEQ ID NO: 2077), EGFR (SEQ ID NO: 153 of US9475845; herein SEQ ID NO: 2078), AGLGVR (SEQ ID NO: 154 of US9475845; herein SEQ ID NO: 2079), GTRQGHTMRLGVSDG (SEQ ID NO: 155 of US9475845; herein SEQ ID NO: 2080), IAGLATPGWSHWLAL (SEQ ID NO: 156 of US9475845; herein SEQ ID NO: 2081), SMSIARL (SEQ ID NO: 157 of US9475845; herein SEQ ID NO: 2082), HTFEPGV (SEQ ID NO: 158 of US9475845; herein SEQ ID NO: 2083), NTSLKRISNKRIRRK (SEQ ID NO: 159 of US9475845; herein SEQ ID NO: 2084), LRIKRKRRKRKKTRK (SEQ ID NO: 160 of US9475845; herein SEQ ID NO: 2085), GGG, GFS, LWS, EGG, LLV, LSP, LBS, AGG, GRR, GGH and GTV.

[00108] In one embodiment, 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: 2086) 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.

[00109] 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: 2087), SPSGASN (SEQ ID NO: 2 of US20160369298; herein SEQ ID NO: 2088), SHSGASN (SEQ ID NO: 3 of US20160369298;

herein SEQ ID NO: 2089), SRSGASN (SEQ ID NO: 4 of US20160369298; herein SEQ ID NO: 2090), SKSGASN (SEQ ID NO: 5 of US20160369298; herein SEQ ID NO: 2091), SNSGASN (SEQ ID NO: 6 of US20160369298; herein SEQ ID NO: 2092), SGSGASN (SEQ ID NO: 7 of US20160369298; herein SEQ ID NO: 2093), SASGASN (SEQ ID NO: 8, 175, and 221 of US20160369298; herein SEQ ID NO: 2094), SESGTSN (SEQ ID NO: 9 of US20160369298; herein SEQ ID NO: 2095), STTGGSN (SEQ ID NO: 10 of US20160369298; herein SEQ ID NO: 2096), SSAGSTN (SEQ ID NO: 11 of US20160369298; herein SEQ ID NO: 2097), NNDSQA (SEQ ID NO: 12 of US20160369298; herein SEQ ID NO: 2098), NNRNQA (SEQ ID NO: 13 of US20160369298; herein SEQ ID NO: 2099), NNNKQA (SEQ ID NO: 14 of US20160369298; herein SEQ ID NO: 2100), NAKRQA (SEQ ID NO: 15 of US20160369298; herein SEQ ID NO: 2101), NDEHQA (SEQ ID NO: 16 of US20160369298; herein SEQ ID NO: 2102), NTSQKA (SEQ ID NO: 17 of US20160369298; herein SEQ ID NO: 2103), YYLSRTNTPSGTDTQSRLVFSQAGA (SEQ ID NO: 18 of US20160369298; herein SEQ ID NO: 2104), YYLSRTNTDSGTETQSGLDFSQAGA (SEQ ID NO: 19 of US20160369298; herein SEQ ID NO: 2105), YYLSRTNTESGTPTQSALEFSQAGA (SEQ ID NO: 20 of US20160369298; herein SEQ ID NO: 2106), YYLSRTNTHSGTHTQSPLHFSQAGA (SEQ ID NO: 21 of US20160369298; herein SEQ ID NO: 2107), YYLSRTNTSSGTITISHLIFSQAGA (SEQ ID NO: 22 of US20160369298; herein SEQ ID NO: 2108), YYLSRTNTRSGIMTKSSLMFSQAGA (SEQ ID NO: 23 of US20160369298; herein SEQ ID NO: 2109), YYLSRTNTKSGRKTLSNLSFSQAGA (SEQ ID NO: 24 of US20160369298; herein SEQ ID NO: 2110), YYLSRTNDGSGPVTPSKLRFSQRGA (SEQ ID NO: 25 of US20160369298; herein SEQ ID NO: 2111), YYLSRTNAASGHATHSDLKFSQPGA (SEQ ID NO: 26 of US20160369298; herein SEQ ID NO: 2112), YYLSRTNGQAGSLTMSELGFSQVGA (SEQ ID NO: 27 of US20160369298; herein SEQ ID NO: 2113), YYLSRTNSTGGNQTTSQLLFSQLSA (SEQ ID NO: 28 of US20160369298; herein SEQ ID NO: 2114), YFLSRTNNNTGLNTNSTLNFSQGRA (SEQ ID NO: 29 of US20160369298; herein SEQ ID NO: 2115), SKTGADNNNSEYSWTG (SEQ ID NO: 30 of US20160369298; herein SEQ ID NO: 2116), SKTDADNNNSEYSWTG (SEQ ID NO: 31 of US20160369298; herein SEQ ID NO: 2117), SKTEADNNNSEYSWTG (SEQ ID NO: 32 of US20160369298; herein SEQ ID NO: 2118), SKTPADNNNSEYSWTG (SEQ ID NO: 33 of US20160369298; herein SEQ ID NO: 2119), SKTHADNNNSEYSWTG (SEQ ID NO: 34 of US20160369298; herein SEQ ID NO: 2120), SKTQADNNNSEYSWTG (SEQ ID NO: 35 of US20160369298; herein SEQ ID NO: 2121), SKTIADNNNSEYSWTG (SEQ ID NO: 36 of

US20160369298; herein SEQ ID NO: 2122), SKTMADNNNSEYSWTG (SEQ ID NO: 37 of US20160369298; herein SEQ ID NO: 2123), SKTRADNNNSEYSWTG (SEQ ID NO: 38 of US20160369298; herein SEQ ID NO: 2124), SKTNADNNNSEYSWTG (SEQ ID NO: 39 of US20160369298; herein SEQ ID NO: 2125), SKTVGRNNNSEYSWTG (SEQ ID NO: 40 of US20160369298; herein SEQ ID NO: 2126), SKTADRNNNSEYSWTG (SEQ ID NO: 41 of US20160369298; herein SEQ ID NO: 2127), SKKLSQNNNSKYSWQG (SEQ ID NO: 42 of US20160369298; herein SEQ ID NO: 2128), SKPTTGNNNSDYSWPG (SEQ ID NO: 43 of US20160369298; herein SEQ ID NO: 2129), STQKNENNNSNYSWPG (SEQ ID NO: 44 of US20160369298; herein SEQ ID NO: 2130), HKDDEGKF (SEQ ID NO: 45 of US20160369298; herein SEQ ID NO: 2131), HKDDNRKF (SEQ ID NO: 46 of US20160369298; herein SEQ ID NO: 2132), HKDDTNKF (SEQ ID NO: 47 of US20160369298; herein SEQ ID NO: 2133), HEDSDKNF (SEQ ID NO: 48 of US20160369298; herein SEQ ID NO: 2134), HRDGADSF (SEQ ID NO: 49 of US20160369298; herein SEQ ID NO: 2135), HGDNKSRF (SEQ ID NO: 50 of US20160369298; herein SEQ ID NO: 2136), KQGSEKTNVDFEEV (SEQ ID NO: 51 of US20160369298; herein SEQ ID NO: 2137), KQGSEKTNVDSEEV (SEQ ID NO: 52 of US20160369298; herein SEQ ID NO: 2138), KQGSEKTNVDVEEV (SEQ ID NO: 53 of US20160369298; herein SEQ ID NO: 2139), KQGSDKTNVDDAGV (SEQ ID NO: 54 of US20160369298; herein SEQ ID NO: 2140), KQGSSKTNVDPREV (SEQ ID NO: 55 of US20160369298; herein SEQ ID NO: 2141), KQGSRKTNVDHKQV (SEQ ID NO: 56 of US20160369298; herein SEQ ID NO: 2142), KQGSKGGNVDTNRV (SEQ ID NO: 57 of US20160369298; herein SEQ ID NO: 2143), KQGSGEANVDNGDV (SEQ ID NO: 58 of US20160369298; herein SEQ ID NO: 2144), KQDAAADNIDYDHV (SEQ ID NO: 59 of US20160369298; herein SEQ ID NO: 2145), KQSGTRSNAAASSV (SEQ ID NO: 60 of US20160369298; herein SEQ ID NO: 2146), KENTNTNDTELTNV (SEQ ID NO: 61 of US20160369298; herein SEQ ID NO: 2147), QRGNNVAATADVNT (SEQ ID NO: 62 of US20160369298; herein SEQ ID NO: 2148), QRGNNEAATADVNT (SEQ ID NO: 63 of US20160369298; herein SEQ ID NO: 2149), QRGNNPAATADVNT (SEQ ID NO: 64 of US20160369298; herein SEQ ID NO: 2150), QRGNNHAATADVNT (SEQ ID NO: 65 of US20160369298; herein SEQ ID NO: 2151), QEENNIAATPGVNT (SEQ ID NO: 66 of US20160369298; herein SEQ ID NO: 2152), QPPNNMAATHEVNT (SEQ ID NO: 67 of US20160369298; herein SEQ ID NO: 2153), QHHNNSAATTIVNT (SEQ ID NO: 68 of US20160369298; herein SEQ ID NO: 2154), QTTNNRAAFNMVET (SEQ ID NO: 69 of

US20160369298; herein SEQ ID NO: 2155), QKKNNNAASKKVAT (SEQ ID NO: 70 of US20160369298; herein SEQ ID NO: 2156), QGGNNKAADDAVKT (SEQ ID NO: 71 of US20160369298; herein SEQ ID NO: 2157), QAAKGGAADDAVKT (SEQ ID NO: 72 of US20160369298; herein SEQ ID NO: 2158), QDDRAAAANESVDT (SEQ ID NO: 73 of US20160369298; herein SEQ ID NO: 2159), QQQHDDAAYQRVHT (SEQ ID NO: 74 of US20160369298; herein SEQ ID NO: 2160), QSSSSLAAVSTVQT (SEQ ID NO: 75 of US20160369298; herein SEQ ID NO: 2161), QNNQTTAAIRNVTT (SEQ ID NO: 76 of US20160369298; herein SEQ ID NO: 2162), NYNKKSDNVDFT (SEQ ID NO: 77 of US20160369298; herein SEQ ID NO: 2163), NYNKKSENVDFT (SEQ ID NO: 78 of US20160369298; herein SEQ ID NO: 2164), NYNKKSLNVDFT (SEQ ID NO: 79 of US20160369298; herein SEQ ID NO: 2165), NYNKKSPNVDFT (SEQ ID NO: 80 of US20160369298; herein SEQ ID NO: 2166), NYSKKSHCVDFT (SEQ ID NO: 81 of US20160369298; herein SEQ ID NO: 2167), NYRKTIYVDFT (SEQ ID NO: 82 of US20160369298; herein SEQ ID NO: 2168), NYKEKKDVHFT (SEQ ID NO: 83 of US20160369298; herein SEQ ID NO: 2169), NYGHRAIVQFT (SEQ ID NO: 84 of US20160369298; herein SEQ ID NO: 2170), NYANHQFVVCT (SEQ ID NO: 85 of US20160369298; herein SEQ ID NO: 2171), NYDDDPTGVLLT (SEQ ID NO: 86 of US20160369298; herein SEQ ID NO: 2172), NYDDPTGVLLT (SEQ ID NO: 87 of US20160369298; herein SEQ ID NO: 2173), NFEQQNSVEWT (SEQ ID NO: 88 of US20160369298; herein SEQ ID NO: 2174), SQSGASN (SEQ ID NO: 89 and SEQ ID NO: 241 of US20160369298; herein SEQ ID NO: 2175), NNGSQA (SEQ ID NO: 90 of US20160369298; herein SEQ ID NO: 2176), YYLSRTNTPSGTTTWSRLQFSQAGA (SEQ ID NO: 91 of US20160369298; herein SEQ ID NO: 2177), SKTSADNNNSEYSWTG (SEQ ID NO: 92 of US20160369298; herein SEQ ID NO: 2178), HKDDEEKF (SEQ ID NO: 93, 209, 214, 219, 224, 234, 239, and 244 of US20160369298; herein SEQ ID NO: 2179), KQGSEKTNVDIEEV (SEQ ID NO: 94 of US20160369298; herein SEQ ID NO: 2180), QRGNNQAATADVNT (SEQ ID NO: 95 of US20160369298; herein SEQ ID NO: 2181), NYNKKSVNVDFT (SEQ ID NO: 96 of US20160369298; herein SEQ ID NO: 2182), SQSGASNYNTPSGTTTQSRLQFSTSADNNNSEYSWTGATKYH (SEQ ID NO: 106 of US20160369298; herein SEQ ID NO: 2183), SASGASNFNSEGGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 107 of US20160369298; herein SEQ ID NO: 2184), SQSGASNYNTPSGTTTQSRLQFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 108 of

US20160369298; herein SEQ ID NO: 2185), SASGASNYNTPSGTTTQSRLQFSTSADNNNSEFSWPGATTYH (SEQ ID NO: 109 of US20160369298; herein SEQ ID NO: 2186), SQSGASNFNSEGGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 110 of US20160369298; herein SEQ ID NO: 2187), SASGASNYNTPSGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 111 of US20160369298; herein SEQ ID NO: 2188), SQSGASNYNTPSGTTTQSRLQFSTSADNNNSDFSWTGATKYH (SEQ ID NO: 112 of US20160369298; herein SEQ ID NO: 2189), SGAGASNFNSEGGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 113 of US20160369298; herein SEQ ID NO: 2190), SGAGASN (SEQ ID NO: 176 of US20160369298; herein SEQ ID NO: 2191), NSEGGSLTQSSLGFS (SEQ ID NO: 177, 185, 193 and 202 of US20160369298; herein SEQ ID NO: 2192), TDGENNNSDFS (SEQ ID NO: 178 of US20160369298; herein SEQ ID NO: 2193), SEFSWPGATT (SEQ ID NO: 179 of US20160369298; herein SEQ ID NO: 2194), TSADNNNSDFSWT (SEQ ID NO: 180 of US20160369298; herein SEQ ID NO: 2195), SQSGASNY (SEQ ID NO: 181, 187, and 198 of US20160369298; herein SEQ ID NO: 2196), NTPSGTTTQSRLQFS (SEQ ID NO: 182, 188, 191, and 199 of US20160369298; herein SEQ ID NO: 2197), TSADNNNSEYSWTGATKYH (SEQ ID NO: 183 of US20160369298; herein SEQ ID NO: 2198), SASGASNF (SEQ ID NO: 184 of US20160369298; herein SEQ ID NO: 2199), TDGENNNSDFSWTGATKYH (SEQ ID NO: 186, 189, 194, 197, and 203 of US20160369298; herein SEQ ID NO: 2200), SASGASNY (SEQ ID NO: 190 and SEQ ID NO: 195 of US20160369298; herein SEQ ID NO: 2201), TSADNNNSEFSWPGATTYH (SEQ ID NO: 192 of US20160369298; herein SEQ ID NO: 2202), NTPSGSLTQSSLGFS (SEQ ID NO: 196 of US20160369298; herein SEQ ID NO: 2203), TSADNNNSDFSWTGATKYH (SEQ ID NO: 200 of US20160369298; herein SEQ ID NO: 2204), SGAGASNF (SEQ ID NO: 201 of US20160369298; herein SEQ ID NO: 2205), CTCCAGVVSVVSMRSRVCVNSGCAGCTDHCVVSRNSGTCVMSACACAA (SEQ ID NO: 204 of US20160369298; herein SEQ ID NO: 2206), CTCCAGAGAGGCAACAGACAAGCAGCTACCGCAGATGTCAACACACAA (SEQ ID NO: 205 of US20160369298; herein SEQ ID NO: 2207), SAAGASN (SEQ ID NO: 206 of US20160369298; herein SEQ ID NO: 2208), YFLSRTNTESGSTTQSTLRFSQAG (SEQ ID NO: 207 of US20160369298; herein SEQ ID NO: 2209), SKTSADNNNSDFS (SEQ ID NO: 208, 228, and 253 of US20160369298; herein SEQ ID NO: 2210), KQGSEKTDVDIDKV (SEQ

ID NO: 210 of US20160369298; herein SEQ ID NO: 2211), STAGASN (SEQ ID NO: 211 of US20160369298; herein SEQ ID NO: 2212), YFLSRTNTTSGIETQSTLRFSQAG (SEQ ID NO: 212 and SEQ ID NO: 247 of US20160369298; herein SEQ ID NO: 213), SKTDGENNNSDFS (SEQ ID NO: 213 and SEQ ID NO: 248 of US20160369298; herein SEQ ID NO: 2214), KQGAAADDVEIDGV (SEQ ID NO: 215 and SEQ ID NO: 250 of US20160369298; herein SEQ ID NO: 2215), SEAGASN (SEQ ID NO: 216 of US20160369298; herein SEQ ID NO: 2216), YYLSRTNTPSGTTTQSRLQFSQAG (SEQ ID NO: 217, 232 and 242 of US20160369298; herein SEQ ID NO: 2217), SKTSADNNNSEYS (SEQ ID NO: 218, 233, 238, and 243 of US20160369298; herein SEQ ID NO: 2218), KQGSEKTNVDIEKV (SEQ ID NO: 220, 225 and 245 of US20160369298; herein SEQ ID NO: 2219), YFLSRTNDASGSDTKSTLLFSQAG (SEQ ID NO: 222 of US20160369298; herein SEQ ID NO: 2220), STTPSENNNSEYS (SEQ ID NO: 223 of US20160369298; herein SEQ ID NO: 2221), SAAGATN (SEQ ID NO: 226 and SEQ ID NO: 251 of US20160369298; herein SEQ ID NO: 2222), YFLSRTNGEAGSATLSELRFSQAG (SEQ ID NO: 227 of US20160369298; herein SEQ ID NO: 2223), HGDDADRF (SEQ ID NO: 229 and SEQ ID NO: 254 of US20160369298; herein SEQ ID NO: 2224), KQGAEKSDVEVDRV (SEQ ID NO: 230 and SEQ ID NO: 255 of US20160369298; herein SEQ ID NO: 2225), KQDSGGDNIDIDQV (SEQ ID NO: 235 of US20160369298; herein SEQ ID NO: 2226), SDAGASN (SEQ ID NO: 236 of US20160369298; herein SEQ ID NO: 2227), YFLSRTNTEGGHDTQSTLRFSQAG (SEQ ID NO: 237 of US20160369298; herein SEQ ID NO: 2228), KEDGGGSDVAIDEV (SEQ ID NO: 240 of US20160369298; herein SEQ ID NO: 2229), SNAGASN (SEQ ID NO: 246 of US20160369298; herein SEQ ID NO: 2230), and YFLSRTNGEAGSATLSELRFSQPG (SEQ ID NO: 252 of US20160369298; herein SEQ ID NO: 2231). 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: 2232), AACRACRRSMRSMAGGCA (SEQ ID NO: 98 of US20160369298; herein SEQ ID NO: 2233), CACRRGGACRRCRMSRRSARSTTT (SEQ ID NO: 99 of US20160369298; herein SEQ ID NO: 2234), TATTTCTTGAGCAGAACAAACRVCVVSRSCGGAMNCVHSACGMHSTCAVVSCTTVDS TTTTCTCAGSBCRGSGCG (SEQ ID NO: 100 of US20160369298; herein SEQ ID NO: 2235), TCAAMAMMAVNSRVCSRSAACAACAACAGTRASTTCTCGTGGMMAGGA (SEQ ID NO: 101 of US20160369298; herein SEQ ID NO: 2236), AAGSAARRCRSCRVSRVARVCRATRYCGMSNHCRVMVRSGTC (SEQ ID NO: 102 of

US20160369298; herein SEQ ID NO: 2237), CAGVVSVVSMRSRVCVNSGCAGCTDHCVVSRNSGTCVMSACA (SEQ ID NO: 103 of US20160369298; herein SEQ ID NO: 2238), AACTWCRVSVASMVSVHSDDTGTGSWSTKSACT (SEQ ID NO: 104 of US20160369298; herein SEQ ID NO: 2239), TTGTTGAACATCACCACGTGACGCACGTTC (SEQ ID NO: 256 of US20160369298; herein SEQ ID NO: 2240), TCCCCGTGGTTCTACTACATAATGTGGCCG (SEQ ID NO: 257 of US20160369298; herein SEQ ID NO: 2241), TTCCACACTCCGTTTTGGATAATGTTGAAC (SEQ ID NO: 258 of US20160369298; herein SEQ ID NO: 2242), AGGGACATCCCCAGCTCCATGCTGTGGTCG (SEQ ID NO: 259 of US20160369298; herein SEQ ID NO: 2243), AGGGACAACCCCTCCGACTCGCCCTAATCC (SEQ ID NO: 260 of US20160369298; herein SEQ ID NO: 2244), TCCTAGTAGAAGACACCCTCTCACTGCCCG (SEQ ID NO: 261 of US20160369298; herein SEQ ID NO: 2245), AGTACCATGTACACCCACTCTCCCAGTGCC (SEQ ID NO: 262 of US20160369298; herein SEQ ID NO: 2246), ATATGGACGTTCATGCTGATCACCATACCG (SEQ ID NO: 263 of US20160369298; herein SEQ ID NO: 2247), AGCAGGAGCTCCTTGGCCTCAGCGTGCGAG (SEQ ID NO: 264 of US20160369298; herein SEQ ID NO: 2248), ACAAGCAGCTTCACTATGACAACCACTGAC (SEQ ID NO: 265 of US20160369298; herein SEQ ID NO: 2249), CAGCCTAGGAACTGGCTTCCTGGACCCTGTTACCGCCAGCAGAGAGTCTCAAMAMM AVNSRVCSRSAACAACAACAGTRASTTCTCCTGGMMAGGAGCTACCAAGTACCACC TCAATGGCAGAGACTCTCTGGTGAATCCCGGACCAGCTATGGCAAGCCACRRGGAC RRCRMSRRSARSTTTTTTCCTCAGAGCGGGGTTCTCATCTTTGGGAAGSAARRCRSCR VSRVARVCRATRYCGMSNHCRVMVRSGTCATGATTACAGACGAAGAGGAGATCTGG AC (SEQ ID NO: 266 of US20160369298; herein SEQ ID NO: 2250), TGGGACAATGGCGGTCGTCTCTCAGAGTTKTKKT (SEQ ID NO: 267 of US20160369298; herein SEQ ID NO: 2251), AGAGGACCKKTCCTCGATGGTTCATGGTGGAGTTA (SEQ ID NO: 268 of US20160369298; herein SEQ ID NO: 2252), CCACTTAGGGCCTGGTCGATACCGTTCGGTG (SEQ ID NO: 269 of US20160369298; herein SEQ ID NO: 2253), and TCTCGCCCCAAGAGTAGAAACCCTTCSTTYYG (SEQ ID NO: 270 of US20160369298; herein SEQ ID NO: 2254).

[00110] 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: 2255), or AAV9 (SEQ ID NO: 11 of WO2016134375; herein SEQ ID NO: 2256). 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: 2257), or GETRAPL (SEQ ID NO: 4 of WO2016134375; herein SEQ ID NO: 2258).

[00111] 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).

[00112] 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).

[00113] 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: 2259) or NKDKLN (SEQ ID NO:2 of WO2017015102; herein SEQ ID NO: 2260). 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).

[00114] In one embodiment, 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 one embodiment, 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.

[00115] 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.

[00116] In one embodiment, 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).

[00117] In one embodiment, peptides for inclusion in an AAV serotype may be identified by isolating human splenocytes, restimulating the splenocytes *in vitro* using individual peptides spanning the amino acid sequence of the AAV capsid protein, IFN-gamma ELISpot with the individual peptides used for the *in vitro* restimulation, bioinformatics analysis to determine the given allele restriction of 15-mers identified by IFN-gamma ELISpot, identification of candidate reactive 9-mer epitopes for a given allele, synthesis candidate 9-mers, second IFN-gamma ELISpot screening of splenocytes from subjects carrying the specific alleles to which identified AAV epitopes are predicted to bind, determine the AAV capsid-reactive CD8+ T cell epitopes and determine the frequency of subjects reacting to a given AAV epitope.

[00118] AAV particles comprising a modulatory polynucleotide encoding the siRNA molecules may be prepared or derived from various serotypes of AAVs, including, but not limited to, AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV9.47, AAV9(hu14), AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAV-DJ8 and AAV-DJ. In some cases, different serotypes of AAVs may be mixed together or with other types of viruses to produce chimeric AAV particles. As a non-limiting example, the AAV particle is derived from the AAV9 serotype.

Viral Genome

[00119] In one embodiment, as shown in an AAV particle comprises a viral genome with a payload region.

[00120] In one embodiment, the viral genome may comprise 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 viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Between the 5' ITR **120** and the payload region **110**, there may be a promoter region **130**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00121] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 2. The payload region **110** is located within the viral genome **100**. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Between the 5' ITR **120** and the payload region **110**, there may be a promoter region **130**.

Between the promoter region **130** and the payload region **110**, there may be an intron region **140**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00122] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 3. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Within the viral genome **100**, there may be an enhancer region **150**, a promoter region **130**, an intron region **140**, and a payload region **110**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00123] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 4. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Within the viral genome **100**, there may be an enhancer region **150**, a promoter region **130**, an intron region **140**, a payload region **110**, and a polyadenylation signal sequence region **160**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00124] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 5. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Within the viral genome **100**, there may be at least one MCS region **170**, an enhancer region **150**, a promoter region **130**, an intron region **140**, a payload region **110**, and a polyadenylation signal sequence region **160**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00125] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 6. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Within the viral genome **100**, there may be at least one MCS region **170**, an enhancer region **150**, a promoter region **130**, at least one exon region **180**, at least one intron region **140**, a payload region **110**, and a polyadenylation signal sequence region **160**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00126] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 7 and 8. Within the viral genome **100**, there may be at least one promoter region **130**, and a payload region **110**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00127] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 9. Within the viral genome **100**, there may be at least one promoter region **130**, a payload region **110**, and a polyadenylation signal sequence region **160**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

Viral Genome Size

[00128] In one embodiment, the viral genome which comprises a payload described herein, may be single stranded or double stranded viral genome. The size of the viral genome may be small, medium, large or the maximum size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00129] In one embodiment, the viral genome which comprises a payload described herein, may be a small single stranded viral genome. A small single stranded viral 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. As a non-limiting example, the small single stranded viral genome may be 3.2 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00130] In one embodiment, the viral genome which comprises a payload described herein, may be a small double stranded viral genome. A small double stranded viral 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. As a non-limiting example, the small double stranded viral genome may be 1.6 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00131] In one embodiment, the viral genome which comprises a payload described herein, may a medium single stranded viral genome. A medium single stranded viral 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. As a non-limiting example, the medium single stranded viral genome may be 4.0 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00132] In one embodiment, the viral genome which comprises a payload described herein, may be a medium double stranded viral genome. A medium double stranded viral 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. As a non-limiting example, the medium double stranded viral genome may be 2.0 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00133] In one embodiment, the viral genome which comprises a payload described herein, may be a large single stranded viral genome. A large single stranded viral 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. As a non-limiting example, the large single stranded viral genome may be 4.7 kb in size. As another non-limiting example, the large single stranded viral genome may be 4.8 kb in size. As yet another non-limiting example, the large single stranded viral genome may be 6.0 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00134] In one embodiment, the viral genome which comprises a payload described herein, may be a large double stranded viral genome. A large double stranded viral 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. As a non-limiting example, the large double stranded viral genome may be 2.4 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

Viral Genome Component: Inverted Terminal Repeats (ITRs)

[00135] The AAV particles of the present invention comprise a viral genome with at least one ITR region and a payload region. In one embodiment 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 invention may be comprised of naturally occurring polynucleotide sequences or recombinantly derived polynucleotide sequences.

[00136] 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 from the capsid. In one embodiment the AAV particle has more than one ITR. In a non-limiting example, the AAV particle has a viral genome comprising two ITRs. In one embodiment 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 one embodiment both ITRs of the viral genome of the AAV particle are AAV2 ITRs.

[00137] 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 one embodiment the ITRs are 140-142 nucleotides in length. Non limiting examples of ITR length are 102, 140, 141, 142, 145 nucleotides in length, and those having at least 95% identity thereto.

[00138] In one embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule which may be located near the 5' end of the flip ITR in an expression vector. In another embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located near the 3' end of the flip ITR in an expression vector. In yet another embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule

may be located near the 5' end of the flop ITR in an expression vector. In yet another embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located near the 3' end of the flop ITR in an expression vector. In one embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located between the 5' end of the flip ITR and the 3' end of the flop ITR in an expression vector. In one embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located between (e.g., half-way between the 5' end of the flip ITR and 3' end of the flop ITR or the 3' end of the flop ITR and the 5' end of the flip ITR), the 3' end of the flip ITR and the 5' end of the flip ITR in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 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 or more than 30 nucleotides downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 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 or more than 30 nucleotides upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector.

Viral Genome Component: Promoters

[00139] In one embodiment, 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.

[00140] A person skilled in the art may recognize that expression of the polypeptides of the invention 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).

[00141] In one embodiment, 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.

[00142] In one embodiment, the promoter is a promoter deemed to be efficient to drive the expression of the modulatory polynucleotide.

[00143] In one embodiment, the promoter is a promoter deemed to be efficient when it drives expression in the cell being targeted.

[00144] In one embodiment, 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.

[00145] In one embodiment, the promoter drives expression of the payload 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.

[00146] 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.

[00147] 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.

[00148] 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)

[00149] 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.

[00150] In one embodiment, 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.

[00151] In one embodiment, 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 one embodiment, the promoter is a combination of a 382 nucleotide CMV-enhancer sequence and a 260 nucleotide CBA-promoter sequence.

[00152] In one embodiment, 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).

[00153] 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).

[00154] Any of promoters taught by the aforementioned Yu, Soderblom, Gill, Husain, Passini, Xu, Drews or Raymond may be used in the present inventions.

[00155] In one embodiment, the promoter is not cell specific.

[00156] In one embodiment, the promoter is an ubiquitin c (UBC) promoter. The UBC promoter may have a size of 300-350 nucleotides. As a non-limiting example, the UBC promoter is 332 nucleotides.

[00157] In one embodiment, the promoter is a β-glucuronidase (GUSB) promoter. The GUSB promoter may have a size of 350-400 nucleotides. As a non-limiting example, the GUSB promoter is 378 nucleotides.

[00158] In one embodiment, the promoter is a neurofilament light (NFL) promoter. The NFL promoter may have a size of 600-700 nucleotides. As a non-limiting example, the NFL promoter is 650 nucleotides. As a non-limiting example, the construct may be AAV-promoter-CMV/globin intron-modulatory polynucleotide-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype.

[00159] In one embodiment, the promoter is a neurofilament heavy (NFH) promoter. The NFH promoter may have a size of 900-950 nucleotides. As a non-limiting example, the NFH promoter is 920 nucleotides. As a non-limiting example, the construct may be AAV-promoter-CMV/globin intron-modulatory polynucleotide-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype.

[00160] In one embodiment, the promoter is a scn8a promoter. The scn8a promoter may have a size of 450-500 nucleotides. As a non-limiting example, the scn8a promoter is 470 nucleotides. As a non-limiting example, the construct may be AAV-promoter-CMV/globin intron-modulatory polynucleotide-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype

[00161] In one embodiment, the viral genome comprises a Pol III promoter.

[00162] In one embodiment, the viral genome comprises a P1 promoter.

[00163] In one embodiment, the viral genome comprises a FXN promoter.

[00164] In one embodiment, the promoter is a phosphoglycerate kinase 1 (PGK) promoter.

[00165] In one embodiment, the promoter is a chicken β-actin (CBA) promoter.

[00166] In one embodiment, the promoter is a CAG promoter which is a construct comprising the cytomegalovirus (CMV) enhancer fused to the chicken beta-actin (CBA) promoter.

[00167] In one embodiment, the promoter is a cytomegalovirus (CMV) promoter.

[00168] In one embodiment, the viral genome comprises a H1 promoter.

[00169] In one embodiment, the viral genome comprises a U6 promoter.

[00170] In one embodiment, 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.

[00171] In one embodiment, the promoter is a RNA pol III promoter. As a non-limiting example, the RNA pol III promoter is U6. As a non-limiting example, the RNA pol III promoter is H1.

[00172] In one embodiment, the viral genome comprises two promoters. As a non-limiting example, the promoters are an EF1α promoter and a CMV promoter.

[00173] In one embodiment, 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. As a non-limiting example, 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, (9) GFAP promoter, (10) H1 promoter; and (11) U6 promoter.

[00174] In one embodiment, the viral genome comprises an engineered promoter.

[00175] In another embodiment the viral genome comprises a promoter from a naturally expressed protein.

Viral Genome Component: Untranslated Regions (UTRs)

[00176] 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.

[00177] Features typically found in abundantly expressed genes of specific target organs may be engineered into UTRs to enhance the stability and protein production. As a non-limiting example, 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 invention to enhance expression in hepatic cell lines or liver.

[00178] 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'.

[00179] In one embodiment, the 5'UTR in the viral genome includes a Kozak sequence.

[00180] In one embodiment, the 5'UTR in the viral genome does not include a Kozak sequence.

[00181] 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*.

[00182] 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.

[00183] In one embodiment, the 3' UTR of the viral genome may include an oligo(dT) sequence for templated addition of a poly-A tail.

[00184] In one embodiment, 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.

[00185] In one embodiment, the viral genome may be engineered to include, alter or remove at least one miRNA binding site, sequence or seed region.

[00186] 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 one embodiment, 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.

[00187] In one embodiment, the viral genome of the AAV particle comprises at least one artificial UTRs which is not a variant of a wild type UTR.

[00188] In one embodiment, 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

[00189] In one embodiment, the viral genome of the AAV particles of the present invention 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.

[00190] In one embodiment, 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.

[00191] In one embodiment, the polyadenylation sequence is 50-100 nucleotides in length.

[00192] In one embodiment, the polyadenylation sequence is 50-150 nucleotides in length.

[00193] In one embodiment, the polyadenylation sequence is 50-160 nucleotides in length.

[00194] In one embodiment, the polyadenylation sequence is 50-200 nucleotides in length.

[00195] In one embodiment, the polyadenylation sequence is 60-100 nucleotides in length.

[00196] In one embodiment, the polyadenylation sequence is 60-150 nucleotides in length.

[00197] In one embodiment, the polyadenylation sequence is 60-160 nucleotides in length.

[00198] In one embodiment, the polyadenylation sequence is 60-200 nucleotides in length.

[00199] In one embodiment, the polyadenylation sequence is 70-100 nucleotides in length.

[00200] In one embodiment, the polyadenylation sequence is 70-150 nucleotides in length.

[00201] In one embodiment, the polyadenylation sequence is 70-160 nucleotides in length.

[00202] In one embodiment, the polyadenylation sequence is 70-200 nucleotides in length.

[00203] In one embodiment, the polyadenylation sequence is 80-100 nucleotides in length.

[00204] In one embodiment, the polyadenylation sequence is 80-150 nucleotides in length.

[00205] In one embodiment, the polyadenylation sequence is 80-160 nucleotides in length.

[00206] In one embodiment, the polyadenylation sequence is 80-200 nucleotides in length.

[00207] In one embodiment, the polyadenylation sequence is 90-100 nucleotides in length.

[00208] In one embodiment, the polyadenylation sequence is 90-150 nucleotides in length.

[00209] In one embodiment, the polyadenylation sequence is 90-160 nucleotides in length.

[00210] In one embodiment, the polyadenylation sequence is 90-200 nucleotides in length.

[00211] In one embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located upstream of the polyadenylation sequence in an expression vector. Further, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located downstream of a promoter such as, but not limited to, CMV, U6, CAG, CBA or a CBA promoter with a SV40 intron or a human betaglobin intron in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 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 or more than 30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector.

[00212] In one embodiment, the AAV particle comprises a rabbit globin polyadenylation (polyA) signal sequence.

[00213] In one embodiment, the AAV particle comprises a human growth hormone polyadenylation (polyA) signal sequence.

Viral Genome Component: Introns

[00214] In one embodiment, 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).

[00215] In one embodiment, 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.

[00216] In one embodiment, the AAV viral genome may comprise a promoter such as, but not limited to, CMV or U6. As a non-limiting example, the promoter for the AAV comprising the nucleic acid sequence for the siRNA molecules of the present invention is a CMV promoter. As another non-limiting example, the promoter for the AAV comprising the nucleic acid sequence for the siRNA molecules of the present invention is a U6 promoter.

[00217] In one embodiment, the AAV viral genome may comprise a CMV promoter.

[00218] In one embodiment, the AAV viral genome may comprise a U6 promoter.

[00219] In one embodiment, the AAV viral genome may comprise a CMV and a U6 promoter.

[00220] In one embodiment, the AAV viral genome may comprise a H1 promoter.

[00221] In one embodiment, the AAV viral genome may comprise a CBA promoter.

[00222] In one embodiment, the encoded siRNA molecule may be located downstream of a promoter in an expression vector such as, but not limited to, CMV, U6, H1, CBA, CAG, or a CBA promoter with an intron such as SV40 or others known in the art. Further, the encoded siRNA molecule may also be located upstream of the polyadenylation sequence in an expression vector. As a non-limiting example, the encoded siRNA molecule may be located within 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 or more than 30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the encoded siRNA molecule may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As a non-limiting example, the encoded siRNA molecule may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an

expression vector. As another non-limiting example, the encoded siRNA molecule may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector.

Viral Genome Component: Filler Sequence

[00223] In one embodiment, the viral genome comprises one or more filler sequences.

[00224] In one embodiment, 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. As a non-limiting example, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 2.3 kb. As a non-limiting example, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 4.6 kb.

[00225] In one embodiment, the viral genome comprises one or more filler sequences in order to reduce the likelihood that a hairpin structure of the vector genome (e.g., a modulatory polynucleotide described herein) may be read as an inverted terminal repeat (ITR) during expression and/or packaging. As a non-limiting example, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 2.3 kb. As a non-limiting example, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 4.6 kb

[00226] In one embodiment, 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. As a non-limiting example, the total length filler sequence in the vector genome is 3.1 kb. As a non-limiting example, the total length filler sequence in the vector genome is 2.7 kb. As a non-limiting example, the total length filler sequence in the vector genome is 0.8 kb. As a non-limiting example, the total length filler sequence in the vector genome is 0.4 kb. As a non-limiting example, the length of each filler sequence in the vector genome is 0.8 kb. As a non-limiting example, the length of each filler sequence in the vector genome is 0.4 kb.

[00227] In one embodiment, 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. As a non-limiting example, the total length filler sequence in the vector genome is 0.8 kb. As a non-limiting example, the total length filler sequence in the vector genome is 0.4 kb. As a non-limiting example, the length of each filler sequence in the vector genome is 0.8 kb. As a non-limiting example, the length of each filler sequence in the vector genome is 0.4 kb

[00228] In one embodiment, 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.

[00229] In one embodiment, 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. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the 5' ITR sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to a promoter sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the polyadenylation signal sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to the 3' ITR sequence. As a non-limiting example, the viral genome comprises at least one filler sequence, and the filler sequence is located between two intron sequences. As a non-limiting example, the viral genome comprises at least one filler sequence, and the filler sequence is located within an intron sequence. As a non-limiting example, 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. As a non-limiting example, 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. As a non-limiting example, 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.

[00230] In one embodiment, 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. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the 5' ITR sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to a promoter

sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the polyadenylation signal sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to the 3' ITR sequence. As a non-limiting example, the viral genome comprises at least one filler sequence, and the filler sequence is located between two intron sequences. As a non-limiting example, the viral genome comprises at least one filler sequence, and the filler sequence is located within an intron sequence. As a non-limiting example, 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. As a non-limiting example, 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. As a non-limiting example, 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.

[00231] In one embodiment, the viral genome may comprise one or more filler sequences between one of more regions of the viral genome. In one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00232] In one embodiment, 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. As a non-limiting example, 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. As a non-limiting example, 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. As a non-limiting example, 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. As a non-limiting example, 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. As a non-limiting example, 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. As a non-limiting example, 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. As a non-limiting example, 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. As a non-limiting example, 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. As a non-limiting example, 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.

[00233] In one embodiment, the viral genome comprises a filler sequence after the 5' ITR.

[00234] In one embodiment, the viral genome comprises a filler sequence after the promoter region. In one embodiment, the viral genome comprises a filler sequence after the payload region. In one embodiment, the viral genome comprises a filler sequence after the intron region. In one embodiment, the viral genome comprises a filler sequence after the enhancer region. In one embodiment, the viral genome comprises a filler sequence after the polyadenylation signal sequence region. In one embodiment, the viral genome comprises a filler sequence after the MCS region. In one embodiment, the viral genome comprises a filler sequence after the exon region.

[00235] In one embodiment, the viral genome comprises a filler sequence before the promoter region. In one embodiment, the viral genome comprises a filler sequence before the payload region. In one embodiment, the viral genome comprises a filler sequence before the intron region. In one embodiment, the viral genome comprises a filler sequence before the enhancer region. In one embodiment, the viral genome comprises a filler sequence before the polyadenylation signal sequence region. In one embodiment, the viral genome comprises a filler

sequence before the MCS region. In one embodiment, the viral genome comprises a filler sequence before the exon region.

[00236] In one embodiment, the viral genome comprises a filler sequence before the 3' ITR.

[00237] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the promoter region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the payload region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the intron region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the enhancer region. In one embodiment, 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 one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the MCS region.

[00238] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the exon region.

[00239] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the payload region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the intron region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the enhancer region. In one embodiment, 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 one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the MCS region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the exon region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the 3' ITR.

[00240] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the intron region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the enhancer region. In one embodiment, 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 one embodiment, a filler sequence may be located between two regions, such as, but not limited to,

the payload region and the MCS region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the exon region.

[00241] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the 3' ITR.

[00242] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the enhancer region. In one embodiment, 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 one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the MCS region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the exon region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the 3' ITR. In one embodiment, 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 one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the MCS region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the exon region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the 3' ITR.

[00243] In one embodiment, 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 one embodiment, 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 one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the polyadenylation signal sequence region and the 3' ITR.

[00244] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the MCS region and the exon region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the MCS region and the 3' ITR.

[00245] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the exon region and the 3' ITR.

[00246] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00247] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00248] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00249] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one

embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00250] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00251] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00252] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00253] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00254] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00255] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00256] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00257] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00258] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00259] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00260] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00261] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00262] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00263] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00264] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00265] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00266] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00267] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00268] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00269] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one

embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00270] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00271] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00272] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00273] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00274] In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00275] In one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00276] In one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00277] In one embodiment, 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 one embodiment, 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 one embodiment, 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.

[00278] In one embodiment, 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.

Payloads of the Invention

[00279] 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 invention typically encode modulatory polynucleotides or fragments or variants thereof.

[00280] 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.

[00281] The payload region may comprise a combination of coding and non-coding nucleic acid sequences.

[00282] In some embodiments, the AAV payload region may encode a coding or non-coding RNA.

[00283] In one embodiment, the AAV particle comprises a viral genome with a payload region comprising nucleic acid sequences encoding a siRNA, miRNA or other RNAi agent. 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 may express the encoded siRNA, miRNA or other RNAi agent inside a single cell.

Modulatory Polynucleotides

[00284] In one embodiment, modulatory polynucleotides, e.g., RNA or DNA molecules, may be used to treat neurodegenerative disease, in particular, Huntington's Disease (HD). As used herein, a "modulatory polynucleotide" is any nucleic acid sequence(s) which functions to modulate (either increase or decrease) the level or amount of a target gene, e.g., mRNA or protein levels.

[00285] In one embodiment, the modulatory polynucleotides may comprise at least one nucleic acid sequence encoding at least one siRNA molecule. The nucleic acids may, independently if there is more than one, encode 1, 2, 3, 4, 5, 6, 7, 8, 9, or more than 9 siRNA molecules.

[00286] In one embodiment, the molecular scaffold may be located downstream of a CMV promoter, fragment or variant thereof.

[00287] In one embodiment, the molecular scaffold may be located downstream of a CBA promoter, fragment or variant thereof.

[00288] In one embodiment, the molecular scaffold may be a natural pri-miRNA scaffold located downstream of a CMV promoter. As a non-limiting example, the natural pri-miRNA scaffold is derived from the human miR155 scaffold.

[00289] In one embodiment, the molecular scaffold may be a natural pri-miRNA scaffold located downstream of a CBA promoter.

[00290] In one embodiment, the selection of a molecular scaffold and modulatory polynucleotide is determined by a method of comparing modulatory polynucleotides in pri-miRNA (see e.g., the method described by Miniarikova et al. *Design, Characterization, and Lead Selection of Therapeutic miRNAs Targeting Huntingtin for Development of Gene Therapy for Huntington's Disease*. Molecular Therapy-Nucleic Acids (2016) 5, e297 and International Publication No. WO2016102664; the contents of each of which are herein incorporated by reference in their entireties). The modulatory polynucleotide may, but it not limited to, targeting exon 1, CAG repeats, SNP rs362331 in exon 50 and/or SNP rs362307 in exon 67. To evaluate the activities of the modulatory polynucleotides, the molecular scaffold used which may be used is a human pri-miRNA scaffold (e.g., miR155 scaffold) and the promoter may be CMV. The activity may be determined *in vitro* using HEK293T cells and a reporter (e.g., Luciferase). For exon 1 targeting, the modulatory polynucleotide is determined to be efficient at HTT knockdown if the knockdown is 80% or greater. For CAG targeting, the modulatory polynucleotide is determined to be efficient at HTT knockdown if the knockdown is at least 60%. For SNP targeting, the modulatory polynucleotide is determined to be efficient at HTT knockdown if the knockdown is at least 60%. For allele selectivity for CAG repeats or SNP targeting the

modulatory polynucleotides may comprise at least 1 substitution in order to improve allele selectivity. As a non-limiting example, substitution may be a G or C replaced with a T or corresponding U and A or T/U replaced by a C.

[00291] In order to evaluate the optimal molecular scaffold for the modulatory polynucleotide, the modulatory polynucleotide is used in pri-miRNA scaffolds with a CAG promoter. The constructs are co-transfected with a reporter (e.g., luciferase reporter) at 50 ng. Constructs with greater than 80% knockdown at 50 ng co-transfection are considered efficient. In one aspect, the constructs with strong guide-strand activity are preferred. The molecular scaffolds can be processed in HEK293T cells by NGS to determine guide-passenger ratios, and processing variability.

[00292] To evaluate the molecular scaffolds and modulatory polynucleotides *in vivo* the molecular scaffolds comprising the modulatory polynucleotides are packaged in AAV (e.g., the serotype may be AAV5 (see e.g., the method and constructs described in WO2015060722, the contents of which are herein incorporated by reference in their entirety)) and administered to an *in vivo* model (e.g., Hu128/21 HD mouse) and the guide-passenger ratios, 5' and 3' end processing, reversal of guide and passenger strands, and knockdown can be determined in different areas of the model.

[00293] In one embodiment, the selection of a molecular scaffold and modulatory polynucleotide is determined by a method of comparing modulatory polynucleotides in natural pri-miRNA and synthetic pri-miRNA. The modulatory polynucleotide may, but it not limited to, targeting an exon other than exon 1. To evaluate the activities of the modulatory polynucleotides, the molecular scaffold is used with a CBA promoter. In one aspect, the activity may be determined *in vitro* using HEK293T cells, HeLa cell and a reporter (e.g., Luciferase) and knockdown efficient modulatory polynucleotides showed HTT knockdown of at least 80% in the cell tested. Additionally, the modulatory polynucleotides which are considered most efficient showed low to no significant passenger strand (p-strand) activity. In another aspect, the endogenous HTT knockdown efficacy is evaluated by transfection *in vitro* using HEK293T cells, HeLa cell and a reporter. Efficient modulatory polynucleotides show greater than 50% endogenous HTT knockdown. In yet another aspect, the endogenous HTT knockdown efficacy is evaluated in different cell types (e.g., HEK293, HeLa, primary astrocytes, U251 astrocytes, SH-SY5Y neuron cells and fibroblasts from HD patients) by infection (e.g., AAV2). Efficient modulatory polynucleotides show greater than 60% endogenous HTT knockdown.

[00294] To evaluate the molecular scaffolds and modulatory polynucleotides *in vivo* the molecular scaffolds comprising the modulatory polynucleotides are packaged in AAV and administered to an *in vivo* model (e.g., YAC128 HD mouse) and the guide-passenger ratios, 5' and 3' end processing, ratio of guide to passenger strands, and knockdown can be determined in different areas of the model (e.g., tissue regions). The molecular scaffolds can be processed from *in vivo* samples by NGS to determine guide-passenger ratios, and processing variability.

[00295] In one embodiment, the modulatory polynucleotide is designed using at least one of the following properties: loop variant, seed mismatch/bulge/wobble variant, stem mismatch, loop variant and vassal stem mismatch variant, seed mismatch and basal stem mismatch variant, stem mismatch and basal stem mismatch variant, seed wobble and basal stem wobble variant, or a stem sequence variant.

siRNA Molecules

[00296] The present invention relates to RNA interference (RNAi) induced inhibition of gene expression for treating neurodegenerative disorders. Provided herein are siRNA duplexes or encoded dsRNA that target the HTT gene (referred to herein collectively as "siRNA molecules"). Such siRNA duplexes or encoded dsRNA can reduce or silence HTT gene expression in cells, for example, medium spiny neurons, cortical neurons and/or astrocytes, thereby, ameliorating symptoms of Huntington's Disease (HD).

[00297] RNAi (also known as post-transcriptional gene silencing (PTGS), quelling, or co-suppression) is a post-transcriptional gene silencing process in which RNA molecules, in a sequence specific manner, inhibit gene expression, typically by causing the destruction of specific mRNA molecules. The active components of RNAi are short/small double stranded RNAs (dsRNAs), called small interfering RNAs (siRNAs), that typically contain 15-30 nucleotides (e.g., 19 to 25, 19 to 24 or 19-21 nucleotides) and 2 nucleotide 3' overhangs and that match the nucleic acid sequence of the target gene. These short RNA species may be naturally produced *in vivo* by Dicer-mediated cleavage of larger dsRNAs and they are functional in mammalian cells.

[00298] Naturally expressed small RNA molecules, named microRNAs (miRNAs), elicit gene silencing by regulating the expression of mRNAs. The miRNAs containing RNA Induced Silencing Complex (RISC) targets mRNAs presenting a perfect sequence complementarity with nucleotides 2-7 in the 5' region of the miRNA which is called the seed region, and other base pairs with its 3' region. miRNA mediated down regulation of gene expression may be caused by cleavage of the target mRNAs, translational inhibition of the target mRNAs, or mRNA decay.

miRNA targeting sequences are usually located in the 3'-UTR of the target mRNAs. A single miRNA may target more than 100 transcripts from various genes, and one mRNA may be targeted by different miRNAs.

[00299] siRNA duplexes or dsRNA targeting a specific mRNA may be designed and synthesized *in vitro* and introduced into cells for activating RNAi processes. Elbashir et al. demonstrated that 21-nucleotide siRNA duplexes (termed small interfering RNAs) were capable of effecting potent and specific gene knockdown without inducing immune response in mammalian cells (Elbashir SM et al., *Nature*, 2001, 411, 494-498). Since this initial report, post-transcriptional gene silencing by siRNAs quickly emerged as a powerful tool for genetic analysis in mammalian cells and has the potential to produce novel therapeutics.

[00300] RNAi molecules which were designed to target against a nucleic acid sequence that encodes poly-glutamine repeat proteins which cause poly-glutamine expansion diseases such as Huntington's Disease, are described in US Patent No. 9,169,483 and 9,181,544 and International Patent Publication No. WO2015179525, the content of each of which is herein incorporated by reference in their entirety. US Patent Nos. 9,169,483 and 9,181,544 and International Patent Publication No. WO2015179525 each provide isolated RNA duplexes comprising a first strand of RNA (e.g., 15 contiguous nucleotides) and second strand of RNA (e.g., complementary to at least 12 contiguous nucleotides of the first strand) where the RNA duplex is about 15 to 30 base pairs in length. The first strand of RNA and second strand of RNA may be operably linked by an RNA loop (~4 to 50 nucleotides) to form a hairpin structure which may be inserted into an expression cassette. Non-limiting examples of loop portions include SEQ ID NO: 9-14 of US Patent No. 9,169,483, the content of which is herein incorporated by reference in its entirety. Non-limiting examples of strands of RNA which may be used, either full sequence or part of the sequence, to form RNA duplexes include SEQ ID NO: 1-8 of US Patent No. 9,169,483 and SEQ ID NO: 1-11, 33-59, 208-210, 213-215 and 218-221 of US Patent No. 9,181,544, the contents of each of which is herein incorporated by reference in its entirety. Non-limiting examples of RNAi molecules include SEQ ID NOs: 1-8 of US Patent No. 9,169,483, SEQ ID NOs: 1-11, 33-59, 208-210, 213-215 and 218-221 of US Patent No. 9,181,544 and SEQ ID NOs: 1, 6, 7, and 35-38 of International Patent Publication No. WO2015179525, the contents of each of which is herein incorporated by reference in their entirety.

[00301] *In vitro* synthetized siRNA molecules may be introduced into cells in order to activate RNAi. An exogenous siRNA duplex, when it is introduced into cells, similar to the endogenous dsRNAs, can be assembled to form the RNA Induced Silencing Complex (RISC), a multiunit

complex that interacts with RNA sequences that are complementary to one of the two strands of the siRNA duplex (i.e., the antisense strand). During the process, the sense strand (or passenger strand) of the siRNA is lost from the complex, while the antisense strand (or guide strand) of the siRNA is matched with its complementary RNA. In particular, the targets of siRNA containing RISC complexes are mRNAs presenting a perfect sequence complementarity. Then, siRNA mediated gene silencing occurs by cleaving, releasing and degrading the target.

[00302] The siRNA duplex comprised of a sense strand homologous to the target mRNA and an antisense strand that is complementary to the target mRNA offers much more advantage in terms of efficiency for target RNA destruction compared to the use of the single strand (ss)-siRNAs (e.g. antisense strand RNA or antisense oligonucleotides). In many cases, it requires higher concentration of the ss-siRNA to achieve the effective gene silencing potency of the corresponding duplex.

[00303] Any of the foregoing molecules may be encoded by a viral genome.

Design and Sequences of siRNA duplexes targeting HTT gene

[00304] The present invention provides small interfering RNA (siRNA) duplexes (and modulatory polynucleotides encoding them) that target HTT mRNA to interfere with HTT gene expression and/or HTT protein production.

[00305] The encoded siRNA duplex of the present invention contains an antisense strand and a sense strand hybridized together forming a duplex structure, wherein the antisense strand is complementary to the nucleic acid sequence of the targeted HTT gene, and wherein the sense strand is homologous to the nucleic acid sequence of the targeted HTT gene. In some aspects, the 5' end of the antisense strand has a 5' phosphate group and the 3' end of the sense strand contains a 3'hydroxyl group. In other aspects, there are none, one or 2 nucleotide overhangs at the 3'end of each strand.

[00306] Some guidelines for designing siRNAs have been proposed in the art. These guidelines generally recommend generating a 19-nucleotide duplexed region, symmetric 2-3 nucleotide 3'overhangs, 5'- phosphate and 3'- hydroxyl groups targeting a region in the gene to be silenced. Other rules that may govern siRNA sequence preference include, but are not limited to, (i) A/U at the 5′ end of the antisense strand; (ii) G/C at the 5′ end of the sense strand; (iii) at least five A/U residues in the 5′ terminal one-third of the antisense strand; and (iv) the absence of any GC stretch of more than 9 nucleotides in length. In accordance with such consideration, together with the specific sequence of a target gene, highly effective siRNA molecules essential for suppressing mammalian target gene expression may be readily designed.

[00307] According to the present invention, siRNA molecules (e.g., siRNA duplexes or encoded dsRNA) that target the HTT gene are designed. Such siRNA molecules can specifically, suppress HTT gene expression and protein production. In some aspects, the siRNA molecules are designed and used to selectively "knock out" HTT gene variants in cells, i.e., mutated HTT transcripts that are identified in patients with HD disease. In some aspects, the siRNA molecules are designed and used to selectively "knock down" HTT gene variants in cells. In other aspects, the siRNA molecules are able to inhibit or suppress both the wild type and mutated HTT gene.

[00308] In one embodiment, an siRNA molecule of the present invention comprises a sense strand and a complementary antisense strand in which both strands are hybridized together to form a duplex structure. The antisense strand has sufficient complementarity to the HTT mRNA sequence to direct target-specific RNAi, i.e., the siRNA molecule has a sequence sufficient to trigger the destruction of the target mRNA by the RNAi machinery or process.

[00309] In one embodiment, an siRNA molecule of the present invention comprises a sense strand and a complementary antisense strand in which both strands are hybridized together to form a duplex structure and where the start site of the hybridization to the HTT mRNA is between nucleotide 100 and 7000 on the HTT mRNA sequence. As a non-limiting example, the start site may be between nucleotide 100-150, 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-70, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1050, 1050-1100, 1100-1150, 1150-1200, 1200-1250, 1250-1300, 1300-1350, 1350-1400, 1400-1450, 1450-1500, 1500-1550, 1550-1600, 1600-1650, 1650-1700, 1700-1750, 1750-1800, 1800-1850, 1850-1900, 1900-1950, 1950-2000, 2000-2050, 2050-2100, 2100-2150, 2150-2200, 2200-2250, 2250-2300, 2300-2350, 2350-2400, 2400-2450, 2450-2500, 2500-2550, 2550-2600, 2600-2650, 2650-2700, 2700-2750, 2750-2800, 2800-2850, 2850-2900, 2900-2950, 2950-3000, 3000-3050, 3050-3100, 3100-3150, 3150-3200, 3200-3250, 3250-3300, 3300-3350, 3350-3400, 3400-3450, 3450-3500, 3500-3550, 3550-3600, 3600-3650, 3650-3700, 3700-3750, 3750-3800, 3800-3850, 3850-3900, 3900-3950, 3950-4000, 4000-4050, 4050-4100, 4100-4150, 4150-4200, 4200-4250, 4250-4300, 4300-4350, 4350-4400, 4400-4450, 4450-4500, 4500-4550, 4550-4600, 4600-4650, 4650-4700, 4700-4750, 4750-4800, 4800-4850, 4850-4900, 4900-4950, 4950-5000, 5000-5050, 5050-5100, 5100-5150, 5150-5200, 5200-5250, 5250-5300, 5300-5350, 5350-5400, 5400-5450, 5450-5500, 5500-5550, 5550-5600, 5600-5650, 5650-5700, 5700-5750, 5750-5800, 5800-5850, 5850-5900, 5900-5950, 5950-6000, 6000-6050, 6050-6100, 6100-6150, 6150-6200, 6200-6250, 6250-6300, 6300-6350, 6350-6400, 6400-6450, 6450-6500, 6500-6550, 6550-6600, 6600-6650, 6650-6700, 6700-6750, 6750-6800, 6800-6850, 6850-6900,

6900-6950, 6950-7000, 7000-7050, 7050-7100, 7100-7150, 7150-7200, 7200-7250, 7250-7300, 7300-7350, 7350-7400, 7400-7450, 7450-7500, 7500-7550, 7550-7600, 7600-7650, 7650-7700, 7700-7750, 7750-7800, 7800-7850, 7850-7900, 7900-7950, 7950-8000, 8000-8050, 8050-8100, 8100-8150, 8150-8200, 8200-8250, 8250-8300, 8300-8350, 8350-8400, 8400-8450, 8450-8500, 8500-8550, 8550-8600, 8600-8650, 8650-8700, 8700-8750, 8750-8800, 8800-8850, 8850-8900, 8900-8950, 8950-9000, 9000-9050, 9050-9100, 9100-9150, 9150-9200, 9200-9250, 9250-9300, 9300-9350, 9350-9400, 9400-9450, 9450-9500, 9500-9550, 9550-9600, 9600-9650, 9650-9700, 9700-9750, 9750-9800, 9800-9850, 9850-9900, 9900-9950, 9950-10000, 10000-10050, 10050-10100, 10100-10150, 10150-10200, 10200-10250, 10250-10300, 10300-10350, 10350-10400, 10400-10450, 10450-10500, 10500-10550, 10550-10600, 10600-10650, 10650-10700, 10700-10750, 10750-10800, 10800-10850, 10850-10900, 10900-10950, 10950-11000, 11050-11100, 11100-11150, 11150-11200, 11200-11250, 11250-11300, 11300-11350, 11350-11400, 11400-11450, 11450-11500, 11500-11550, 11550-11600, 11600-11650, 11650-11700, 11700-11750, 11750-11800, 11800-11850, 11850-11900, 11900-11950, 11950-12000, 12000-12050, 12050-12100, 12100-12150, 12150-12200, 12200-12250, 12250-12300, 12300-12350, 12350-12400, 12400-12450, 12450-12500, 12500-12550, 12550-12600, 12600-12650, 12650-12700, 12700-12750, 12750-12800, 12800-12850, 12850-12900, 12900-12950, 12950-13000, 13050-13100, 13100-13150, 13150-13200, 13200-13250, 13250-13300, 13300-13350, 13350-13400, 13400-13450, and 13450-13500 on the HTT mRNA sequence. As yet another non-limiting example, the start site may be nucleotide 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, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443, 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1660, 1661, 1662, 1663, 1664, 1665, 1666, 1667, 1668, 1669, 1670, 1671, 1672, 1673, 1674, 1675, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081,

2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 4525, 4526, 4527, 4528, 4529, 4530, 4531, 4532, 4533, 4534, 4535, 4536, 4537, 4538, 4539, 4540, 4541, 4542, 4543, 4544, 4545, 4546, 4547, 4548, 4549, 4550, 4575, 4576, 4577, 4578, 4579, 4580, 4581, 4582, 4583, 4584, 4585, 4586, 4587, 4588, 4589, 4590, 4591, 4592, 4593, 4594, 4595, 4596, 4597, 4598, 4599, 4600, 4850, 4851, 4852, 4853, 4854, 4855, 4856, 4857, 4858, 4859, 4860, 4861, 4862, 4863, 4864, 4865, 4866, 4867, 4868, 4869, 4870, 4871, 4872, 4873, 4874, 4875, 4876, 4877, 4878, 4879, 4880, 4881, 4882, 4883, 4884, 4885, 4886, 4887, 4888, 4889, 4890, 4891, 4892, 4893, 4894, 4895, 4896, 4897, 4898, 4899, 4900, 5460, 5461, 5462, 5463, 5464, 5465, 5466, 5467, 5468, 5469, 5470, 5471, 5472, 5473, 5474, 5475, 5476, 5477, 5478, 5479, 5480, 6175, 6176, 6177, 6178, 6179, 6180, 6181, 6182, 6183, 6184, 6185, 6186, 6187, 6188, 6189, 6190, 6191, 6192, 6193, 6194, 6195, 6196, 6197, 6198, 6199, 6200, 6315, 6316, 6317, 6318, 6319, 6320, 6321, 6322, 6323, 6324, 6325, 6326, 6327, 6328, 6329, 6330, 6331, 6332, 6333, 6334, 6335, 6336, 6337, 6338, 6339, 6340, 6341, 6342, 6343, 6344, 6345, 6600, 6601, 6602, 6603, 6604, 6605, 6606, 6607, 6608, 6609, 6610, 6611, 6612, 6613, 6614, 6615, 6725, 6726, 6727, 6728, 6729, 6730, 6731, 6732, 6733, 6734, 6735, 6736, 6737, 6738, 6739, 6740, 6741, 6742, 6743, 6744, 6745, 6746, 6747, 6748, 6749, 6750, 6751, 6752, 6753, 6754, 6755, 6756, 6757, 6758, 6759, 6760, 6761, 6762, 6763, 6764, 6765, 6766, 6767, 6768, 6769, 6770, 6771, 6772, 6773, 6774, 6775, 7655, 7656, 7657, 7658, 7659, 7660, 7661, 7662, 7663, 7664, 7665, 7666, 7667, 7668, 7669, 7670, 7671, 7672, 8510, 8511, 8512, 8513, 8514, 8515, 8516, 8715, 8716, 8717, 8718, 8719, 8720, 8721, 8722, 8723, 8724, 8725, 8726, 8727, 8728, 8729, 8730, 8731, 8732, 8733, 8734, 8735, 8736, 8737, 8738, 8739, 8740, 8741, 8742, 8743, 8744, 8745, 9250, 9251, 9252, 9253, 9254, 9255, 9256, 9257, 9258, 9259, 9260, 9261, 9262, 9263, 9264, 9265, 9266, 9267, 9268, 9269, 9270, 9480, 9481, 9482, 9483, 9484, 9485, 9486, 9487, 9488, 9489, 9490, 9491, 9492, 9493, 9494, 9495, 9496, 9497, 9498, 9499, 9500, 9575, 9576, 9577, 9578, 9579, 9580, 9581, 9582, 9583, 9584, 9585, 9586, 9587, 9588, 9589, 9590, 10525, 10526, 10527, 10528, 10529, 10530, 10531, 10532, 10533, 10534, 10535, 10536, 10537, 10538, 10539, 10540, 11545, 11546, 11547, 11548, 11549, 11550, 11551, 11552, 11553, 11554, 11555, 11556, 11557, 11558, 11559, 11560, 11875, 11876, 11877, 11878, 11879, 11880, 11881, 11882, 11883, 11884, 11885, 11886, 11887, 11888, 11889, 11890, 11891, 11892, 11893, 11894, 11895, 11896, 11897, 11898, 11899, 11900, 11915, 11916, 11917, 11918, 11919, 11920, 11921, 11922, 11923, 11924, 11925, 11926, 11927, 11928, 11929, 11930, 11931, 11932,

11933, 11934, 11935, 11936, 11937, 11938, 11939, 11940, 13375, 13376, 13377, 13378, 13379, 13380, 13381, 13382, 13383, 13384, 13385, 13386, 13387, 13388, 13389 and 13390 on the HTT mRNA sequence.

[00310] In some embodiments, the antisense strand and target mRNA sequences have 100% complementarity. The antisense strand may be complementary to any part of the target mRNA sequence.

[00311] In other embodiments, the antisense strand and target mRNA sequences comprise at least one mismatch. As a non-limiting example, the antisense strand and the target mRNA sequence have at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% complementarity.

[00312] In one embodiment, an siRNA or dsRNA includes at least two sequences that are complementary to each other.

[00313] According to the present invention, the siRNA molecule has a length from about 10-50 or more nucleotides, i.e., each strand comprising 10-50 nucleotides (or nucleotide analogs). Preferably, the siRNA molecule has a length from about 15-30, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in each strand, wherein one of the strands is sufficiently complementarity to a target region. In one embodiment, each strand of the siRNA molecule has a length from about 19 to 25, 19 to 24 or 19 to 21 nucleotides. In one embodiment, at least one strand of the siRNA molecule is 19 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 20 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 21 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 22 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 23 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 24 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 25 nucleotides in length.

[00314] In some embodiments, the siRNA molecules of the present invention can be synthetic RNA duplexes comprising about 19 nucleotides to about 25 nucleotides, and two overhanging nucleotides at the 3'-end. In some aspects, the siRNA molecules may be unmodified RNA

molecules. In other aspects, the siRNA molecules may contain at least one modified nucleotide, such as base, sugar or backbone modifications.

[00315] In one embodiment, the siRNA molecules of the present invention may comprise a nucleotide sequence such as, but not limited to, the antisense (guide) sequences in Table 2 or a fragment or variant thereof. As a non-limiting example, the antisense sequence used in the siRNA molecule of the present invention is at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% of a nucleotide sequence in Table 2. As another non-limiting example, the antisense sequence used in the siRNA molecule of the present invention comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more than 21 consecutive nucleotides of a nucleotide sequence in Table 2. As yet another non-limiting example, the antisense sequence used in the siRNA molecule of the present invention comprises nucleotides 1 to 22, 1 to 21, 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 2 to 22, 2 to 21, 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 3 to 22, 3 to 21, 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 4 to 22, 4 to 21, 4 to 20, 4 to 19, 4 to 18, 4 to 17, 4 to 16, 4 to 15, 4 to 14, 4 to 13, 4 to 12, 4 to 11, 4 to 10, 4 to 9, 4 to 8, 5 to 22, 5 to 21, 5 to 20, 5 to 19, 5 to 18, 5 to 17, 5 to 16, 5 to 15, 5 to 14, 5 to 13, 5 to 12, 5 to 11, 5 to 10, 5 to 9, 5 to 8, 6 to 22, 6 to 21, 6 to 20, 6 to 19, 6 to 18, 6 to 17, 6 to 16, 6 to 15, 6 to 14, 6 to 13, 6 to 12, 6 to 11, 6 to 10, 7 to 22, 7 to 21, 7 to 20, 7 to 19, 7 to 18, 7 to 17, 7 to 16, 7 to 15, 7 to 14, 7 to 13, 7 to 12, 8 to 22, 8 to 21, 8 to 20, 8 to 19, 8 to 18, 8 to 17, 8 to 16, 8 to 15, 8 to 14, 8 to 13, 8 to 12, 9 to 22, 9 to 21, 9 to 20, 9 to 19, 9 to 18, 9 to 17, 9 to 16, 9 to 15, 9 to 14, 10 to 22, 10 to 21, 10 to 20, 10 to 19, 10 to 18, 10 to 17, 10 to 16, 10 to 15, 10 to 14, 11 to 22, 11 to 21, 11 to 20, 11 to 19, 11 to 18, 11 to 17, 11 to 16, 11 to 15, 11 to 14, 12 to 22, 12 to 21, 12 to 20, 12 to 19, 12 to 18, 12 to 17, 12 to 16, 13 to 22, 13 to 21, 13 to 20, 13 to 19, 13 to 18, 13 to 17, 13 to 16, 14 to 22, 14 to 21, 14 to 20, 14 to 19, 14 to 18, 14 to 17, 15 to 22, 15 to 21, 15 to 20, 15 to 19, 15 to 18, 16 to 22, 16 to 21, 16 to 20, 17 to 22, 17 to 21, or 18 to 22 of the sequences in Table 2.

Table 2. Antisense Sequences

Antisense ID	Sequence	SEQ ID NO
A-2000	UUAACGUCAGUUCAUAAACUU	914
A-2000dt	UUAACGUCAGUUCAUAAACdTdT	915
A-2001	UGUCGGUACCGUCUAACACUU	916
A-2001dt	UGUCGGUACCGUCUAACACdTdT	917
A-2002	UAAGCAUGGAGCUAGCAGGUU	918
A-2002dt	UAAGCAUGGAGCUAGCAGGdTdT	919
A-2003	UACAACGAGACUGAAUUGCUU	920
A-2003dt	UACAACGAGACUGAAUUGCdTdT	921
A-2004	UUCAGUUCAUAAACCUGGAUU	922
A-2004dt	UUCAGUUCAUAAACCUGGAdTdT	923
A-2005	UAACGUCAGUUCAUAAACCUU	924
A-2005dt	UAACGUCAGUUCAUAAACCdTdT	925
A-2006	UCCGGUCACAACAUUGUGGUU	926
A-2006dt	UCCGGUCACAACAUUGUGGdTdT	927
A-2007	UUGCACGGUUCUUUGUGACUU	928
A-2007dt	UUGCACGGUUCUUUGUGACdTdT	929
A-2008	UUUUAUAACAAGAGGUUCAUU	930
A-2008dt	UUUUAUAACAAGAGGUUCAdTdT	931
A-2009	UCCAAAUACUGGUUGUCGGUU	932
A-2009dt	UCCAAAUACUGGUUGUCGGdTdT	933
A-2010	UAUUUUAGGAAUUCCAAUGUU	934
A-2010dt	UAUUUUAGGAAUUCCAAUGdTdT	935
A-2011	UUUAGGAAUUCCAAUGAUCUU	936
A-2011dt	UUUAGGAAUUCCAAUGAUCdTdT	937
A-2012dt	UUAAUCUCUUUACUGAUAUdTdT	938
A-2013dt	GAUUUUAGGAAUUCCAAUGdTdT	939
A-2014	UAAGCAUGGAGCUAGCAGGCUU	940
A-2015	UAAGCAUGGAGCUAGCAGGGU	941
A-2016	AAGGACUUGAGGGACUCGAAGU	942
A-2017	AAGGACUUGAGGGACUCGAAG	943
A-2018	AAGGACUUGAGGGACUCGA	944
A-2019	AGGACUUGAGGGACUCGAAGU	945
A-2020	GAGGACUUGAGGGACUCGAAGU	946
A-2021	AAGGACUUGAGGGACUCGAAGU	947
A-2022	AAGGACUUGAGGGACUCGAAGUU	948
A-2023	AAGGACUUGAGGGACUCGAAG	949
A-2024	AAGGACUUGAGGGACUCGA	950
A-2025	AAGGACUUGAGGGACUCGAAGG	951
A-2026	AAGGACUUGAGGGACUCGAAU	952
A-2027	AAGGACUUGAGGGACUCGAAGA	953
A-2028	AAGGACUUGAGGGACUCGAAGG	954
A-2029	AAGGACUUGAGGGACUCGAAGGU	955
A-2030	AAGGACUUGAGGGACUCGAAGGA	956
A-2031	AAGGACUUGAGGGACUCGAAG	957
A-2032	AAGGACUUGAGGGACUCGAAGU	958
A-2033	AAGGACUUGAGGGACUCGA	959
A-2034	AAGGACUUGAGGGACUCGAAGGA	960
A-2035	AAGGACUUGAGGGACUCGAAGG	961
A-2036	AAGGACUUGAGGGACUCGAAGGAU	962
A-2037	AAGGACUUGAGGGACUCGAAGGAUU	963
A-2038	AAGGACUUGAGGGACUCGAAG	964
A-2039	AAGGACUUGAGGGACUCGAAGGAA	965
A-2040	GAUGAAGUGCACACAUUGGAUGA	966
A-2041	GAUGAACUGCACACAUUGGAUG	967
A-2042	GAUGAAUUGCACACAGUAGAUGA	968

A-2043	AAGGACUUGAGGGACUCGAAGGUU	969
A-2044	AAGGACUUGAGGGACUCGAAGGUUU	970
A-2045	AAGGACUUGAGGGACUCGAAGGU	971
A-2046	AAGGACUUGAGGGACUCGAAGGUUUU	972
A-2047	AAGGACUUGAGGGACUCGAAGGUUUUU	973
A-2048	AAGGACUUGAGGGACUCGAAGG	974
A-2049	UAAGGACUUGAGGGACUCGAAG	975
A-2050	AAGGACUUGAGGGACUCGAAG	976
A-2051	AAGGACUUGAGGGACUCGAAGU	977
A-2052	AAGGACUUGAGGGACUCGAAGACGAGUCCC	978
A-2053	AAGGACUUGAGGGACUCGAAGACGAGUCCCA	979
A-2054	AAGGACUUGAGGGACUCGAAGACGAGUCCCU	980
A-2055	GAUGAAGUGCACACAUUGGAUAC	981
A-2056	GAUGAAGUGCACACAUUGGAUACA	982
A-2057	GAUGAAGUGCACACAUUGGAUACAAUGUGU	983
A-2058	GAUGAAGUGCACACAUUGGAU	984
A-2059	GAUGAAGUGCACACAUUGGAUA	985
A-2060	GAUGAAUUGCACACAGUAGAUAU	986
A-2061	GAUGAAUUGCACACAGUAGAUAUAC	987
A-2062	GAUGAAUUGCACACAGUAGAUAUACUGUGU	988
A-2063	GAUGAAUUGCACACAGUAGAUAUA	989
A-2064	AUGAAUUGCACACAGUAGAUAUAC	990
A-2065	GAUGAAUUGCACACAGUAGAUA	991
A-2066	GAUGAAUUGCACACAGUAGAUAUACUGUGU	992
A-2067	UACAACGAGACUGAAUUGCU	993
A-2068	ACAACGAGACUGAAUUGCUU	994
A-2069	UCCGGUCACAACAUUGUGGUUC	995
A-2070	UCCGGUCACAACAUUGUGGU	996
A-2071	UCCGGUCACAACAUUGUG	997
A-2072	CCGGUCACAACAUUGUGGUU	998
A-2073	UUUUAUAACAAGAGGUUCAU	999
A-2074	UUUAUAACAAGAGGUUCAUU	1000
A-2075	UAAGCAUGGAGCUAGCAGGU	1001
A-2076	AAGCAUGGAGCUAGCAGGUU	1002
A-2077	CCAAAUACUGGUUGUCGGUU	1003
A-2078	UACAACGAGACUGAAUUGCUUU	1004
A-2079	UAACGUCAGUUCAUAAACCUUU	1005
A-2080	GUCCGGUCACAACAUUGUGGUU	1006
A-2081	UCCGGUCACAACAUUGUGGUUUG	1007
A-2082	UCCGGUCACAACAUUGUGGUUU	1008
A-2083	UCCGGUCACAACAUUGUGG	1009
A-2084	UAAGCAUGGAGCUAGCAGGUUU	1010
A-2085	AAGCAUGGAGCUAGCAGGUUU	1011
A-2086	UCCAAAUACUGGUUGUCGGUUU	1012
A-2087	CCAAAUACUGGUUGUCGGUUU	1013

[00316] In one embodiment, the siRNA molecules of the present invention may comprise a nucleotide sequence such as, but not limited to, the sense (passenger) sequences in Table 3 or a fragment or variant thereof. As a non-limiting example, the sense sequence used in the siRNA molecule of the present invention is at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-

40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% of a nucleotide sequence in Table 3. As another non-limiting example, the sense sequence used in the siRNA molecule of the present invention comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more than 21 consecutive nucleotides of a nucleotide sequence in Table 3. As yet another non-limiting example, the sense sequence used in the siRNA molecule of the present invention comprises nucleotides 1 to 22, 1 to 21, 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 2 to 22, 2 to 21, 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 3 to 22, 3 to 21, 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 4 to 22, 4 to 21, 4 to 20, 4 to 19, 4 to 18, 4 to 17, 4 to 16, 4 to 15, 4 to 14, 4 to 13, 4 to 12, 4 to 11, 4 to 10, 4 to 9, 4 to 8, 5 to 22, 5 to 21, 5 to 20, 5 to 19, 5 to 18, 5 to 17, 5 to 16, 5 to 15, 5 to 14, 5 to 13, 5 to 12, 5 to 11, 5 to 10, 5 to 9, 5 to 8, 6 to 22, 6 to 21, 6 to 20, 6 to 19, 6 to 18, 6 to 17, 6 to 16, 6 to 15, 6 to 14, 6 to 13, 6 to 12, 6 to 11, 6 to 10, 7 to 22, 7 to 21, 7 to 20, 7 to 19, 7 to 18, 7 to 17, 7 to 16, 7 to 15, 7 to 14, 7 to 13, 7 to 12, 8 to 22, 8 to 21, 8 to 20, 8 to 19, 8 to 18, 8 to 17, 8 to 16, 8 to 15, 8 to 14, 8 to 13, 8 to 12, 9 to 22, 9 to 21, 9 to 20, 9 to 19, 9 to 18, 9 to 17, 9 to 16, 9 to 15, 9 to 14, 10 to 22, 10 to 21, 10 to 20, 10 to 19, 10 to 18, 10 to 17, 10 to 16, 10 to 15, 10 to 14, 11 to 22, 11 to 21, 11 to 20, 11 to 19, 11 to 18, 11 to 17, 11 to 16, 11 to 15, 11 to 14, 12 to 22, 12 to 21, 12 to 20, 12 to 19, 12 to 18, 12 to 17, 12 to 16, 13 to 22, 13 to 21, 13 to 20, 13 to 19, 13 to 18, 13 to 17, 13 to 16, 14 to 22, 14 to 21, 14 to 20, 14 to 19, 14 to 18, 14 to 17, 15 to 22, 15 to 21, 15 to 20, 15 to 19, 15 to 18, 16 to 22, 16 to 21, 16 to 20, 17 to 22, 17 to 21, or 18 to 22 of the sequences in Table 3.

Table 3. Sense Sequences

Sense ID	Sequence	SEQ ID NO
S-1000	GUUUAUGAACUGAUCUUACCC	1014
S-1001	GUGUUAGACGGUACUGAUCCC	1015
S-1002	CCUGCUAGCUCCAUGCUUCCC	1016
S-1003	GUUUAUGAACUGAUCUUAGCC	1017
S-1004	GUGUUAGACGGUACUGAUGCC	1018
S-1005	CCUGCUAGCUCCAUGCUUGCC	1019
S-1006	GUUUAUGAAGUGAUCUUAACC	1020
S-1007	GUGUUAGACCGUACUGAUACC	1021
S-1008	CCUGCUAGCACCAUGCUUACC	1022
S-1009	GUUUAUGAACUGAUCUUAACC	1023
S-1010	GUGUUAGACGGUACUGAUACC	1024
S-1011	CCUGCUAGCUCCAUGCUUACC	1025
S-1011dt	CCUGCUAGCUCCAUGCUUAdTdT	1026

S-1012	GUUUAUGAACUGAUCUUGCCC	1027
S-1013	GUUUAUGAACUGAUCUUGGCC	1028
S-1014	GUUUAUGAACUGAUCUUGACC	1029
S-1015	GCAAUUCAGUCUCGUUGUCCC	1030
S-1016	UCCAGGUUUAUGAACUGACCC	1031
S-1017	GGUUUAUGAACUGACGUUCCC	1032
S-1018	CCACAAUGUUGUGACUGGCCC	1033
S-1019	GUCACAAAGAACCGUGUACCC	1034
S-1020	UGAACCUCUUGUUAUAAACCC	1035
S-1021	CCGACAACCAGUAUUUGGCCC	1036
S-1022	GCAAUUCAGUCUCGUUGUGCC	1037
S-1023	UCCAGGUUUAUGAACUGAGCC	1038
S-1024	GGUUUAUGAACUGACGUUGCC	1039
S-1025	CCACAAUGUUGUGACUGGGCC	1040
S-1026	GUCACAAAGAACCGUGUAGCC	1041
S-1027	UGAACCUCUUGUUAUAAAGCC	1042
S-1028	CCGACAACCAGUAUUUGGGCC	1043
S-1029	GCAAUUCAGUCUCGUUGUACC	1044
S-1029dt	GCAAUUCAGUCUCGUUGUAdTdT	1045
S-1030	UCCAGGUUUAUGAACUGAACC	1046
S-1030dt	UCCAGGUUUAUGAACUGAAdTdT	1047
S-1031	GGUUUAUGAACUGACGUUACC	1048
S-1032	CCACAAUGUUGUGACUGGACC	1049
S-1033	GUCACAAAGAACCGUGUAACC	1050
S-1034	UGAACCUCUUGUUAUAAAACC	1051
S-1034dt	UGAACCUCUUGUUAUAAAAdTdT	1052
S-1035	CCGACAACCAGUAUUUGGACC	1053
S-1035dt	CCGACAACCAGUAUUUGGAdTdT	1054
S-1036	GCAAUUCAGACUCGUUGUACC	1055
S-1037	UCCAGGUUUUUGAACUGAACC	1056
S-1038	GGUUUAUGAUCUGACGUUACC	1057
S-1039	CCACAAUGUAGUGACUGGACC	1058
S-1040	GUCACAAAGUACCGUGUAACC	1059
S-1041	UGAACCUCUAGUUAUAAAACC	1060
S-1042	CCGACAACCUGUAUUUGGACC	1061
S-1043	CAUUGGAAUUCCUAAAAUUCC	1062
S-1044	GAUCAUUGGAAUUCCUAAUCC	1063
S-1045	CAUUGGAAUUCCUAAAAUGCC	1064
S-1046	GAUCAUUGGAAUUCCUAAGCC	1065
S-1047	CAUUGGAAUUCCUAAAAUACC	1066
S-1047dt	CAUUGGAAUUCCUAAAAUAdTdT	1067
S-1048	GAUCAUUGGAAUUCCUAAACC	1068
S-1048dt	GAUCAUUGGAAUUCCUAAAdTdT	1069
S-1049	CAUUGGAAUACCUAAAAUACC	1070
S-1050	GAUCAUUGGUAUUCCUAAACC	1071
S-1051dt	GUUUAUGAACUGACGUUAAdTdT	1072
S-1052dt	GUGUUAGACGGUACCGACAdTdT	1073
S-1053dt	AUAUCAGUAAAGAGAUUAAdTdT	1074
S-1054dt	GGUUUAUGAACUGACGUUAdTdT	1075
S-1055dt	CCACAAUGUUGUGACCGGAdTdT	1076
S-1056dt	GUCACAAAGAACCGUGCAAdTdT	1077
S-1057dt	CAUUGGAAUUCCUAAAAUCdTdT	1078
S-1058	CCUGCUAGCUCCAUGCUUGCU	1079
S-1059	CCUGCUAGCUCCAUGCUUGAU	1080
S-1060	CCUGCUAGCUCCAUGCUUAUU	1081
S-1061	CCUGCUAGCUCCAUGCUUGUU	1082
S-1062	UUCGAGUCCCUCAAGUAGCU	1083

S-1063	UUCGAGUCCCUCAAGUAGCUUU	1084
S-1064	UCGAGUCCCUCAAGUCCAUUCU	1085
S-1065	UUCCAGUCCAUCAAGUCAAUU	1086
S-1066	UUCCGAGUCUAAAAGUCCUUGG	1087
S-1067	UUCCGAGUCUAAAAGUCCUUGGC	1088
S-1068	CUUCCGAGUCUAAAAGUCCUUGG	1089
S-1069	UUCCGAGUCUAAAAGUCCUUGGU	1090
S-1070	UUCCGAGUCUAAAAGUCCUUGGCU	1091
S-1071	UCCAAUGUGAAACUUCAUCGGCU	1092
S-1072	UCCAAUGUGAAACUUCAUCGGC	1093
S-1073	AUCCAAUGUGAAACUUCAUCGU	1094
S-1074	AUCCAAUGUGAAACUUCAUCGGU	1095
S-1075	UCCAAUGUGAAACUUCAUCGGU	1096
S-1076	UCCAAUGUGAAACUUCAUCGGCUU	1097
S-1077	AUCUACUGUGAAAAUUCAUCGG	1098
S-1078	UCUACUGUGAAAAUUCAUCGG	1099
S-1079	UCUACUGUGAAAAUUCAUCGGC	1100
S-1080	AUCUACUGUGAAAAUUCAUCGGU	1101
S-1081	UCUACUGUGAAAAUUCAUCGGU	1102
S-1082	UCUACUGUGAAAAUUCAUCGGCU	1103
S-1083	CCUUCGGUCCUCAAGUCCUUCA	1104
S-1084	UUCGAGUCCAUCAAAUCCUAUAGU	1105
S-1085	UACAAUGUGUGCACUUCAUAU	1106
S-1086	UAUACUGUGUGCAAUUCAUUUCU	1107
S-1087	GCAAUUCAGUCUCGUUGUCC	1108
S-1088	GCAAUUCAGUCUCGUUGUC	1109
S-1089	CAAUUCAGUCUCGUUGUCCC	1110
S-1090	CAAUUCAGUCUCGUUGUCC	1111
S-1091	GCAAUUCAGUCUCGUUGUGC	1112
S-1092	CAAUUCAGUCUCGUUGUGCC	1113
S-1093	CCACAAUGUUGUGACUGGGCCU	1114
S-1094	CCACAAUGUUGUGACUGGGC	1115
S-1095	CACAAUGUUGUGACUGGGCC	1116
S-1096	UGAACCUCUUGUUAUAAAGCCU	1117
S-1097	UGAACCUCUUGUUAUAAAGC	1118
S-1098	GAACCUCUUGUUAUAAAGCC	1119
S-1099	CCUGCUAGCUCCAUGCUUGCCU	1120
S-1100	CCUGCUAGCUCCAUGCUUGC	1121
S-1101	CCUGCUAGCUCCAUGCUUG	1122
S-1102	CUGCUAGCUCCAUGCUUGCC	1123
S-1103	CCGACAACCAGUAUUUGGGCCU	1124
S-1104	CCGACAACCAGUAUUUGGGC	1125
S-1105	CCGACAACCAGUAUUUGGG	1126
S-1106	CGACAACCAGUAUUUGGGCC	1127
S-1107	CGACAACCAGUAUUUGGGC	1128
S-1108	GCAAUUCAGUCUCGUUGUACCU	1129
S-1109	GCAAUUCAGUCUCGUUGUAC	1130
S-1110	GCAAUUCAGUCUCGUUGUA	1131
S-1111	CAAUUCAGUCUCGUUGUACC	1132
S-1112	GCAAUUCAGACUCGUUGUACCU	1133
S-1113	GCAAUUCAGACUCGUUGUAC	1134
S-1114	GCAAUUCAGACUCGUUGUA	1135
S-1115	CAAUUCAGACUCGUUGUACC	1136
S-1116	AGCAAUUCAGUCUCGUUGUACC	1137
S-1117	AGCAAUUCAGUCUCGUUGUAC	1138
S-1118	AGGUUUAUGAACUGACGUUAC	1139
S-1119	AGGUUUAUGAACUGACGUUACC	1140

S-1120	ACCACAAUGUUGUGACUGGAC	1141
S-1121	ACCACAAUGUUGUGACUGGACC	1142
S-1122	CCACAAUGUUGUGACUGGACCGU	1143
S-1123	CCACAAUGUUGUGACUGGACCG	1144
S-1124	CCACAAUGUUGUGACUGGAC	1145
S-1125	CACAAUGUUGUGACUGGACC	1146
S-1126	ACCUGCUAGCUCCAUGCUUCCC	1147
S-1127	ACCUGCUAGCUCCAUGCUUCC	1148
S-1128	ACCUGCUAGCUCCAUGCUUC	1149
S-1129	CCUGCUAGCUCCAUGCUUCC	1150
S-1130	CCUGCUAGCUCCAUGCUUC	1151
S-1131	CUGCUAGCUCCAUGCUUCCC	1152
S-1132	CUGCUAGCUCCAUGCUUCC	1153
S-1133	ACCGACAACCAGUAUUUGGACC	1154
S-1134	ACCGACAACCAGUAUUUGGAC	1155
S-1135	CCGACAACCAGUAUUUGGACCGU	1156
S-1136	CCGACAACCAGUAUUUGGACCGU	1157
S-1137	CCGACAACCAGUAUUUGGAC	1158
S-1138	CGACAACCAGUAUUUGGACC	1159
S-1139	CCUGCUAGCACCGUGCUUACC	1160

[00317] In one embodiment, the siRNA molecules of the present invention may comprise an antisense sequence from Table 2 and a sense sequence from Table 3, or a fragment or variant thereof. As a non-limiting example, the antisense sequence and the sense sequence have at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% complementarity.

[00318] In one embodiment, the siRNA molecules of the present invention may comprise the sense and antisense siRNA duplex as described in Tables 4-6. As a non-limiting example, these siRNA duplexes may be tested for *in vitro* inhibitory activity on endogenous HTT gene expression. The start site for the sense and antisense sequence is compared to HTT gene sequence known as NM_002111.7 (SEQ ID NO: 1425) from NCBI.

Table 4. Sense and antisense strand sequences of HTT dsRNA

siRNA Duplex ID	SS ID	Start SS	Sense Strand Sequence (5'-3')	SS SEQ ID	AS ID	Start AS	Antisense Strand Sequence (5'-3')	AS SEQ ID
D-3566	S-1058	6751	CCUGCUAGCUC CAUGCUUGCU	1079	A-2002	6751	UAAGCAUGGAG CUAGCAGGUU	918
D-3567	S-1058	6751	CCUGCUAGCUC CAUGCUUGCU	1079	A-2014	6748	UAAGCAUGGAG CUAGCAGGCUU	940

D-3568	S-1059	6751	CCUGCUAGCUC CAUGCUUGAU	1080	A-2002	6751	UAAGCAUGGAG CUAGCAGGUU	918
D-3569	S-1060	6751	CCUGCUAGCUC CAUGCUUAUU	1081	A-2015	6751	UAAGCAUGGAG CUAGCAGGGU	941
D-3570	S-1061	6751	CCUGCUAGCUC CAUGCUUGUU	1082	A-2002	6751	UAAGCAUGGAG CUAGCAGGUU	918
D-3500	S-1016	1386	UCCAGGUUUAU GAACUGACCC	1031	A-2004	1386	UUCAGUUCAUA AACCUGGAUU	922
D-3501	S-1023	1386	UCCAGGUUUAU GAACUGAGCC	1038	A-2004	1386	UUCAGUUCAUA AACCUGGAUU	922
D-3502	S-1030	1386	UCCAGGUUUAU GAACUGAACC	1046	A-2004	1386	UUCAGUUCAUA AACCUGGAUU	922
D-3503	S-1037	1386	UCCAGGUUUUU GAACUGAACC	1056	A-2004	1386	UUCAGUUCAUA AACCUGGAUU	922
D-3504	S-1030	1386	UCCAGGUUUAU GAACUGAACC	1046	A-2001	2066	UGUCGGUACCG UCUAACACUU	916
D-3505	S-1017	1390	GGUUUAUGAAC UGACGUUCCC	1032	A-2005	1389	UAACGUCAGUU CAUAAACCUU	924
D-3506	S-1024	1390	GGUUUAUGAAC UGACGUUGCC	1039	A-2005	1389	UAACGUCAGUU CAUAAACCUU	924
D-3507	S-1031	1390	GGUUUAUGAAC UGACGUUACC	1048	A-2005	1389	UAACGUCAGUU CAUAAACCUU	924
D-3508	S-1038	1390	GGUUUAUGAUC UGACGUUACC	1057	A-2005	1389	UAACGUCAGUU CAUAAACCUU	924
D-3509	S-1000	1391	GUUUAUGAACU GAUCUUACCC	1014	A-2000	1391	UUAACGUCAGU UCAUAAACUU	914
D-3510	S-1003	1391	GUUUAUGAACU GAUCUUAGCC	1017	A-2000	1391	UUAACGUCAGU UCAUAAACUU	914
D-3511	S-1006	1391	GUUUAUGAAG UGAUCUUAACC	1020	A-2000	1391	UUAACGUCAGU UCAUAAACUU	914
D-3512	S-1009	1391	GUUUAUGAACU GAUCUUAACC	1023	A-2000	1391	UUAACGUCAGU UCAUAAACUU	914
D-3513	S-1012	1391	GUUUAUGAACU GAUCUUGCCC	1027	A-2000	1391	UUAACGUCAGU UCAUAAACUU	914
D-3514	S-1013	1391	GUUUAUGAACU GAUCUUGGCC	1028	A-2000	1391	UUAACGUCAGU UCAUAAACUU	914
D-3515	S-1014	1391	GUUUAUGAACU GAUCUUGACC	1029	A-2000	1391	UUAACGUCAGU UCAUAAACUU	914
D-3516	S-1018	1429	CCACAAUGUUG UGACUGGCCC	1033	A-2006	1428	UCCGGUCACAA CAUUGUGGUU	926
D-3517	S-1025	1429	CCACAAUGUUG UGACUGGGCC	1040	A-2006	1428	UCCGGUCACAA CAUUGUGGUU	926
D-3518	S-1032	1429	CCACAAUGUUG UGACUGGACC	1049	A-2006	1428	UCCGGUCACAA CAUUGUGGUU	926
D-3519	S-1039	1429	CCACAAUGUAG UGACUGGACC	1058	A-2006	1428	UCCGGUCACAA CAUUGUGGUU	926
D-3520	S-1001	2066	GUGUUAGACGG UACUGAUCCC	1015	A-2001	2066	UGUCGGUACCG UCUAACACUU	916
D-3521	S-1004	2066	GUGUUAGACGG UACUGAUGCC	1018	A-2001	2066	UGUCGGUACCG UCUAACACUU	916
D-3522	S-1007	2066	GUGUUAGACCG UACUGAUACC	1021	A-2001	2066	UGUCGGUACCG UCUAACACUU	916
D-3523	S-1010	2066	GUGUUAGACGG UACUGAUACC	1024	A-2001	2066	UGUCGGUACCG UCUAACACUU	916
D-3524	S-1021	2079	CCGACAACCAG UAUUUGGCCC	1036	A-2009	2078	UCCAAAUACUG GUUGUCGGUU	932
D-3525	S-1028	2079	CCGACAACCAG UAUUUGGGCC	1043	A-2009	2078	UCCAAAUACUG GUUGUCGGUU	932

D-3526	S-1035	2079	CCGACAACCAG UAUUUGGACC	1053	A-2009	2078	UCCAAAUACUG GUUGUCGGUU	932
D-3527	S-1042	2079	CCGACAACCUG UAUUUGGACC	1061	A-2009	2078	UCCAAAUACUG GUUGUCGGUU	932
D-3528	S-1019	4544	GUCACAAAGAA CCGUGUACCC	1034	A-2007	4544	UUGCACGGUUC UUUGUGACUU	928
D-3529	S-1026	4544	GUCACAAAGAA CCGUGUAGCC	1041	A-2007	4544	UUGCACGGUUC UUUGUGACUU	928
D-3530	S-1033	4544	GUCACAAAGAA CCGUGUAACC	1050	A-2007	4544	UUGCACGGUUC UUUGUGACUU	928
D-3531	S-1040	4544	GUCACAAAGUA CCGUGUAACC	1059	A-2007	4544	UUGCACGGUUC UUUGUGACUU	928
D-3532	S-1020	4597	UGAACCUCUUG UUAUAAACCC	1035	A-2008	4597	UUUUAUAACAA GAGGUUCAUU	930
D-3533	S-1027	4597	UGAACCUCUUG UUAUAAAGCC	1042	A-2008	4597	UUUUAUAACAA GAGGUUCAUU	930
D-3534	S-1034	4597	UGAACCUCUUG UUAUAAAACC	1051	A-2008	4597	UUUUAUAACAA GAGGUUCAUU	930
D-3535	S-1041	4597	UGAACCUCUAG UUAUAAAACC	1060	A-2008	4597	UUUUAUAACAA GAGGUUCAUU	930
D-3536	S-1044	4861	GAUCAUUGGAA UUCCUAAUCC	1063	A-2011	4860	UUUAGGAAUUC CAAUGAUCUU	936
D-3537	S-1046	4861	GAUCAUUGGAA UUCCUAAGCC	1065	A-2011	4860	UUUAGGAAUUC CAAUGAUCUU	936
D-3538	S-1048	4861	GAUCAUUGGAA UUCCUAAACC	1068	A-2011	4860	UUUAGGAAUUC CAAUGAUCUU	936
D-3539	S-1050	4861	GAUCAUUGGUA UUCCUAAACC	1071	A-2011	4860	UUUAGGAAUUC CAAUGAUCUU	936
D-3540	S-1043	4864	CAUUGGAAUUC CUAAAAUUCC	1062	A-2010	4864	UAUUUUAGGA AUUCCAAUGUU	934
D-3541	S-1045	4864	CAUUGGAAUUC CUAAAAUGCC	1064	A-2010	4864	UAUUUUAGGA AUUCCAAUGUU	934
D-3542	S-1047	4864	CAUUGGAAUUC CUAAAAUACC	1066	A-2010	4864	UAUUUUAGGA AUUCCAAUGUU	934
D-3543	S-1049	4864	CAUUGGAAUAC CUAAAAUACC	1070	A-2010	4864	UAUUUUAGGA AUUCCAAUGUU	934
D-3544	S-1015	6188	GCAAUUCAGUC UCGUUGUCCC	1030	A-2003	6188	UACAACGAGAC UGAAUUGCUU	920
D-3545	S-1022	6188	GCAAUUCAGUC UCGUUGUGCC	1037	A-2003	6188	UACAACGAGAC UGAAUUGCUU	920
D-3546	S-1029	6188	GCAAUUCAGUC UCGUUGUACC	1044	A-2003	6188	UACAACGAGAC UGAAUUGCUU	920
D-3547	S-1036	6188	GCAAUUCAGAC UCGUUGUACC	1055	A-2003	6188	UACAACGAGAC UGAAUUGCUU	920
D-3548	S-1002	6751	CCUGCUAGCUC CAUGCUUCCC	1016	A-2002	6751	UAAGCAUGGAG CUAGCAGGUU	918
D-3549	S-1005	6751	CCUGCUAGCUC CAUGCUUGCC	1019	A-2002	6751	UAAGCAUGGAG CUAGCAGGUU	918
D-3550	S-1008	6751	CCUGCUAGCAC CAUGCUUACC	1022	A-2002	6751	UAAGCAUGGAG CUAGCAGGUU	918
D-3551	S-1011	6751	CCUGCUAGCUC CAUGCUUACC	1025	A-2002	6751	UAAGCAUGGAG CUAGCAGGUU	918

Table 5. Sense and antisense strand sequences of HTT dsRNA

siRNA Duplex ID	SS ID	Start SS	Sense Strand Sequence (5'-3')	SS SEQ ID	AS ID	Start AS	Antisense Strand Sequence (5'-3')	AS SEQ ID

D-3552	S-1051dt	1391	GUUUAUGAACUG ACGUUAAdTdT	1072	A-2000dt	1391	UUAACGUCAGU UCAUAAACdTdT	915
D-3553	S-1052dt	2066	GUGUUAGACGGU ACCGACAdTdT	1073	A-2001dt	2066	UGUCGGUACCG UCUAACACdTdT	917
D-3554	S-1011dt	6751	CCUGCUAGCUCC AUGCUUAdTdT	1026	A-2002dt	6751	UAAGCAUGGAG CUAGCAGGdTdT	919
D-3555	S-1053dt	10322	AUAUCAGUAAAG AGAUUAAdTdT	1074	A-2012dt	10322	UUAAUCUCUUU ACUGAUAUdTdT	938
D-3556	S-1030dt	1386	UCCAGGUUUAUG AACUGAAdTdT	1047	A-2004dt	1386	UUCAGUUCAUA AACCUGGAdTdT	923
D-3557	S-1054dt	1390	GGUUUAUGAACU GACGUUAdTdT	1075	A-2005dt	1390	UAACGUCAGUU CAUAAACCdTdT	925
D-3558	S-1055dt	1429	CCACAAUGUUGU GACCGGAdTdT	1076	A-2006dt	1429	UCCGGUCACAA CAUUGUGGdTdT	927
D-3559	S-1035dt	2079	CCGACAACCAGU AUUUGGAdTdT	1054	A-2009dt	2079	UCCAAAUACUG GUUGUCGGdTdT	933
D-3560	S-1056dt	4544	GUCACAAAGAAC CGUGCAAdTdT	1077	A-2007dt	4544	UUGCACGGUUC UUUGUGACdTdT	929
D-3561	S-1034dt	4597	UGAACCUCUUGU UAUAAAAdTdT	1052	A-2008dt	4597	UUUUAUAACAA GAGGUUCAdTdT	931
D-3562	S-1029dt	6188	GCAAUUCAGUCU CGUUGUAdTdT	1045	A-2003dt	6188	UACAACGAGAC UGAAUUGCdTdT	921
D-3563	S-1047dt	4864	CAUUGGAAUUCC UAAAAUAdTdT	1067	A-2010dt	4864	UAUUUUAGGAA UUCCAAUGdTdT	935
D-3564	S-1048dt	4861	GAUCAUUGGAAU UCCUAAAdTdT	1069	A-2011dt	4861	UUUAGGAAUUC CAAUGAUCdTdT	937
D-3565	S-1057dt	4864	CAUUGGAAUUCC UAAAAUCdTdT	1078	A-2013dt	4864	GAUUUUAGGAA UUCCAAUGdTdT	939

Table 6. Antisense and Sense strand sequences of HTT dsRNA

siRNA Duplex ID	AS ID	Start AS	Antisense Strand Sequence (5'-3')	AS SEQ ID	SS ID	Start SS	Sense Strand Sequence (5'-3')	SS SEQ ID
D-3569	S-1060	6751	CCUGCUAGCUC CAUGCUUAUU	1081	A-2015	6751	UAAGCAUGGAG CUAGCAGGGU	941
D-3570	S-1061	6751	CCUGCUAGCUC CAUGCUUGUU	1082	A-2002	6751	UAAGCAUGGAG CUAGCAGGUU	918

[00319] In other embodiments, the siRNA molecules of the present invention can be encoded in plasmid vectors, AAV particles, viral genome or other nucleic acid expression vectors for delivery to a cell.

[00320] DNA expression plasmids can be used to stably express the siRNA duplexes or dsRNA of the present invention in cells and achieve long-term inhibition of the target gene expression. In one aspect, the sense and antisense strands of a siRNA duplex are typically linked by a short spacer sequence leading to the expression of a stem-loop structure termed short hairpin RNA (shRNA). The hairpin is recognized and cleaved by Dicer, thus generating mature siRNA molecules.

[00321] According to the present invention, AAV particles comprising the nucleic acids encoding the siRNA molecules targeting HTT mRNA are produced, the AAV serotypes may be

any of the serotypes listed in Table 1. Non-limiting examples of the AAV serotypes include, AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV9.47, AAV9(hu14), AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAV-DJ8, AAV-DJ, AAV-PHP.A, and/or AAV-PHP.B, and variants thereof.

[00322] In some embodiments, the siRNA duplexes or encoded dsRNA of the present invention suppress (or degrade) target mRNA (e.g., HTT). Accordingly, the siRNA duplexes or encoded dsRNA can be used to substantially inhibit HTT gene expression in a cell, for example a neuron. In some aspects, the inhibition of HTT gene expression refers to an inhibition by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. Accordingly, the protein product of the targeted gene may be inhibited by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[00323] According to the present invention, the siRNA molecules are designed and tested for their ability in reducing HTT mRNA levels in cultured cells. Such siRNA molecules may form a duplex such as, but not limited to, include those listed in Table 4, Table 5 or Table 6. As a non-limiting example, the siRNA duplexes may be siRNA duplex IDs: D-3500 to D-3570.

[00324] In one embodiment, the siRNA molecules comprise a miRNA seed match for the target (e.g., HTT) located in the guide strand. In another embodiment, the siRNA molecules comprise a miRNA seed match for the target (e.g., HTT) located in the passenger strand. In yet another embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene do not comprise a seed match for the target (e.g., HTT) located in the guide or passenger strand.

[00325] In one embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene may have almost no significant full-length off target effects for the guide strand. In another embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene may have almost no

significant full-length off target effects for the passenger strand. The siRNA duplexes or encoded dsRNA targeting HTT gene may have less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%,11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 1-5%, 2-6%, 3-7%, 4-8%, 5-9%, 5-10%, 6-10%, 5-15%, 5-20%, 5-25% 5-30%, 10-20%, 10-30%, 10-40%, 10-50%, 15-30%, 15-40%, 15-45%, 20-40%, 20-50%, 25-50%, 30-40%, 30-50%, 35-50%, 40-50%, 45-50% full-length off target effects for the passenger strand. In yet another embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene may have almost no significant full-length off target effects for the guide strand or the passenger strand. The siRNA duplexes or encoded dsRNA targeting HTT gene may have less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%,11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 1-5%, 2-6%, 3-7%, 4-8%, 5-9%, 5-10%, 6-10%, 5-15%, 5-20%, 5-25% 5-30%, 10-20%, 10-30%, 10-40%, 10-50%, 15-30%, 15-40%, 15-45%, 20-40%, 20-50%, 25-50%, 30-40%, 30-50%, 35-50%, 40-50%, 45-50% full-length off target effects for the guide or passenger strand.

[00326] In one embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene may have high activity *in vitro*. In another embodiment, the siRNA molecules may have low activity *in vitro*. In yet another embodiment, the siRNA duplexes or dsRNA targeting the HTT gene may have high guide strand activity and low passenger strand activity *in vitro*.

[00327] In one embodiment, the siRNA molecules have a high guide strand activity and low passenger strand activity *in vitro*. The target knock-down (KD) by the guide strand may be at least 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 99.5% or 100%. The target knock-down by the guide strand may be 40-50%, 45-50%, 50-55%, 50-60%, 60-65%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 60-99%, 60-99.5%, 60-100%, 65-70%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 65-99%, 65-99.5%, 65-100%, 70-75%, 70-80%, 70-85%, 70-90%, 70-95%, 70-99%, 70-99.5%, 70-100%, 75-80%, 75-85%, 75-90%, 75-95%, 75-99%, 75-99.5%, 75-100%, 80-85%, 80-90%, 80-95%, 80-99%, 80-99.5%, 80-100%, 85-90%, 85-95%, 85-99%, 85-99.5%, 85-100%, 90-95%, 90-99%, 90-99.5%, 90-100%, 95-99%, 95-99.5%, 95-100%, 99-99.5%, 99-100% or 99.5-100%. As a non-limiting example, the target knock-down (KD) by the guide strand is greater than 70%. As a non-limiting example, the target knock-down (KD) by the guide strand is greater than 60%.

[00328] In one embodiment, the siRNA duplex is designed so there is no miRNA seed match for the sense or antisense sequence to non-Htt sequence.

[00329] In one embodiment, the IC_{50} of the guide strand for the nearest off target is greater than 100 multiplied by the IC_{50} of the guide strand for the on-target gene, Htt. As a non-limiting

example, if the IC_{50} of the guide strand for the nearest off target is greater than 100 multiplied by the IC_{50} of the guide strand for the target then the siRNA molecule is said to have high guide strand selectivity for inhibiting Htt *in vitro*.

[00330] In one embodiment, the 5' processing of the guide strand has a correct start (n) at the 5' end at least 75%, 80%, 85%, 90%, 95%, 99% or 100% of the time *in vitro* or *in vivo*. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time *in vitro*. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time *in vivo*. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 90% of the time *in vitro*. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 90% of the time *in vivo*. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 85% of the time *in vitro*. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 85% of the time *in vivo*.

[00331] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1;1, 2:10, 2:9, 2:8, 2:7, 2:6, 2:5, 2:4, 2:3, 2:2, 2:1, 3:10, 3:9, 3:8, 3:7, 3:6, 3:5, 3:4, 3:3, 3:2, 3:1, 4:10, 4:9, 4:8, 4:7, 4:6, 4:5, 4:4, 4:3, 4:2, 4:1, 5:10, 5:9, 5:8, 5:7, 5:6, 5:5, 5:4, 5:3, 5:2, 5:1, 6:10, 6:9, 6:8, 6:7, 6:6, 6:5, 6:4, 6:3, 6:2, 6:1, 7:10, 7:9, 7:8, 7:7, 7:6, 7:5, 7:4, 7:3, 7:2, 7:1, 8:10, 8:9, 8:8, 8:7, 8:6, 8:5, 8:4, 8:3, 8:2, 8:1, 9:10, 9:9, 9:8, 9:7, 9:6, 9:5, 9:4, 9:3, 9:2, 9:1, 10:10, 10:9, 10:8, 10:7, 10:6, 10:5, 10:4, 10:3, 10:2, 10:1, 1:99, 5:95, 10:90, 15:85, 20:80, 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 85:15, 90:10, 95:5, or 99:1 *in vitro* or *in vivo*. The guide to passenger ratio refers to the ratio of the guide strands to the passenger strands after intracellular processing of the pri-microRNA. For example, a 80:20 guide-to-passenger ratio would have 8 guide strands to every 2 passenger strands processed from the precursor. As a non-limiting example, the guide-to-passenger strand ratio is 8:2 *in vitro*. As a non-limiting example, the guide-to-passenger strand ratio is 8:2 *in vivo*. As a non-limiting example, the guide-to-passenger strand ratio is 9:1 *in vitro*. As a non-limiting example, the guide-to-passenger strand ratio is 9:1 *in vivo*.

[00332] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 1.

[00333] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 2.

[00334] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 5.

[00335] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 10.

[00336] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 20.

[00337] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 50.

[00338] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 3:1.

[00339] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 5:1.

[00340] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 10:1.

[00341] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 20:1.

[00342] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 50:1.

[00343] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1;1, 2:10, 2:9, 2:8, 2:7, 2:6, 2:5, 2:4, 2:3, 2:2, 2:1, 3:10, 3:9, 3:8, 3:7, 3:6, 3:5, 3:4, 3:3, 3:2, 3:1, 4:10, 4:9, 4:8, 4:7, 4:6, 4:5, 4:4, 4:3, 4:2, 4:1, 5:10, 5:9, 5:8, 5:7, 5:6, 5:5, 5:4, 5:3, 5:2, 5:1, 6:10, 6:9, 6:8, 6:7, 6:6, 6:5, 6:4, 6:3, 6:2, 6:1, 7:10, 7:9, 7:8, 7:7, 7:6, 7:5, 7:4, 7:3, 7:2, 7:1, 8:10, 8:9, 8:8, 8:7, 8:6, 8:5, 8:4, 8:3, 8:2, 8:1, 9:10, 9:9, 9:8, 9:7, 9:6, 9:5, 9:4, 9:3, 9:2, 9:1, 10:10, 10:9, 10:8, 10:7, 10:6, 10:5, 10:4, 10:3, 10:2, 10:1, 1:99, 5:95, 10:90, 15:85, 20:80, 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 85:15, 90:10, 95:5, or 99:1 *in vitro* or *in vivo*. The passenger to guide ratio refers to the ratio of the passenger strands to the guide strands after the intracellular processing of the pri-microRNA. For example, a 80:20 of passenger-to-guide ratio would have 8 passenger strands to every 2 guide strands processed from the precursor. As a non-limiting example, the passenger-to-guide strand ratio is 80:20 *in vitro*. As a non-limiting example, the passenger-to-guide strand ratio is 80:20 *in vivo*. As a non-limiting example, the passenger-to-guide strand ratio is 8:2 *in vitro*. As a non-limiting example, the passenger-to-guide

strand ratio is 8:2 *in vivo*. As a non-limiting example, the passenger-to-guide strand ratio is 9:1 *in vitro*. As a non-limiting example, the passenger-to-guide strand ratio is 9:1 *in vivo*.

[00344] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 1.

[00345] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 2.

[00346] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 5.

[00347] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 10.

[00348] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 20.

[00349] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 50.

[00350] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 3:1.

[00351] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 5:1.

[00352] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 10:1.

[00353] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 20:1.

[00354] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 50:1.

[00355] In one embodiment, a passenger-guide strand duplex is considered effective when the pri- or pre-microRNAs demonstrate, but methods known in the art and described herein, greater than 2-fold guide to passenger strand ratio when processing is measured. As a non-limiting examples, the pri- or pre-microRNAs demonstrate great than 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, or 2 to 5-fold, 2 to 10-fold, 2 to 15-fold, 3 to 5-fold, 3 to 10-fold, 3 to 15-fold, 4 to 5-fold, 4 to 10-fold, 4 to 15-fold, 5 to 10-fold, 5 to 15-fold, 6 to 10-fold, 6 to 15-fold, 7 to 10-fold, 7 to 15-fold, 8 to 10-fold, 8 to 15-fold, 9 to 10-fold, 9 to 15-fold, 10 to 15-fold, 11 to 15-fold, 12 to 15-fold, 13 to 15-fold, or 14 to 15-fold guide to passenger strand ratio when processing is measured.

[00356] In one embodiment, the vector genome encoding the dsRNA comprises a sequence which is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more than 99% of the full length of the construct. As a non-limiting example, the vector genome comprises a sequence which is at least 80% of the full length sequence of the construct.

[00357] In one embodiment, the siRNA molecules may be used to silence wild type or mutant HTT by targeting at least one exon on the htt sequence. The exon may be exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, exon 16, exon 17, exon 18, exon 19, exon 20, exon 21, exon 22, exon 23, exon 24, exon 25, exon 26, exon 27, exon 28, exon 29, exon 30, exon 31, exon 32, exon 33, exon 34, exon 35, exon 36, exon 37, exon 38, exon 39, exon 40, exon 41, exon 42, exon 43, exon 44, exon 45, exon 46, exon 47, exon 48, exon 49, exon 50, exon 51, exon 52, exon 53, exon 54, exon 55, exon 56, exon 57, exon 58, exon 59, exon 60, exon 61, exon 62, exon 63, exon 64, exon 65, exon 66, and/or exon 67. As a non-limiting example, the siRNA molecules may be used to silence wild type or mutant HTT by targeting exon 1. As another non-limiting example, the siRNA molecules may be used to silence wild type or mutant HTT by targeting an exon other than exon 1. As another non-limiting example, the siRNA molecules may be used to silence wild type or mutant HTT by targeting exon 50. As another non-limiting example, the siRNA molecules may be used to silence wild type or mutant HTT by targeting exon 67.

[00358] In one embodiment, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting at least one exon on the htt sequence. The exon may be exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, exon 16, exon 17, exon 18, exon 19, exon 20, exon 21, exon 22, exon 23, exon 24, exon 25, exon 26, exon 27, exon 28, exon 29, exon 30, exon 31, exon 32, exon 33, exon 34, exon 35, exon 36, exon 37, exon 38, exon 39, exon 40, exon 41, exon 42, exon 43, exon 44, exon 45, exon 46, exon 47, exon 48, exon 49, exon 50, exon 51, exon 52, exon 53, exon 54, exon 55, exon 56, exon 57, exon 58, exon 59, exon 60, exon 61, exon 62, exon 63, exon 64, exon 65, exon 66, and/or exon 67. As a non-limiting example, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting exon 1. As another non-limiting example, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting an exon other than exon 1. As another non-limiting example, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting exon 50. As another non-limiting example, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting exon 67.

siRNA modification

[00359] In some embodiments, the siRNA molecules of the present invention, when not delivered as a precursor or DNA, may be chemically modified to modulate some features of RNA molecules, such as, but not limited to, increasing the stability of siRNAs *in vivo*. The chemically modified siRNA molecules can be used in human therapeutic applications, and are improved without compromising the RNAi activity of the siRNA molecules. As a non-limiting example, the siRNA molecules modified at both the 3′ and the 5′ end of both the sense strand and the antisense strand.

[00360] In some aspects, the siRNA duplexes of the present invention may contain one or more modified nucleotides such as, but not limited to, sugar modified nucleotides, nucleobase modifications and/or backbone modifications. In some aspects, the siRNA molecule may contain combined modifications, for example, combined nucleobase and backbone modifications.

[00361] In one embodiment, the modified nucleotide may be a sugar-modified nucleotide. Sugar modified nucleotides include, but are not limited to 2′-fluoro, 2′-amino and 2′-thio modified ribonucleotides, e.g. 2′-fluoro modified ribonucleotides. Modified nucleotides may be modified on the sugar moiety, as well as nucleotides having sugars or analogs thereof that are not ribosyl. For example, the sugar moieties may be, or be based on, mannoses, arabinoses, glucopyranoses, galactopyranoses, 4′-thioribose, and other sugars, heterocycles, or carbocycles.

[00362] In one embodiment, the modified nucleotide may be a nucleobase-modified nucleotide.

[00363] In one embodiment, the modified nucleotide may be a backbone-modified nucleotide. In some embodiments, the siRNA duplexes of the present invention may further comprise other modifications on the backbone. A normal “backbone”, as used herein, refers to the repeating alternating sugar-phosphate sequences in a DNA or RNA molecule. The deoxyribose/ribose sugars are joined at both the 3'-hydroxyl and 5'-hydroxyl groups to phosphate groups in ester links, also known as "phosphodiester" bonds/linker (PO linkage). The PO backbones may be modified as “phosphorothioate backbone (PS linkage). In some cases, the natural phosphodiester bonds may be replaced by amide bonds but the four atoms between two sugar units are kept. Such amide modifications can facilitate the solid phase synthesis of oligonucleotides and increase the thermodynamic stability of a duplex formed with siRNA complement. See e.g. Mesmaeker et al., *Pure & Appl. Chem.*, 1997, 3, 437-440; the content of which is incorporated herein by reference in its entirety.

[00364] Modified bases refer to nucleotide bases such as, for example, adenine, guanine, cytosine, thymine, uracil, xanthine, inosine, and queuosine that have been modified by the replacement or addition of one or more atoms or groups. Some examples of modifications on the

nucleobase moieties include, but are not limited to, alkylated, halogenated, thiolated, aminated, amidated, or acetylated bases, individually or in combination. More specific examples include, for example, 5-propynyluridine, 5-propynylcytidine, 6-methyladenine, 6-methylguanine, N,N,-dimethyladenine, 2-propyladenine, 2-propylguanine, 2-aminoadenine, 1-methylinosine, 3-methyluridine, 5-methylcytidine, 5-methyluridine and other nucleotides having a modification at the 5 position, 5-(2-amino)propyl uridine, 5-halocytidine, 5-halouridine, 4-acetylcytidine, 1-methyladenosine, 2-methyladenosine, 3-methylcytidine, 6-methyluridine, 2-methylguanosine, 7-methylguanosine, 2,2-dimethylguanosine, 5-methylaminoethyluridine, 5-methyloxyuridine, deazanucleotides such as 7-deaza-adenosine, 6-azouridine, 6-azocytidine, 6-azothymidine, 5-methyl-2-thiouridine, other thio bases such as 2-thiouridine and 4-thiouridine and 2-thiocytidine, dihydrouridine, pseudouridine, queuosine, archaeosine, naphthyl and substituted naphthyl groups, any O- and N-alkylated purines and pyrimidines such as N6-methyladenosine, 5-methylcarbonylmethyluridine, uridine 5-oxyacetic acid, pyridine-4-one, pyridine-2-one, phenyl and modified phenyl groups such as aminophenol or 2,4,6-trimethoxy benzene, modified cytosines that act as G-clamp nucleotides, 8-substituted adenines and guanines, 5-substituted uracils and thymines, azapyrimidines, carboxyhydroxyalkyl nucleotides, carboxyalkylaminoalkyl nucleotides, and alkylcarbonylalkylated nucleotides.

[00365] In one embodiment, the modified nucleotides may be on just the sense strand.

[00366] In another embodiment, the modified nucleotides may be on just the antisense strand.

[00367] In some embodiments, the modified nucleotides may be in both the sense and antisense strands.

[00368] In some embodiments, the chemically modified nucleotide does not affect the ability of the antisense strand to pair with the target mRNA sequence, such as the HTT mRNA sequence.

[00369] In one embodiment, the AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may encode siRNA molecules which are polycistronic molecules. The siRNA molecules may additionally comprise one or more linkers between regions of the siRNA molecules.

Molecular Scaffold

[00370] In one embodiment, the siRNA molecules may be encoded in a modulatory polynucleotide which also comprises a molecular scaffold. As used herein a "molecular scaffold" is a framework or starting molecule that forms the sequence or structural basis against which to design or make a subsequent molecule.

[00371] In one embodiment, the molecular scaffold comprises at least one 5' flanking region. As a non-limiting example, the 5' flanking region may comprise a 5' flanking sequence which may be of any length and may be derived in whole or in part from wild type microRNA sequence or be a completely artificial sequence.

[00372] In one embodiment, the molecular scaffold comprises at least one 3' flanking region. As a non-limiting example, the 3' flanking region may comprise a 3' flanking sequence which may be of any length and may be derived in whole or in part from wild type microRNA sequence or be a completely artificial sequence.

[00373] In one embodiment, the molecular scaffold comprises at least one loop motif region. As a non-limiting example, the loop motif region may comprise a sequence which may be of any length.

[00374] In one embodiment, the molecular scaffold comprises a 5' flanking region, a loop motif region and/or a 3' flanking region.

[00375] In one embodiment, at least one siRNA, miRNA or other RNAi agent described herein, may be encoded by a modulatory polynucleotide which may also comprise at least one molecular scaffold. The molecular scaffold may comprise a 5' flanking sequence which may be of any length and may be derived in whole or in part from wild type microRNA sequence or be completely artificial. The 3' flanking sequence may mirror the 5' flanking sequence and/or a 3' flanking sequence in size and origin. Either flanking sequence may be absent. The 3' flanking sequence may optionally contain one or more CNNC motifs, where "N" represents any nucleotide.

[00376] Forming the stem of a stem loop structure is a minimum of the modulatory polynucleotide encoding at least one siRNA, miRNA or other RNAi agent described herein. In some embodiments, the siRNA, miRNA or other RNAi agent described herein comprises at least one nucleic acid sequence which is in part complementary or will hybridize to a target sequence. In some embodiments the payload is an siRNA molecule or fragment of an siRNA molecule.

[00377] In some embodiments, the 5' arm of the stem loop structure of the modulatory polynucleotide comprises a nucleic acid sequence encoding a sense sequence. Non-limiting examples of sense sequences, or fragments or variants thereof, which may be encoded by the modulatory polynucleotide are described in Table 3.

[00378] In some embodiments, the 3' arm of the stem loop of the modulatory polynucleotide comprises a nucleic acid sequence encoding an antisense sequence. The antisense sequence, in some instances, comprises a "G" nucleotide at the 5' most end. Non-limiting examples of

antisense sequences, or fragments or variants thereof, which may be encoded by the modulatory polynucleotide are described in Table 2.

[00379] In other embodiments, the sense sequence may reside on the 3' arm while the antisense sequence resides on the 5' arm of the stem of the stem loop structure of the modulatory polynucleotide. Non-limiting examples of sense and antisense sequences which may be encoded by the modulatory polynucleotide are described in Tables 2 and 3.

[00380] In one embodiment, the sense and antisense sequences may be completely complementary across a substantial portion of their length. In other embodiments the sense sequence and antisense sequence may be at least 70, 80, 90, 95 or 99% complementarity across independently at least 50, 60, 70, 80, 85, 90, 95, or 99 % of the length of the strands.

[00381] Neither the identity of the sense sequence nor the homology of the antisense sequence need to be 100% complementarity to the target sequence.

[00382] In one embodiment, separating the sense and antisense sequence of the stem loop structure of the modulatory polynucleotide is a loop sequence (also known as a loop motif, linker or linker motif). The loop sequence may be of any length, between 4-30 nucleotides, between 4-20 nucleotides, between 4-15 nucleotides, between 5-15 nucleotides, between 6-12 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, 10 nucleotides, 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, and/or 15 nucleotides.

[00383] In some embodiments, the loop sequence comprises a nucleic acid sequence encoding at least one UGUG motif. In some embodiments, the nucleic acid sequence encoding the UGUG motif is located at the 5' terminus of the loop sequence.

[00384] In one embodiment, spacer regions may be present in the modulatory polynucleotide to separate one or more modules (e.g., 5' flanking region, loop motif region, 3' flanking region, sense sequence, antisense sequence) from one another. There may be one or more such spacer regions present.

[00385] In one embodiment, a spacer region of between 8-20, i.e., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides may be present between the sense sequence and a flanking region sequence.

[00386] In one embodiment, the length of the spacer region is 13 nucleotides and is located between the 5' terminus of the sense sequence and the 3' terminus of the flanking sequence. In one embodiment, a spacer is of sufficient length to form approximately one helical turn of the sequence.

[00387] In one embodiment, a spacer region of between 8-20, i.e., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides may be present between the antisense sequence and a flanking sequence.

[00388] In one embodiment, the spacer sequence is between 10-13, i.e., 10, 11, 12 or 13 nucleotides and is located between the 3' terminus of the antisense sequence and the 5' terminus of a flanking sequence. In one embodiment, a spacer is of sufficient length to form approximately one helical turn of the sequence.

[00389] In one embodiment, the molecular scaffold of the modulatory polynucleotide comprises in the 5' to 3' direction, a 5' flanking sequence, a 5' arm, a loop motif, a 3' arm and a 3' flanking sequence. As a non-limiting example, the 5' arm may comprise a nucleic acid sequence encoding a sense sequence and the 3' arm comprises a nucleic acid sequence encoding the antisense sequence. In another non-limiting example, the 5' arm comprises a nucleic acid sequence encoding the antisense sequence and the 3' arm comprises a nucleic acid sequence encoding the sense sequence.

[00390] In one embodiment, the 5' arm, sense and/or antisense sequence, loop motif and/or 3' arm sequence may be altered (e.g., substituting 1 or more nucleotides, adding nucleotides and/or deleting nucleotides). The alteration may cause a beneficial change in the function of the construct (e.g., increase knock-down of the target sequence, reduce degradation of the construct, reduce off target effect, increase efficiency of the payload, and reduce degradation of the payload).

[00391] In one embodiment, the molecular scaffold of the modulatory polynucleotides is aligned in order to have the rate of excision of the guide strand (also referred to herein as the antisense strand) be greater than the rate of excision of the passenger strand (also referred to herein as the sense strand). The rate of excision of the guide or passenger strand may be, independently, 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more than 99%. As a non-limiting example, the rate of excision of the guide strand is at least 80%. As another non-limiting example, the rate of excision of the guide strand is at least 90%.

[00392] In one embodiment, the rate of excision of the guide strand is greater than the rate of excision of the passenger strand. In one aspect, the rate of excision of the guide strand may be at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more than 99% greater than the passenger strand.

[00393] In one embodiment, the efficiency of excision of the guide strand is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more than 99%. As a non-limiting example, the efficiency of the excision of the guide strand is greater than 80%.

[00394] In one embodiment, the efficiency of the excision of the guide strand is greater than the excision of the passenger strand from the molecular scaffold. The excision of the guide strand may be 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 times more efficient than the excision of the passenger strand from the molecular scaffold.

[00395] In one embodiment, the molecular scaffold comprises a dual-function targeting modulatory polynucleotide. As used herein, a "dual-function targeting" modulatory polynucleotide is a polynucleotide where both the guide and passenger strands knock down the same target or the guide and passenger strands knock down different targets.

[00396] In one embodiment, the molecular scaffold of the modulatory polynucleotides described herein may comprise a 5' flanking region, a loop motif region and a 3' flanking region. Non-limiting examples of the sequences for the 5' flanking region, loop motif region (may also be referred to as a linker region) and the 3' flanking region which may be used, or fragments thereof used, in the modulatory polynucleotides described herein are shown in Tables 7 –9.

Table 7. 5' Flanking Regions for Molecular Scaffold

5' Flanking Region Name	5' Flanking Region Sequence	5' Flanking Region SEQ ID
5F3	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGC AGAACACCATGCGCTCCACGGAA	1163
5F1	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGC AGAACACCATGCGCTCTTCGGAA	1161
5F2	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTG AGCTGAGTGGGCCAGGGACTGGGAGAAGGAG TGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGA	1162
5F4	GGGCCCTCCCGCAGAACACCATGCGCTCCAC GGAA	1164
5F5	CTCCCGCAGAACACCATGCGCTCCACGGAA	1165
5F6	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGC AGAACACCATGCGCTCCACGGAAG	1166
5F7	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGC AGAACACCATGCGCTCCTCGGAA	1167

Table 8. Loop Motif Regions for Molecular Scaffold

Loop Motif Region Name	Loop Motif Region Sequence	Loop Motif Region SEQ ID
L5	GTGGCCACTGAGAAG	1172
L1	TGTGACCTGG	1168
L2	TGTGATTTGG	1169
L3	GTCTGCACCTGTCACTAG	1170

L4	GTGACCCAAG	1171
L6	GTGACCCAAT	1173
L7	GTGACCCAAC	1174
L8	GTGGCCACTGAGAAA	1175

Table 9. 3' Flanking Regions for Molecular Scaffold

3' Flanking Region Name	3' Flanking Region Sequence	3' Flanking Region SEQ ID
3F1	CTGAGGAGCGCCTTGACAGCAGCCATGGGAG GGCCGCCCCCTACCTCAGTGA	1178
3F2	CTGTGGAGCGCCTTGACAGCAGCCATGGGAG GGCCGCCCCCTACCTCAGTGA	1179
3F3	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCC TCCTCAGCATTGCAATTCCTCTCCCATCTGGG CACCAGTCAGCTACCCTGGTGGGAATCTGGGT AGCC	1180
3F4	CTGAGGAGCGCCTTGACAGCAGCCATGGGAG GGCC	1181
3F5	CTGCGGAGCGCCTTGACAGCAGCCATGGGAG GGCCGCCCCCTACCTCAGTGA	1182

[00397] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region, fragment or variant thereof listed in Table 7. As a non-limiting example, the 5' flanking region may be 5F1, 5F2, 5F3, 5F4, 5F5, 5F6, or 5F7.

[00398] In one embodiment, the molecular scaffold may comprise at least one 5F1 flanking region.

[00399] In one embodiment, the molecular scaffold may comprise at least one 5F2 flanking region.

[00400] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region.

[00401] In one embodiment, the molecular scaffold may comprise at least one 5F4 flanking region.

[00402] In one embodiment, the molecular scaffold may comprise at least one 5F5 flanking region.

[00403] In one embodiment, the molecular scaffold may comprise at least one 5F6 flanking region.

[00404] In one embodiment, the molecular scaffold may comprise at least one 5F7 flanking region.

[00405] In one embodiment, the molecular scaffold may comprise at least one loop motif region, fragment or variant thereof listed in Table 8. As a non-limiting example, the loop motif region may be L1, L2, L3, L4, L5, L6, L7, or L8.

[00406] In one embodiment, the molecular scaffold may comprise at least one L1 loop motif region.

[00407] In one embodiment, the molecular scaffold may comprise at least one L2 loop motif region.

[00408] In one embodiment, the molecular scaffold may comprise at least one L3 loop motif region.

[00409] In one embodiment, the molecular scaffold may comprise at least one L4 loop motif region.

[00410] In one embodiment, the molecular scaffold may comprise at least one L5 loop motif region.

[00411] In one embodiment, the molecular scaffold may comprise at least one L6 loop motif region.

[00412] In one embodiment, the molecular scaffold may comprise at least one L7 loop motif region.

[00413] In one embodiment, the molecular scaffold may comprise at least one L8 loop motif region.

[00414] In one embodiment, the molecular scaffold may comprise at least one 3' flanking region, fragment or variant thereof listed in Table 9. As a non-limiting example, the 3' flanking region may be 3F1, 3F2, 3F3, 3F4, or 3F5.

[00415] In one embodiment, the molecular scaffold may comprise at least one 3F1 flanking region.

[00416] In one embodiment, the molecular scaffold may comprise at least one 3F2 flanking region.

[00417] In one embodiment, the molecular scaffold may comprise at least one 3F3 flanking region.

[00418] In one embodiment, the molecular scaffold may comprise at least one 3F4 flanking region.

[00419] In one embodiment, the molecular scaffold may comprise at least one 3F5 flanking region.

[00420] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region, fragment or variant thereof, and at least one loop motif region, fragment or variant thereof, as described in Tables 7 and 8. As a non-limiting example, the 5' flanking region and the loop motif region may be 5F1 and L1, 5F1 and L2, 5F1 and L3, 5F1 and L4, 5F1 and L5,

5F1 and L6, 5F1 and L7, 5F1 and L8, 5F2 and L1, 5F2 and L2, 5F2 and L3, 5F2 and L4, 5F2 and L5, 5F2 and L6, 5F2 and L7, 5F2 and L8, 5F3 and L1, 5F3 and L2, 5F3 and L3, 5F3 and L4, 5F3 and L5, 5F3 and L6, 5F3 and L7, 5F3 and L8, 5F4 and L1, 5F4 and L2, 5F4 and L3, 5F4 and L4, 5F4 and L5, 5F4 and L6, 5F4 and L7, 5F4 and L8, 5F5 and L1, 5F5 and L2, 5F5 and L3, 5F5 and L4, 5F5 and L5, 5F5 and L6, 5F5 and L7, 5F5 and L8, 5F6 and L1, 5F6 and L2, 5F6 and L3, 5F6 and L4, 5F6 and L5, 5F6 and L6, 5F6 and L7, 5F6 and L8, 5F7 and L1, 5F7 and L2, 5F7 and L3, 5F7 and L4, 5F7 and L5, 5F7 and L6, 5F7 and L7, and 5F7 and L8.

[00421] In one embodiment, the molecular scaffold may comprise at least one 5F2 flanking region and at least one L1 loop motif region.

[00422] In one embodiment, the molecular scaffold may comprise at least one 5F1 flanking region and at least one L4 loop motif region.

[00423] In one embodiment, the molecular scaffold may comprise at least one 5F7 flanking region and at least one L8 loop motif region.

[00424] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region and at least one L4 loop motif region.

[00425] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region and at least one L5 loop motif region.

[00426] In one embodiment, the molecular scaffold may comprise at least one 5F4 flanking region and at least one L4 loop motif region.

[00427] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region and at least one L7 loop motif region.

[00428] In one embodiment, the molecular scaffold may comprise at least one 5F5 flanking region and at least one L4 loop motif region.

[00429] In one embodiment, the molecular scaffold may comprise at least one 5F6 flanking region and at least one L4 loop motif region.

[00430] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region and at least one L6 loop motif region.

[00431] In one embodiment, the molecular scaffold may comprise at least one 5F7 flanking region and at least one L4 loop motif region.

[00432] In one embodiment, the molecular scaffold may comprise at least one 5F2 flanking region and at least one L2 loop motif region.

[00433] In one embodiment, the molecular scaffold may comprise at least one 5F1 flanking region and at least one L1 loop motif region.

[00434] In one embodiment, the molecular scaffold may comprise at least one 5F1 flanking region and at least one L2 loop motif region.

[00435] In one embodiment, the molecular scaffold may comprise at least one 3' flanking region, fragment or variant thereof, and at least one motif region, fragment or variant thereof, as described in Tables 8 and 9. As a non-limiting example, the 3' flanking region and the loop motif region may be 3F1 and L1, 3F1 and L2, 3F1 and L3, 3F1 and L4, 3F1 and L5, 3F1 and L6, 3F1 and L7, 3F1 and L8, 3F2 and L1, 3F2 and L2, 3F2 and L3, 3F2 and L4, 3F2 and L5, 3F2 and L6, 3F2 and L7, 3F2 and L8, 3F3 and L1, 3F3 and L2, 3F3 and L3, 3F3 and L4, 3F3 and L5, 3F3 and L6, 3F3 and L7, 3F3 and L8, 3F4 and L1, 3F4 and L2, 3F4 and L3, 3F4 and L4, 3F4 and L5, 3F4 and L6, 3F4 and L7, 3F4 and L8, 3F5 and L1, 3F5 and L2, 3F5 and L3, 3F5 and L4, 3F5 and L5, 3F5 and L6, 3F5 and L7, and 3F5 and L8.

[00436] In one embodiment, the molecular scaffold may comprise at least one L1 loop motif region and at least one 3F2 flanking region.

[00437] In one embodiment, the molecular scaffold may comprise at least one L4 loop motif region and at least one 3F1 flanking region.

[00438] In one embodiment, the molecular scaffold may comprise at least one L8 loop motif region and at least one 3F5 flanking region.

[00439] In one embodiment, the molecular scaffold may comprise at least one L5 loop motif region and at least 3F1 flanking region.

[00440] In one embodiment, the molecular scaffold may comprise at least one L4 loop motif region and at least one 3F4 flanking region.

[00441] In one embodiment, the molecular scaffold may comprise at least one L7 loop motif region and at least one 3F1 flanking region.

[00442] In one embodiment, the molecular scaffold may comprise at least one L6 loop motif region and at least one 3F1 flanking region.

[00443] In one embodiment, the molecular scaffold may comprise at least one L4 loop motif region and at least one 3F5 flanking region.

[00444] In one embodiment, the molecular scaffold may comprise at least one L2 loop motif region and at least one 3F2 flanking region.

[00445] In one embodiment, the molecular scaffold may comprise at least one L1 loop motif region and at least one 3F3 flanking region.

[00446] In one embodiment, the molecular scaffold may comprise at least one L5 loop motif region and at least one 3F4 flanking region.

[00447] In one embodiment, the molecular scaffold may comprise at least one L1 loop motif region and at least one 3F1 flanking region.

[00448] In one embodiment, the molecular scaffold may comprise at least one L2 loop motif region and at least one 3F1 flanking region.

[00449] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region, fragment or variant thereof, and at least one 3' flanking region, fragment or variant thereof, as described in Tables 7 and 9. As a non-limiting example, the flanking regions may be 5F1 and 3F1, 5F1 and 3F2, 5F1 and 3F3, 5F1 and 3F4, 5F1 and 3F5, 5F2 and 3F1, 5F2 and 3F2, 5F2 and 3F3, 5F2 and 3F4, 5F2 and 3F5, 5F3 and 3F1, 5F3 and 3F2, 5F3 and 3F3, 5F3 and 3F4, 5F3 and 3F5, 5F4 and 3F1, 5F4 and 3F2, 5F4 and 3F3, 5F4 and 3F4, 5F4 and 3F5, 5F5 and 3F1, 5F5 and 3F2, 5F5 and 3F3, 5F5 and 3F4, 5F5 and 3F5, 5F6 and 3F1, 5F6 and 3F2, 5F6 and 3F3, 5F6 and 3F4, 5F6 and 3F5, 5F7 and 3F1, 5F7 and 3F2, 5F7 and 3F3, 5F7 and 3F4, and 5F7 and 3F5.

[00450] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region and at least one 3F2 3' flanking region.

[00451] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region and at least one 3F1 3' flanking region.

[00452] In one embodiment, the molecular scaffold may comprise at least one 5F7 5' flanking region and at least one 3F5 3' flanking region.

[00453] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region and at least one 3F1 3' flanking region.

[00454] In one embodiment, the molecular scaffold may comprise at least one 5F4 5' flanking region and at least one 3F4 3' flanking region.

[00455] In one embodiment, the molecular scaffold may comprise at least one 5F5 5' flanking region and at least one 3F4 3' flanking region.

[00456] In one embodiment, the molecular scaffold may comprise at least one 5F6 5' flanking region and at least one 3F1 3' flanking region.

[00457] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region and at least one 3F3 3' flanking region.

[00458] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region and at least one 3F4 3' flanking region.

[00459] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region and at least one 3F2 3' flanking region.

[00460] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region, fragment or variant thereof, at least one loop motif region, fragment or variant thereof, and at least one 3' flanking region as described in Tables 7 – 9. As a non-limiting example, the flanking and loop motif regions may be 5F1, L1 and 3F1; 5F1, L1 and 3F2; 5F1, L1 and 3F3; 5F1, L1 and 3F4; 5F1, L1 and 3F5; 5F2, L1 and 3F1; 5F2, L1 and 3F2; 5F2, L1 and 3F3; 5F2, L1 and 3F4; 5F2, L1 and 3F5; 5F3, L1 and 3F3; 5F3, L1 and 3F2; 5F3, L1 and 3F3; 5F3, L1 and 3F4; 5F3, L1 and 3F5; 5F4, L1 and 3F4; 5F4, L1 and 3F2; 5F4, L1 and 3F3; 5F4, L1 and 3F4; 5F4, L1 and 3F5; 5F5, L1 and 3F1; 5F5, L1 and 3F2; 5F5, L1 and 3F3; 5F5, L1 and 3F4; 5F5, L1 and 3F5; 5F6, L1 and 3F1; 5F6, L1 and 3F2; 5F6, L1 and 3F3; 5F6, L1 and 3F4; 5F6, L1 and 3F5; 5F7, L1 and 3F1; 5F7, L1 and 3F2; 5F7, L1 and 3F3; 5F7, L1 and 3F4; 5F7, L1 and 3F5; 5F1, L2 and 3F1; 5F1, L2 and 3F2; 5F1, L2 and 3F3; 5F1, L2 and 3F4; 5F1, L2 and 3F5; 5F2, L2 and 3F1; 5F2, L2 and 3F2; 5F2, L2 and 3F3; 5F2, L2 and 3F4; 5F2, L2 and 3F5; 5F3, L2 and 3F1; 5F3, L2 and 3F2; 5F3, L2 and 3F3; 5F3, L2 and 3F4; 5F3, L2 and 3F5; 5F4, L2 and 3F1; 5F4, L2 and 3F2; 5F4, L2 and 3F3; 5F4, L2 and 3F4; 5F4, L2 and 3F5; 5F5, L2 and 3F1; 5F5, L2 and 3F2; 5F5, L2 and 3F3; 5F5, L2 and 3F4; 5F5, L2 and 3F5; 5F6, L2 and 3F1; 5F6, L2 and 3F2; 5F6, L2 and 3F3; 5F6, L2 and 3F4; 5F6, L2 and 3F5; 5F7, L2 and 3F1; 5F7, L2 and 3F2; 5F7, L2 and 3F3; 5F7, L2 and 3F4; 5F7, L2 and 3F5; 5F1, L3 and 3F1; 5F1, L3 and 3F2; 5F1, L3 and 3F3; 5F1, L3 and 3F4; 5F1, L3 and 3F5; 5F2, L3 and 3F1; 5F2, L3 and 3F2; 5F2, L3 and 3F3; 5F2, L3 and 3F4; 5F2, L3 and 3F5; 5F3, L3 and 3F1; 5F3, L3 and 3F2; 5F3, L3 and 3F3; 5F3, L3 and 3F4; 5F3, L3 and 3F5; 5F4, L3 and 3F1; 5F4, L3 and 3F2; 5F4, L3 and 3F3; 5F4, L3 and 3F4; 5F4, L3 and 3F5; 5F5, L3 and 3F1; 5F5, L3 and 3F2; 5F5, L3 and 3F3; 5F5, L3 and 3F4; 5F5, L3 and 3F5; 5F6, L3 and 3F1; 5F6, L3 and 3F2; 5F6, L3 and 3F3; 5F6, L3 and 3F4; 5F6, L3 and 3F5; 5F7, L3 and 3F1; 5F7, L3 and 3F2; 5F7, L3 and 3F3; 5F7, L3 and 3F4; 5F7, L3 and 3F5; 5F1, L4 and 3F1; 5F1, L4 and 3F2; 5F1, L4 and 3F3; 5F1, L4 and 3F4; 5F1, L4 and 3F5; 5F2, L4 and 3F1; 5F2, L4 and 3F2; 5F2, L4 and 3F3; 5F2, L4 and 3F4; 5F2, L4 and 3F5; 5F3, L4 and 3F1; 5F3, L4 and 3F2; 5F3, L4 and 3F3; 5F3, L4 and 3F4; 5F3, L4 and 3F5; 5F4, L4 and 3F1; 5F4, L4 and 3F2; 5F4, L4 and 3F3; 5F4, L4 and 3F4; 5F4, L4 and 3F5; 5F5, L4 and 3F1; 5F5, L4 and 3F2; 5F5, L4 and 3F3; 5F5, L4 and 3F4; 5F5, L4 and 3F5; 5F6, L4 and 3F1; 5F6, L4 and 3F2; 5F6, L4 and 3F3; 5F6, L4 and 3F4; 5F6, L4 and 3F5; 5F7, L4 and 3F1; 5F7, L4 and 3F2; 5F7, L4 and 3F3; 5F7, L4 and 3F4; 5F7, L4 and 3F5; 5F1, L5 and 3F1; 5F1, L5 and 3F2; 5F1, L5 and 3F3; 5F1, L5 and 3F4; 5F1, L5 and 3F5; 5F2, L5 and 3F1; 5F2, L5 and 3F2; 5F2, L5 and 3F3; 5F2, L5 and 3F4; 5F2, L5 and 3F5; 5F3, L5 and 3F1; 5F3, L5 and 3F2; 5F3, L5 and 3F3; 5F3, L5 and 3F4; 5F3, L5 and 3F5; 5F4, L5 and 3F1; 5F4, L5 and 3F2; 5F4, L5 and

3F3; 5F4, L5 and 3F4; 5F4, L5 and 3F5; 5F5, L5 and 3F1; 5F5, L5 and 3F2; 5F5, L5 and 3F3; 5F5, L5 and 3F4; 5F5, L5 and 3F5; 5F6, L5 and 3F1; 5F6, L5 and 3F2; 5F6, L5 and 3F3; 5F6, L5 and 3F4; 5F6, L5 and 3F5; 5F7, L5 and 3F1; 5F7, L5 and 3F2; 5F7, L5 and 3F3; 5F7, L5 and 3F4; 5F7, L5 and 3F5; 5F1, L6 and 3F1; 5F1, L6 and 3F2; 5F1, L6 and 3F3; 5F1, L6 and 3F4; 5F1, L6 and 3F5; 5F2, L6 and 3F1; 5F2, L6 and 3F2; 5F2, L6 and 3F3; 5F2, L6 and 3F4; 5F2, L6 and 3F5; 5F3, L6 and 3F1; 5F3, L6 and 3F2; 5F3, L6 and 3F3; 5F3, L6 and 3F4; 5F3, L6 and 3F5; 5F4, L6 and 3F1; 5F4, L6 and 3F2; 5F4, L6 and 3F3; 5F4, L6 and 3F4; 5F4, L6 and 3F5; 5F5, L6 and 3F1; 5F5, L6 and 3F2; 5F5, L6 and 3F3; 5F5, L6 and 3F4; 5F5, L6 and 3F5; 5F6, L6 and 3F1; 5F6, L6 and 3F2; 5F6, L6 and 3F3; 5F6, L6 and 3F4; 5F6, L6 and 3F5; 5F7, L6 and 3F1; 5F7, L6 and 3F2; 5F7, L6 and 3F3; 5F7, L6 and 3F4; 5F7, L6 and 3F5; 5F1, L7 and 3F1; 5F1, L7 and 3F2; 5F1, L7 and 3F3; 5F1, L7 and 3F4; 5F1, L7 and 3F5; 5F2, L7 and 3F1; 5F2, L7 and 3F2; 5F2, L7 and 3F3; 5F2, L7 and 3F4; 5F2, L7 and 3F5; 5F3, L7 and 3F1; 5F3, L7 and 3F2; 5F3, L7 and 3F3; 5F3, L7 and 3F4; 5F3, L7 and 3F5; 5F4, L7 and 3F1; 5F4, L7 and 3F2; 5F4, L7 and 3F3; 5F4, L7 and 3F4; 5F4, L7 and 3F5; 5F5, L7 and 3F1; 5F5, L7 and 3F2; 5F5, L7 and 3F3; 5F5, L7 and 3F4; 5F5, L7 and 3F5; 5F6, L7 and 3F1; 5F6, L7 and 3F2; 5F6, L7 and 3F3; 5F6, L7 and 3F4; 5F6, L7 and 3F5; 5F7, L7 and 3F1; 5F7, L7 and 3F2; 5F7, L7 and 3F3; 5F7, L7 and 3F4; 5F7, L7 and 3F5; 5F1, L8 and 3F1; 5F1, L8 and 3F2; 5F1, L8 and 3F3; 5F1, L8 and 3F4; 5F1, L8 and 3F5; 5F2, L8 and 3F1; 5F2, L8 and 3F2; 5F2, L8 and 3F3; 5F2, L8 and 3F4; 5F2, L8 and 3F5; 5F3, L8 and 3F1; 5F3, L8 and 3F2; 5F3, L8 and 3F3; 5F3, L8 and 3F4; 5F3, L8 and 3F5; 5F4, L8 and 3F1; 5F4, L8 and 3F2; 5F4, L8 and 3F3; 5F4, L8 and 3F4; 5F4, L8 and 3F5; 5F5, L8 and 3F1; 5F5, L8 and 3F2; 5F5, L8 and 3F3; 5F5, L8 and 3F4; 5F5, L8 and 3F5; 5F6, L8 and 3F1; 5F6, L8 and 3F2; 5F6, L8 and 3F3; 5F6, L8 and 3F4; 5F6, L8 and 3F5; 5F7, L8 and 3F1; 5F7, L8 and 3F2; 5F7, L8 and 3F3; 5F7, L8 and 3F4; and 5F7, L8 and 3F5.

[00461] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region, at least one L1 loop motif region, and at least one 3F2 3' flanking region.

[00462] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region, at least one L4 loop motif region, and at least one 3F1 3' flanking region.

[00463] In one embodiment, the molecular scaffold may comprise at least one 5F7 5' flanking region, at least one L8 loop motif region, and at least one 3F5 3' flanking region.

[00464] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L4 loop motif region, and at least one 3F1 3' flanking region.

[00465] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L5 loop motif region, and at least one 3F1 3' flanking region.

[00466] In one embodiment, the molecular scaffold may comprise at least one 5F4 5' flanking region, at least one L4 loop motif region, and at least one 3F4 3' flanking region.

[00467] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L7 loop motif region, and at least one 3F1 3' flanking region.

[00468] In one embodiment, the molecular scaffold may comprise at least one 5F5 5' flanking region, at least one L4 loop motif region, and at least one 3F4 3' flanking region.

[00469] In one embodiment, the molecular scaffold may comprise at least one 5F6 5' flanking region, at least one L4 loop motif region, and at least one 3F1 3' flanking region.

[00470] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L6 loop motif region, and at least one 3F1 3' flanking region.

[00471] In one embodiment, the molecular scaffold may comprise at least one 5F7 5' flanking region, at least one L4 loop motif region, and at least one 3F5 3' flanking region.

[00472] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region, at least one L2 loop motif region, and at least one 3F2 3' flanking region.

[00473] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region, at least one L1 loop motif region, and at least one 3F3 3' flanking region.

[00474] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L5 loop motif region, and at least one 3F4 3' flanking region.

[00475] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region, at least one L1 loop motif region, and at least one 3F1 3' flanking region.

[00476] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region, at least one L2 loop motif region, and at least one 3F1 3' flanking region.

[00477] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region, at least one L1 loop motif region, and at least one 3F2 3' flanking region.

[00478] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region, at least one L3 loop motif region, and at least one 3F3 3' flanking region.

[00479] In one embodiment, the molecular scaffold may be a natural pri-miRNA scaffold. As a non-limiting example, the molecular scaffold may be a scaffold derived from the human miR155 scaffold.

[00480] In one embodiment, the molecular scaffold may comprise one or more linkers known in the art. The linkers may separate regions or one molecular scaffold from another. As a non-limiting example, the molecular scaffold may be polycistronic.

Modulatory Polynucleotide Comprising Molecular Scaffold and siRNA Molecule

[00481] In one embodiment, the modulatory polynucleotide may comprise 5' and 3' flanking regions, loop motif region, and nucleic acid sequences encoding sense sequence and antisense sequence as described in Tables 10 and 11. In Tables 10 and 11, the DNA sequence identifier for the passenger and guide strands are described as well as the 5' and 3' Flanking Regions and the Loop region (also referred to as the linker region). In Tables 10 and 11, the "miR" component of the name of the sequence does not necessarily correspond to the sequence numbering of miRNA genes (e.g., VOYHTmiR-102 is the name of the sequence and does not necessarily mean that miR-102 is part of the sequence).

Table 10. Modulatory Polynucleotide Sequence Region (5' to 3')

Modulatory Polynucleotide Construct Name	5' Flanking to 3' Flanking SEQ ID NO	5' Flanking SEQ ID NO	Passenger SEQ ID NO	Loop SEQ ID NO	Guide SEQ ID NO	3' Flanking SEQ ID NO
VOYHTmiR-102.214	1183	1161	1296	1168	1337	1178
VOYHTmiR-104.214	1184	1161	1303	1168	1337	1178
VOYHTmiR-109.214	1185	1161	1310	1169	1337	1178
VOYHTmiR-114.214	1186	1161	1317	1168	1337	1179
VOYHTmiR-116.214	1187	1161	1310	1168	1337	1179
VOYHTmiR-127.214	1188	1162	1310	1170	1334	1180
VOYHTmiR-102.218	1189	1161	1297	1168	1338	1178
VOYHTmiR-104.218	1190	1161	1304	1168	1338	1178
VOYHTmiR-109.218	1191	1161	1311	1169	1338	1178
VOYHTmiR-114.218	1192	1161	1318	1168	1338	1179
VOYHTmiR-116.218	1193	1161	1311	1168	1338	1179
VOYHTmiR-127.218	1194	1162	1311	1170	1338	1180
VOYHTmiR-102.219.o	1195	1161	1280	1168	1333	1178
VOYHTmiR-104.219.o	1196	1161	1283	1168	1333	1178
VOYHTmiR-109.219.o	1197	1161	1280	1169	1333	1178
VOYHTmiR-114.219	1198	1161	1286	1168	1333	1179
VOYHTmiR-116.219.o	1199	1161	1289	1168	1333	1179
VOYHTmiR-127.219.o	1200	1162	1280	1170	1333	1180
VOYHTmiR-102.219.n	1201	1161	1292	1168	1333	1178
VOYHTmiR-104.219.n	1202	1161	1293	1168	1333	1178
VOYHTmiR-109.219.n	1203	1161	1292	1169	1333	1178
VOYHTmiR-116.219.n	1204	1161	1294	1168	1333	1179
VOYHTmiR-127.219.n	1205	1162	1292	1170	1333	1180
VOYHTmiR-102.257	1206	1161	1298	1168	1339	1178
VOYHTmiR-104.257	1207	1161	1305	1168	1339	1178
VOYHTmiR-109.257	1208	1161	1312	1169	1339	1178
VOYHTmiR-114.257	1209	1161	1319	1168	1339	1179
VOYHTmiR-116.257	1210	1161	1312	1168	1339	1179
VOYHTmiR-127.257	1211	1162	1312	1170	1339	1180
VOYHTmiR-102.894	1212	1161	1281	1168	1334	1178
VOYHTmiR-104.894	1213	1161	1284	1168	1334	1178
VOYHTmiR-109.894	1214	1161	1281	1169	1334	1178
VOYHTmiR-114.894	1215	1161	1287	1168	1334	1179
VOYHTmiR-116.894	1216	1161	1290	1168	1334	1179
VOYHTmiR-127.894	1217	1162	1281	1170	1334	1180
VOYHTmiR-102.907	1218	1161	1301	1168	1342	1178
VOYHTmiR-104.907	1219	1161	1308	1168	1342	1178
VOYHTmiR-109.907	1220	1161	1315	1169	1342	1178

VOYHTmiR-114.907	1221	1161	1322	1168	1342	1179
VOYHTmiR-116.907	1222	1161	1315	1168	1342	1179
VOYHTmiR-127.907	1223	1162	1315	1170	1342	1180
VOYHTmiR-102.372	1224	1161	1299	1168	1340	1178
VOYHTmiR-104.372	1225	1161	1306	1168	1340	1178
VOYHTmiR-109.372	1226	1161	1313	1169	1340	1178
VOYHTmiR-114.372	1227	1161	1320	1168	1340	1179
VOYHTmiR-116.372	1228	1161	1313	1168	1340	1179
VOYHTmiR-127.372	1229	1162	1313	1170	1340	1180
VOYHTmiR-102.425	1230	1161	1300	1168	1341	1178
VOYHTmiR-104.425	1231	1161	1307	1168	1341	1178
VOYHTmiR-109.425	1232	1161	1314	1169	1341	1178
VOYHTmiR-114.425	1233	1161	1321	1168	1341	1179
VOYHTmiR-116.425	1234	1161	1314	1168	1341	1179
VOYHTmiR-127.425	1235	1162	1314	1170	1341	1180
VOYHTmiR-102.032	1236	1161	1324	1168	1344	1178
VOYHTmiR-104.032	1237	1161	1326	1168	1344	1178
VOYHTmiR-109.032	1238	1161	1328	1169	1344	1178
VOYHTmiR-114.032	1239	1161	1330	1168	1344	1179
VOYHTmiR-116.032	1240	1161	1328	1168	1344	1179
VOYHTmiR-127.032	1241	1162	1328	1170	1344	1180
VOYHTmiR-102.020	1242	1161	1323	1168	1343	1178
VOYHTmiR-104.020	1243	1161	1325	1168	1343	1178
VOYHTmiR-109.020	1244	1161	1327	1169	1343	1178
VOYHTmiR-114.020	1245	1161	1329	1168	1343	1179
VOYHTmiR-116.020	1246	1161	1327	1168	1343	1179
VOYHTmiR-127.020	1247	1162	1327	1170	1343	1180
VOYHTmiR-102.016	1248	1161	1295	1168	1336	1178
VOYHTmiR-104.016	1249	1161	1302	1168	1336	1178
VOYHTmiR-109.016	1250	1161	1309	1169	1336	1178
VOYHTmiR-114.016	1251	1161	1316	1168	1336	1179
VOYHTmiR-116.016	1252	1161	1309	1168	1336	1179
VOYHTmiR-127.016	1253	1162	1309	1170	1336	1180
VOYHTmiR-102.579	1254	1161	1282	1168	1335	1178
VOYHTmiR-104.579	1255	1161	1285	1168	1335	1178
VOYHTmiR-109.579	1256	1161	1282	1169	1335	1178
VOYHTmiR-114.579	1257	1161	1288	1168	1335	1179
VOYHTmiR-116.579	1258	1161	1291	1168	1335	1179
VOYHTmiR-127.579	1259	1162	1282	1170	1335	1180
VOYHTmiR-104.579.1	1260	1161	1331	1171	1335	1178
VOYHTmiR-104.579.2	1261	1163	1331	1171	1335	1178
VOYHTmiR-104.579.3	1262	1163	1331	1172	1335	1178
VOYHTmiR-104.579.4	1263	1164	1331	1171	1335	1181
VOYHTmiR-104.579.6	1264	1165	1331	1171	1335	1181
VOYHTmiR-104.579.7	1265	1166	1331	1171	1345	1178
VOYHTmiR-104.579.8	1266	1163	1332	1173	1335	1178
VOYHTmiR-104.579.9	1267	1167	1331	1171	1335	1182
VOYHTmiR-102.020	1268	1161	1323	1168	1343	1178
VOYHTmiR-102.032	1269	1161	1324	1168	1344	1178
VOYHTmiR-104.020	1270	1161	1325	1168	1343	1178
VOYHTmiR-104.032	1271	1161	1326	1168	1344	1178
VOYHTmiR-109.020	1272	1161	1327	1169	1343	1178
VOYHTmiR-109.032	1273	1161	1328	1169	1344	1178
VOYHTmiR-114.020	1274	1161	1329	1168	1343	1179
VOYHTmiR-114.032	1275	1161	1330	1168	1344	1179
VOYHTmiR-116.020	1276	1161	1327	1168	1343	1179
VOYHTmiR-116.032	1277	1161	1328	1168	1344	1179

VOYHTmiR-127.020	1278	1162	1327	1170	1343	1180
VOYHTmiR-127.032	1279	1162	1328	1170	1344	1180

Table 11. Modulatory Polynucleotide Sequence Region (5' to 3')

Name	5' Flanking to 3' Flanking SEQ ID NO	5' Flanking SEQ ID NO	Guide SEQ ID NO	Loop SEQ ID NO	Passenger SEQ ID NO	3' Flanking SEQ ID NO
VOYHTmiR-104.579.5	1346	1163	1350	1174	1348	1178
VOYHTmiR-104.579.10	1347	1167	1351	1175	1349	1182

AAV Particles Comprising Modulatory Polynucleotides

[00482] In one embodiment, the AAV particle comprises a viral genome with a payload region comprising a modulatory polynucleotide sequences. 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 a modulatory polynucleotide may express the encoded sense and/or antisense sequences in a single cell.

[00483] 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.

[00484] Non-limiting examples of ITR to ITR sequences of AAV particles comprising a viral genome with a payload region comprising a modulatory polynucleotide sequence are described in Table 12.

Table 12. ITR to ITR Sequences of AAV Particles comprising Modulatory Polynucleotides

ITR to ITR Construct Name	ITR to ITR SEQ ID NO	Modulatory Polynucleotide SEQ ID NO
VOYHT1	1352	1262
VOYHT2	1353	1262
VOYHT3	1354	1250
VOYHT4	1355	1347
VOYHT5	1356	1262
VOYHT6	1357	1262
VOYHT7	1358	1250
VOYHT8	1359	1347
VOYHT9	1360	1262
VOYHT10	1361	1262
VOYHT11	1362	1250
VOYHT12	1363	1347
VOYHT13	1364	1262
VOYHT14	1365	1249
VOYHT15	1366	1259
VOYHT16	1367	1249
VOYHT17	1368	1262
VOYHT18	1369	1262
VOYHT19	1370	1262

VOYHT20	1371	1262
VOYHT21	1372	1262
VOYHT22	1373	1262
VOYHT23	1374	1262
VOYHT24	1375	1262
VOYHT25	1376	1249
VOYHT26	1377	1262
VOYHT27	1378	1259
VOYHT28	1379	1249
VOYHT35	1388	1255
VOYHT36	1426	1248
VOYHT37	1427	1231
VOYHT38	1428	1219
VOYHT39	1429	1207
VOYHT40	1430	1250
VOYHT41	1431	1251
VOYHT42	1432	1252
VOYHT43	1433	1253
VOYHT44	1434	1194
VOYHT45	1435	1223
VOYHT46	1436	1211
VOYHT47	1437	1262
VOYHT48	1438	1347

[00485] In one embodiment, the AAV particle comprises a viral genome which comprises a sequence which has a percent identity to any of SEQ ID NOs: 1352-1379, 1388, and 1426-1438. The viral genome 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 NOs: 1352-1379, 1388, and 1426-1438. The viral genome 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 NOs: 1352-1379, 1388, and 1426-1438. As a non-limiting example, the viral genome comprises a sequence which as 80% identity to any of SEQ ID NO: 1352-1379, 1388, and 1426-1438. As another non-limiting example, the viral genome comprises a sequence which as 85% identity to any of SEQ ID NO: 1352-1379, 1388, and 1426-1438. As another non-limiting example, the viral genome comprises a sequence which as 90% identity to any of SEQ ID NO: 1352-1379, 1388, and 1426-1438. As another non-limiting example, the viral genome comprises a sequence which as 95% identity to any of SEQ ID NO: 1352-1379, 1388, and 1426-1438. As another non-limiting example, the viral genome comprises a sequence which as 99% identity to any of SEQ ID NO: 1352-1379, 1388, and 1426-1438.

[00486] In one embodiment, the AAV particles comprising modulatory polynucleotide sequence which comprises a nucleic acid sequence encoding at least one siRNA molecule may be introduced into mammalian cells.

[00487] Where the AAV particle payload region comprises a modulatory polynucleotide, the modulatory polynucleotide may comprise sense and/or antisense sequences to knock down a target gene. The AAV viral genomes encoding modulatory polynucleotides 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.

[00488] In one embodiment, the AAV particle viral genome may comprise at least one inverted terminal repeat (ITR) region. The ITR region(s) may, independently, have a length such as, but not limited to, 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, and 175 nucleotides. The length of the ITR region for the viral genome may be 75-80, 75-85, 75-100, 80-85, 80-90, 80-105, 85-90, 85-95, 85-110, 90-95, 90-100, 90-115, 95-100, 95-105, 95-120, 100-105, 100-110, 100-125, 105-110, 105-115, 105-130, 110-115, 110-120, 110-135, 115-120, 115-125, 115-140, 120-125, 120-130, 120-145, 125-130, 125-135, 125-150, 130-135, 130-140, 130-155, 135-140, 135-145, 135-160, 140-145, 140-150, 140-165, 145-150, 145-155, 145-170, 150-155, 150-160, 150-175, 155-160, 155-165, 160-165, 160-170, 165-170, 165-175, and 170-175 nucleotides. As a non-limiting example, the viral genome comprises an ITR that is about 105 nucleotides in length. As a non-limiting example, the viral genome comprises an ITR that is about 141 nucleotides in length. As a non-limiting example, the viral genome comprises an ITR that is about 130 nucleotides in length.

[00489] In one embodiment, the AAV particle viral genome may comprises two inverted terminal repeat (ITR) regions. Each of the ITR regions may independently have a length such as, but not limited to, 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, and 175 nucleotides. The length of the ITR regions for the viral genome may be 75-80,

75-85, 75-100, 80-85, 80-90, 80-105, 85-90, 85-95, 85-110, 90-95, 90-100, 90-115, 95-100, 95-105, 95-120, 100-105, 100-110, 100-125, 105-110, 105-115, 105-130, 110-115, 110-120, 110-135, 115-120, 115-125, 115-140, 120-125, 120-130, 120-145, 125-130, 125-135, 125-150, 130-135, 130-140, 130-155, 135-140, 135-145, 135-160, 140-145, 140-150, 140-165, 145-150, 145-155, 145-170, 150-155, 150-160, 150-175, 155-160, 155-165, 160-165, 160-170, 165-170, 165-175, and 170-175 nucleotides. As a non-limiting example, the viral genome comprises an ITR that is about 105 nucleotides in length and 141 nucleotides in length. As a non-limiting example, the viral genome comprises an ITR that is about 105 nucleotides in length and 130 nucleotides in length. As a non-limiting example, the viral genome comprises an ITR that is about 130 nucleotides in length and 141 nucleotides in length.

[00490] In one embodiment, the AAV particle viral genome may comprise at least one sequence region as described in Tables 13-20. The regions may be located before or after any of the other sequence regions described herein.

[00491] In one embodiment, the AAV particle viral genome comprises at least one inverted terminal repeat (ITR) sequence region. Non-limiting examples of ITR sequence regions are described in Table 13.

Table 13. Inverted Terminal Repeat (ITR) Sequence Regions

Sequence Region Name	SEQ ID NO
ITR1	1380
ITR2	1381
ITR3	1382
ITR4	1383

[00492] In one embodiment, the AAV particle viral genome comprises two ITR sequence regions. In one embodiment, the ITR sequence regions are the ITR1 sequence region and the ITR3 sequence region. In one embodiment, the ITR sequence regions are the ITR1 sequence region and the ITR4 sequence region. In one embodiment, the ITR sequence regions are the ITR2 sequence region and the ITR3 sequence region. In one embodiment, the ITR sequence regions are the ITR2 sequence region and the ITR4 sequence region.

[00493] In one embodiment, the AAV particle viral genome may comprise at least one multiple cloning site (MCS) sequence region. The MCS region(s) may, independently, have a length such as, but not limited to, 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, and 150 nucleotides. The length of the MCS region for the viral genome may be 2-10, 5-10, 5-15, 10-20, 10-30, 10-40, 15-20, 15-25, 20-30, 20-40, 20-50, 25-30, 25-35, 30-40, 30-50, 30-60, 35-40, 35-45, 40-50, 40-60, 40-70, 45-50, 45-55, 50-60, 50-70, 50-80, 55-60, 55-65, 60-70, 60-80, 60-90, 65-70, 65-75, 70-80, 70-90, 70-100, 75-80, 75-85, 80-90, 80-100, 80-110, 85-90, 85-95, 90-100, 90-110, 90-120, 95-100, 95-105, 100-110, 100-120, 100-130, 105-110, 105-115, 110-120, 110-130, 110-140, 115-120, 115-125, 120-130, 120-140, 120-150, 125-130, 125-135, 130-140, 130-150, 135-140, 135-145, 140-150, and 145-150 nucleotides. As a non-limiting example, the viral genome comprises a MCS region that is about 5 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 10 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 14 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 18 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 73 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 121 nucleotides in length.

[00494] In one embodiment, the AAV particle viral genome comprises at least one multiple cloning site (MCS) sequence regions. Non-limiting examples of MCS sequence regions are described in Table 14.

Table 14. Multiple Cloning Site (MCS) Sequence Regions

Sequence Region Name	SEQ ID NO or Sequence
MCS1	1384
MCS2	1385
MCS3	1386
MCS4	1387
MCS5	TCGAG
MCS6	1389

[00495] In one embodiment, the AAV particle viral genome comprises one MCS sequence region. In one embodiment, the MCS sequence region is the MCS1 sequence region. In one embodiment, the MCS sequence region is the MCS2 sequence region. In one embodiment, the MCS sequence region is the MCS3 sequence region. In one embodiment, the MCS sequence region is the MCS4 sequence region. In one embodiment, the MCS sequence region is the MCS5 sequence region. In one embodiment, the MCS sequence region is the MCS6 sequence region.

[00496] In one embodiment, the AAV particle viral genome comprises two MCS sequence regions. In one embodiment, the two MCS sequence regions are the MCS1 sequence region and the MCS2 sequence region. In one embodiment, the two MCS sequence regions are the MCS1 sequence region and the MCS3 sequence region. In one embodiment, the two MCS sequence

regions are the MCS1 sequence region and the MCS4 sequence region. In one embodiment, the two MCS sequence regions are the MCS1 sequence region and the MCS5 sequence region. In one embodiment, the two MCS sequence regions are the MCS1 sequence region and the MCS6 sequence region. In one embodiment, the two MCS sequence regions are the MCS2 sequence region and the MCS3 sequence region. In one embodiment, the two MCS sequence regions are the MCS2 sequence region and the MCS4 sequence region. In one embodiment, the two MCS sequence regions are the MCS2 sequence region and the MCS5 sequence region. In one embodiment, the two MCS sequence regions are the MCS2 sequence region and the MCS6 sequence region. In one embodiment, the two MCS sequence regions are the MCS3 sequence region and the MCS4 sequence region. In one embodiment, the two MCS sequence regions are the MCS3 sequence region and the MCS5 sequence region. In one embodiment, the two MCS sequence regions are the MCS3 sequence region and the MCS6 sequence region. In one embodiment, the two MCS sequence regions are the MCS4 sequence region and the MCS5 sequence region. In one embodiment, the two MCS sequence regions are the MCS4 sequence region and the MCS6 sequence region. In one embodiment, the two MCS sequence regions are the MCS5 sequence region and the MCS6 sequence region.

[00497] In one embodiment, the AAV particle viral genome comprises two or more MCS sequence regions.

[00498] In one embodiment, the AAV particle viral genome comprises three MCS sequence regions. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS2 sequence region, and the MCS3 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS2 sequence region, and the MCS4 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS2 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS2 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS3 sequence region, and the MCS4 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS3 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS3 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS4 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS4 sequence region, and the MCS6

sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS5 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS3 sequence region, and the MCS4 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS3 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS3 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS4 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS4 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS5 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS3 sequence region, the MCS4 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS3 sequence region, the MCS4 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS3 sequence region, the MCS5 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS4 sequence region, the MCS5 sequence region, and the MCS6 sequence region.

[00499] In one embodiment, the AAV particle viral genome may comprise at least one multiple filler sequence region. The filler region(s) may, independently, have a length such as, but not limited to, 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, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934,

935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1054, 1055, 1056, 1057, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1069, 1070, 1071, 1072, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1083, 1084, 1085, 1086, 1087, 1088, 1089, 1090, 1091, 1092, 1093, 1094, 1095, 1096, 1097, 1098, 1099, 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1170, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1180, 1181, 1182, 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1190, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1200, 1201, 1202, 1203, 1204, 1205, 1206, 1207, 1208, 1209, 1210, 1211, 1212, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1220, 1221, 1222, 1223, 1224, 1225, 1226, 1227, 1228, 1229, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1237, 1238, 1239, 1240, 1241, 1242, 1243, 1244, 1245, 1246, 1247, 1248, 1249, 1250, 1251, 1252, 1253, 1254, 1255, 1256, 1257, 1258, 1259, 1260, 1261, 1262, 1263, 1264, 1265, 1266, 1267, 1268, 1269, 1270, 1271, 1272, 1273, 1274, 1275, 1276, 1277, 1278, 1279, 1280, 1281, 1282, 1283, 1284, 1285, 1286, 1287, 1288, 1289, 1290, 1291, 1292, 1293, 1294, 1295, 1296, 1297, 1298, 1299, 1300, 1301, 1302, 1303, 1304, 1305, 1306, 1307, 1308, 1309, 1310, 1311, 1312, 1313, 1314, 1315, 1316, 1317, 1318, 1319, 1320, 1321, 1322, 1323, 1324, 1325, 1326, 1327, 1328, 1329, 1330, 1331, 1332, 1333, 1334, 1335, 1336, 1337, 1338, 1339, 1340, 1341, 1342, 1343, 1344, 1345, 1346, 1347, 1348, 1349, 1350, 1351, 1352, 1353, 1354, 1355, 1356, 1357, 1358, 1359, 1360, 1361, 1362, 1363, 1364, 1365, 1366, 1367, 1368, 1369, 1370, 1371, 1372, 1373, 1374, 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443,

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2929, 2930, 2931, 2932, 2933, 2934, 2935, 2936, 2937, 2938, 2939, 2940, 2941, 2942, 2943, 2944, 2945, 2946, 2947, 2948, 2949, 2950, 2951, 2952, 2953, 2954, 2955, 2956, 2957, 2958, 2959, 2960, 2961, 2962, 2963, 2964, 2965, 2966, 2967, 2968, 2969, 2970, 2971, 2972, 2973, 2974, 2975, 2976, 2977, 2978, 2979, 2980, 2981, 2982, 2983, 2984, 2985, 2986, 2987, 2988, 2989, 2990, 2991, 2992, 2993, 2994, 2995, 2996, 2997, 2998, 2999, 3000, 3001, 3002, 3003, 3004, 3005, 3006, 3007, 3008, 3009, 3010, 3011, 3012, 3013, 3014, 3015, 3016, 3017, 3018, 3019, 3020, 3021, 3022, 3023, 3024, 3025, 3026, 3027, 3028, 3029, 3030, 3031, 3032, 3033, 3034, 3035, 3036, 3037, 3038, 3039, 3040, 3041, 3042, 3043, 3044, 3045, 3046, 3047, 3048, 3049, 3050, 3051, 3052, 3053, 3054, 3055, 3056, 3057, 3058, 3059, 3060, 3061, 3062, 3063, 3064, 3065, 3066, 3067, 3068, 3069, 3070, 3071, 3072, 3073, 3074, 3075, 3076, 3077, 3078, 3079, 3080, 3081, 3082, 3083, 3084, 3085, 3086, 3087, 3088, 3089, 3090, 3091, 3092, 3093, 3094, 3095, 3096, 3097, 3098, 3099, 3100, 3101, 3102, 3103, 3104, 3105, 3106, 3107, 3108, 3109, 3110, 3111, 3112, 3113, 3114, 3115, 3116, 3117, 3118, 3119, 3120, 3121, 3122, 3123, 3124, 3125, 3126, 3127, 3128, 3129, 3130, 3131, 3132, 3133, 3134, 3135, 3136, 3137, 3138, 3139, 3140, 3141, 3142, 3143, 3144, 3145, 3146, 3147, 3148, 3149, 3150, 3151, 3152, 3153, 3154, 3155, 3156, 3157, 3158, 3159, 3160, 3161, 3162, 3163, 3164, 3165, 3166, 3167, 3168, 3169, 3170, 3171, 3172, 3173, 3174, 3175, 3176, 3177, 3178, 3179, 3180, 3181, 3182, 3183, 3184, 3185, 3186, 3187, 3188, 3189, 3190, 3191, 3192, 3193, 3194, 3195, 3196, 3197, 3198, 3199, 3200, 3201, 3202, 3203, 3204, 3205, 3206, 3207, 3208, 3209, 3210, 3211, 3212, 3213, 3214, 3215, 3216, 3217, 3218, 3219, 3220, 3221, 3222, 3223, 3224, 3225, 3226, 3227, 3228, 3229, 3230, 3231, 3232, 3233, 3234, 3235, 3236, 3237, 3238, 3239, 3240, 3241, 3242, 3243, 3244, 3245, 3246, 3247, 3248, 3249, and 3250 nucleotides. The length of any filler region for the viral genome may be 50-100, 100-150, 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1050, 1050-1100, 1100-1150, 1150-1200, 1200-1250, 1250-1300, 1300-1350, 1350-1400, 1400-1450, 1450-1500, 1500-1550, 1550-1600, 1600-1650, 1650-1700, 1700-1750, 1750-1800, 1800-1850, 1850-1900, 1900-1950, 1950-2000, 2000-2050, 2050-2100, 2100-2150, 2150-2200, 2200-2250, 2250-2300, 2300-2350, 2350-2400, 2400-2450, 2450-2500, 2500-2550, 2550-2600, 2600-2650, 2650-2700, 2700-2750, 2750-2800, 2800-2850, 2850-2900, 2900-2950, 2950-3000, 3000-3050, 3050-3100, 3100-3150, 3150-3200, and 3200-3250 nucleotides. As a non-limiting example, the viral genome comprises a filler region that is about 55 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 56 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that

is about 97 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 103 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 105 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 357 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 363 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 712 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 714 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1203 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1209 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1512 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1519 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 2395 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 2403 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 2405 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 3013 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 3021 nucleotides in length.

[00500] In one embodiment, the AAV particle viral genome comprises at least one filler sequence regions. Non-limiting examples of filler sequence regions are described in Table 15.

Table 15. Filler Sequence Regions

Sequence Region Name	SEQ ID NO o
FILL1	1390
FILL2	1391
FILL3	1392
FILL4	1393
FILL5	1394
FILL6	1395
FILL7	1396
FILL8	1397
FILL9	1398
FILL10	1399
FILL11	1400
FILL12	1401
FILL13	1402
FILL14	1403
FILL15	1404
FILL16	1405
FILL17	1406
FILL18	1407

[00501] In one embodiment, the AAV particle viral genome comprises one filler sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region. In one embodiment, the filler sequence region is the FILL2 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL18 sequence region.

[00502] In one embodiment, the AAV particle viral genome comprises two filler sequence regions. In one embodiment, the two filler sequence regions are the FILL1 sequence region, and the FILL2 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL3 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL4 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence

region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL2 sequence region, and the FILL3 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL4 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the

FILL4 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL14 sequence region. In one embodiment, the filler

sequence region is the FILL6 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL12 sequence region. In one

embodiment, the filler sequence region is the FILL9 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence

region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL17 sequence region, and the FILL18 sequence region.

[00503] In one embodiment, the AAV particle viral genome comprises three filler sequence regions. In one embodiment, the two filler sequence regions are the FILL1 sequence region, the FILL2 sequence region, and the FILL3 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL4 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the

FILL1 sequence region, the FILL2 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL2 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL4 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL3 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the

FILL1 sequence region, the FILL4 sequence region, and the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL4 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL5 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL5 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL5 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL5 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL5 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL5 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL5 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, the FILL5 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the

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FILL4 sequence region, the FILL5 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL5 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL6 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL6 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL6 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL6 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL6 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL6 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL6 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL6 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, the FILL6 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the

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FILL6 sequence region, the FILL7 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL7 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL7 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL7 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL8 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL9 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL9 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL9 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL9 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL9 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL9 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL9 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL9 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the

FILL6 sequence region, the FILL9 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL10 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL10 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL10 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL10 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL10 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL10 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL10 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL10 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL11 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL11 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL11 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL11 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL11 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL11 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL11 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL12 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL12 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL12 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL12 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL12 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL12 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the

FILL6 sequence region, the FILL13 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL13 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL13 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL13 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL13 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL8 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL8 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL8 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL8 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL8 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL8 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL8 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the

FILL7 sequence region, the FILL8 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL8 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL8 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL9 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL9 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL9 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL9 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL9 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL9 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL9 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL9 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL9 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL10 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL10 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL10 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL10 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL10 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL10 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL10 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL10 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL11 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL11 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the

FILL7 sequence region, the FILL11 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL11 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL11 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL11 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL11 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL12 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL12 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL12 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL12 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL12 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL12 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL13 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL13 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL13 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL13 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL13 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the

FILL7 sequence region, the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL9 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL9 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL9 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL9 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL9 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL9 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL9 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL9 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL9 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL10 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL10 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL10 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL10 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL10 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL10 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL10 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL10 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL11 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the

FILL8 sequence region, the FILL11 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL11 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL11 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL11 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL11 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL11 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL12 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL12 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL12 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL12 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL12 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL12 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL13 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL13 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL13 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL13 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL13 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the

FILL8 sequence region, the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL10 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL10 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL10 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL10 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL10 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL10 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL10 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL10 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL11 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL11 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL11 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL11 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL11 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL11 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL11 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL12 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL12 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the

FILL9 sequence region, the FILL12 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL12 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL12 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL12 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL13 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL13 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL13 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL13 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL13 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL11 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL11 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL11 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the

FILL10 sequence region, the FILL11 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL11 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL11 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL11 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL12 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL12 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL12 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL12 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL12 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL12 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL13 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL13 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL13 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL13 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL13 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the

FILL10 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL12 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL12 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL12 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL12 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL12 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL12 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL13 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL13 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL13 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL13 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL13 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the

FILL11 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL13 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL13 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL13 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL13 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL13 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the

FILL13 sequence region, the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region, the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region, the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region, the FILL17 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL16 sequence region, the FILL17 sequence region, and the FILL18 sequence region.

[00504] In one embodiment, the AAV particle viral genome may comprise at least one enhancer sequence region. The enhancer sequence region(s) may, independently, have a length such as, but not limited to, 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, and 400 nucleotides. The length of the enhancer region for the viral genome may be 300-310, 300-325, 305-315, 310-320, 315-325, 320-330, 325-335, 325-350, 330-340, 335-345, 340-350, 345-355, 350-360, 350-375, 355-365, 360-370, 365-375, 370-380, 375-385, 375-400, 380-390, 385-395, and 390-400 nucleotides. As a non-

limiting example, the viral genome comprises an enhancer region that is about 303 nucleotides in length. As a non-limiting example, the viral genome comprises an enhancer region that is about 382 nucleotides in length.

[00505] In one embodiment, the AAV particle viral genome comprises at least one enhancer sequence region. Non-limiting examples of enhancer sequence regions are described in Table 16.

Table 16. Enhancer Sequence Regions

Sequence Region Name	SEQ ID NO
Enhancer1	1408
Enhancer2	1409

[00506] In one embodiment, the AAV particle viral genome comprises one enhancer sequence region. In one embodiment, the enhancer sequence regions is the Enhancer1 sequence region. In one embodiment, the enhancer sequence regions is the Enhancer2 sequence region.

[00507] In one embodiment, the AAV particle viral genome comprises two enhancer sequence regions. In one embodiment, the enhancer sequence regions are the Enhancer1 sequence region and the Enhancer 2 sequence region.

[00508] In one embodiment, the AAV particle viral genome may comprise at least one promoter sequence region. The promoter sequence region(s) may, independently, have a length such as, but not limited to, 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, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, and 600 nucleotides. The length of the promoter region for the viral genome may be 4-10, 10-20, 10-50, 20-30, 30-40, 40-50, 50-60, 50-100, 60-70, 70-80, 80-90, 90-100, 100-110, 100-150, 110-120, 120-130, 130-140, 140-150, 150-160, 150-200, 160-170, 170-180, 180-190, 190-200, 200-210, 200-250, 210-220, 220-230, 230-240, 240-250, 250-260, 250-300, 260-270, 270-280, 280-290, 290-300, 300-310, 300-350, 310-320, 320-330, 330-340, 340-350, 350-360, 350-400, 360-370, 370-380, 380-390, 390-400, 400-410, 400-450, 410-420, 420-430, 430-440, 440-450, 450-460, 450-500, 460-470, 470-480, 480-490, 490-500, 500-510, 500-550, 510-520, 520-530, 530-540, 540-550, 550-560, 550-600, 560-570, 570-580, 580-590, and 590-600 nucleotides. As a non-limiting example, the viral genome comprises a promoter region that is about 4 nucleotides in length. As a non-limiting example, the viral genome comprises a promoter region that is about 17 nucleotides in length. As a non-limiting example, the viral genome comprises a promoter region that is about 204 nucleotides in length. As a non-limiting example, the viral genome comprises a promoter region that is about 219 nucleotides in length. As a non-limiting example, the viral genome comprises a promoter region that is about 260 nucleotides in length. As a non-limiting example, the viral genome comprises a promoter region that is about 303 nucleotides in length. As a non-limiting example, the viral genome comprises a promoter region that is about 382 nucleotides in length. As a non-limiting example, the viral genome comprises a promoter region that is about 588 nucleotides in length.

[00509] In one embodiment, the AAV particle viral genome comprises at least one promoter sequence region. Non-limiting examples of promoter sequence regions are described in Table 17.

Table 17. Promoter Sequence Regions

Sequence Region Name	SEQ ID NO or Sequence
Promoter1	1410
Promoter2	1411
Promoter3	GTTG
Promoter4	1412
Promoter5	1413
Promoter6	1414

[00510] In one embodiment, the AAV particle viral genome comprises one promoter sequence region. In one embodiment, the promoter sequence region is Promoter1. In one embodiment, the promoter sequence region is Promoter2. In one embodiment, the promoter sequence region is Promoter3. In one embodiment, the promoter sequence region is Promoter4. In one embodiment, the promoter sequence region is Promoter5. In one embodiment, the promoter sequence region is Promoter6.

[00511] In one embodiment, the AAV particle viral genome comprises two promoter sequence regions. In one embodiment, the promoter sequence region is Promoter1 sequence region, and the Promoter2 sequence region. In one embodiment, the promoter sequence region is Promoter1 sequence region, and the Promoter3 sequence region. In one embodiment, the promoter sequence region is Promoter1 sequence region, and the Promoter4 sequence region. In one embodiment, the promoter sequence region is Promoter1 sequence region, and the Promoter5 sequence region. In one embodiment, the promoter sequence region is Promoter1 sequence region, and the Promoter6 sequence region. In one embodiment, the promoter sequence region is Promoter2 sequence region, and the Promoter3 sequence region. In one embodiment, the promoter sequence region is Promoter2 sequence region, and the Promoter4 sequence region. In one embodiment, the promoter sequence region is Promoter2 sequence region, and the Promoter5 sequence region. In one embodiment, the promoter sequence region is Promoter2 sequence region, and the Promoter6 sequence region. In one embodiment, the promoter sequence region is Promoter3 sequence region, and the Promoter4 sequence region. In one embodiment, the promoter sequence region is Promoter3 sequence region, and the Promoter5 sequence region. In one embodiment, the promoter sequence region is Promoter3 sequence region, and the Promoter6 sequence region. In one embodiment, the promoter sequence region is Promoter4 sequence region, and the Promoter5 sequence region. In one embodiment, the promoter sequence region is Promoter4 sequence region, and the Promoter6 sequence region. In one embodiment, the promoter sequence region is Promoter5 sequence region, and the Promoter6 sequence region.

[00512] In one embodiment, the AAV particle viral genome may comprise at least one exon sequence region. The exon region(s) may, independently, have a length such as, but not limited

to, 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, and 150 nucleotides. The length of the exon region for the viral genome may be 2-10, 5-10, 5-15, 10-20, 10-30, 10-40, 15-20, 15-25, 20-30, 20-40, 20-50, 25-30, 25-35, 30-40, 30-50, 30-60, 35-40, 35-45, 40-50, 40-60, 40-70, 45-50, 45-55, 50-60, 50-70, 50-80, 55-60, 55-65, 60-70, 60-80, 60-90, 65-70, 65-75, 70-80, 70-90, 70-100, 75-80, 75-85, 80-90, 80-100, 80-110, 85-90, 85-95, 90-100, 90-110, 90-120, 95-100, 95-105, 100-110, 100-120, 100-130, 105-110, 105-115, 110-120, 110-130, 110-140, 115-120, 115-125, 120-130, 120-140, 120-150, 125-130, 125-135, 130-140, 130-150, 135-140, 135-145, 140-150, and 145-150 nucleotides. As a non-limiting example, the viral genome comprises an exon region that is about 53 nucleotides in length. As a non-limiting example, the viral genome comprises an exon region that is about 134 nucleotides in length.

[00513] In one embodiment, the AAV particle viral genome comprises at least one Exon sequence region. Non-limiting examples of Exon sequence regions are described in Table 18.

Table 18. Exon Sequence Regions

Sequence Region Name	SEQ ID NO
Exon1	1415
Exon2	1416

[00514] In one embodiment, the AAV particle viral genome comprises one Exon sequence region. In one embodiment, the Exon sequence regions is the Exon1 sequence region. In one embodiment, the Exon sequence regions is the Exon2 sequence region.

[00515] In one embodiment, the AAV particle viral genome comprises two Exon sequence regions. In one embodiment, the Exon sequence regions are the Exon1 sequence region and the Exon 2 sequence region.

[00516] In one embodiment, the AAV particle viral genome may comprise at least one intron sequence region. The intron region(s) may, independently, have a length such as, but not limited to, 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, and 350 nucleotides. The length of the intron region for the viral genome may be 25-35, 25-50, 35-45, 45-55, 50-75, 55-65, 65-75, 75-85, 75-100, 85-95, 95-105, 100-125, 105-115, 115-125, 125-135, 125-150, 135-145, 145-155, 150-175, 155-165, 165-175, 175-185, 175-200, 185-195, 195-205, 200-225, 205-215, 215-225, 225-235, 225-250, 235-245, 245-255, 250-275, 255-265, 265-275, 275-285, 275-300, 285-295, 295-305, 300-325, 305-315, 315-325, 325-335, 325-350, and 335-345 nucleotides. As a non-limiting example, the viral genome comprises an intron region that is about 32 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 172 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 201 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 347 nucleotides in length.

[00517] In one embodiment, the AAV particle viral genome comprises at least one intron sequence region. Non-limiting examples of intron sequence regions are described in Table 19.

Table 19. Intron Sequence Regions

Sequence Region Name	SEQ ID NO
Intron1	1417
Intron2	1418
Intron3	1419

[00518] In one embodiment, the AAV particle viral genome comprises one intron sequence region. In one embodiment, the intron sequence regions is the Intron1 sequence region. In one embodiment, the intron sequence regions is the Intron2 sequence region. In one embodiment, the intron sequence regions is the Intron3 sequence region.

[00519] In one embodiment, the AAV particle viral genome comprises two intron sequence regions. In one embodiment, the intron sequence regions are the Intron1 sequence region and the

Intron2 sequence region. In one embodiment, the intron sequence regions are the Intron2 sequence region and the Intron3 sequence region. In one embodiment, the intron sequence regions are the Intron1 sequence region and the Intron3 sequence region.

[00520] In one embodiment, the AAV particle viral genome comprises three intron sequence regions. In one embodiment, the intron sequence regions are the Intron1 sequence region, the Intron2 sequence region, and the Intron3 sequence region.

[00521] In one embodiment, the AAV particle viral genome may comprise at least one polyadenylation signal sequence region. The polyadenylation signal region sequence region(s) may, independently, have a length such as, but not limited to, 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, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, and 600 nucleotides. The length of the polyadenylation signal sequence region for the viral genome may be 4-10, 10-20, 10-50, 20-30, 30-40, 40-50, 50-60, 50-100, 60-70, 70-80, 80-90, 90-100, 100-110, 100-150, 110-120, 120-130, 130-140, 140-150, 150-160, 150-200, 160-170, 170-180, 180-190, 190-200, 200-210, 200-250, 210-220, 220-230, 230-240, 240-250, 250-260, 250-300, 260-270, 270-280, 280-290, 290-300, 300-310, 300-350, 310-320, 320-330, 330-340, 340-350, 350-360, 350-400, 360-370, 370-380, 380-390, 390-400, 400-410, 400-450, 410-420, 420-430, 430-440, 440-450, 450-460, 450-500, 460-470, 470-480, 480-490, 490-500, 500-510, 500-550, 510-520, 520-530, 530-540, 540-550, 550-560, 550-600, 560-570, 570-580, 580-590, and 590-600 nucleotides. As a non-limiting example, the viral genome comprises a polyadenylation signal sequence region that is about 127 nucleotides in length. As a non-limiting example, the viral genome comprises a polyadenylation signal sequence region that is about 225 nucleotides in length. As a non-limiting example, the viral genome comprises a polyadenylation signal sequence region that is about 476 nucleotides in length. As a non-limiting example, the viral genome comprises a polyadenylation signal sequence region that is about 477 nucleotides in length.

[00522] In one embodiment, the AAV particle viral genome comprises at least one polyadenylation (polyA) signal sequence region. Non-limiting examples of polyA signal sequence regions are described in Table 20.

Table 20. PolyA Signal Sequence Regions

Sequence Region Name	SEQ ID NO
PolyA1	1420
PolyA2	1421
PolyA3	1422
PolyA4	1423

[00523] In one embodiment, the AAV particle viral genome comprises one polyA signal sequence region. In one embodiment, the polyA signal sequence regions is the PolyA1 sequence region. In one embodiment, the polyA signal sequence regions is the PolyA2 sequence region. In one embodiment, the polyA signal sequence regions is the PolyA3 sequence region. In one embodiment, the polyA signal sequence regions is the PolyA4 sequence region.

[00524] In one embodiment, the AAV particle viral genome comprises more than one polyA signal sequence region.

[00525] In one embodiment, the AAV particle viral genome comprises at least one inverted terminal repeat (ITR) sequence region, at least one multiple cloning site (MCS) sequence region, at least one enhancer sequence region, at least one promoter sequence region, at least one exon sequence region, at least one intron sequence region, at least one modulatory polynucleotide region, at least one polyadenylation signal sequence region, and at least one filler sequence region.

[00526] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, an enhancer sequence region, a promoter sequence region, an intron sequence region, a modulatory polynucleotide region, a polyadenylation signal sequence region, and a filler sequence region.

[00527] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region. Non-limiting examples of ITR to ITR sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 21. In Table 21, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT1 (SEQ ID NO: 1352)).

Table 21. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT1 (SEQ ID NO: 1352)		VOYHT2 (SEQ ID NO: 1353)		VOYHT3 (SEQ ID NO: 1354)		VOYHT4 (SEQ ID NO: 1355)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1380	141	1380	141	1380	141	1380	141
MCS	1384	10	1384	10	1384	10	1384	10
CMV enhancer	1408	382	1408	382	1408	382	1408	382
CBA Promoter	1410	260	1410	260	1410	260	1410	260
SV40 Intron	1417	172	1417	172	1417	172	1417	172
Modulatory Polynucleotide	1262	163	1262	163	1250	158	1347	163
MCS	TCGAG	5	TCGAG	5	TCGAG	5	TCGAG	5
Rabbit globin PolyA Signal	1420	127	1420	127	1420	127	1420	127
Filler	1400	714	1401	3021	1400	714	1400	714
3' ITR	1382	141	1382	141	1382	141	1382	141

[00528] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1352 (VOYHT1) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region.

[00529] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1353 (VOYHT2) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region.

[00530] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1354 (VOYHT3) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region.

[00531] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1355 (VOYHT4) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region.

[00532] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region. Non-limiting examples of ITR to ITR sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 22. In Table 22, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are

described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT5 (SEQ ID NO: 1356)).

Table 22. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT5 (SEQ ID NO: 1356)		VOYHT6 (SEQ ID NO: 1357)		VOYHT7 (SEQ ID NO: 1358)		VOYHT8 (SEQ ID NO: 1359)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1380	141	1380	141	1380	141	1380	141
MCS	1384	10	1384	10	1384	10	1384	10
Filler	1390	3013	1391	712	1391	712	1391	712
CMV enhancer	1408	382	1408	382	1408	382	1408	382
CBA Promoter	1410	260	1410	260	1410	260	1410	260
SV40 Intron	1417	172	1417	172	1417	172	1417	172
Modulatory Polynucleotide	1262	163	1262	163	1250	158	1347	163
MCS	TCGAG	5	TCGAG	5	TCGAG	5	TCGAG	5
Rabbit globin PolyA Signal	1420	127	1420	127	1420	127	1420	127
3' ITR	1382	141	1382	141	1382	141	1382	141

[00533] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1356 (VOYHT5) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region.

[00534] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1357 (VOYHT6) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region.

[00535] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1358 (VOYHT7) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region.

[00536] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1359 (VOYHT8) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and a filler sequence region.

[00537] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, an enhancer sequence region, a promoter sequence region, an intron sequence region, a modulatory polynucleotide region, a polyadenylation signal sequence region, and two filler sequence regions.

[00538] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and two filler sequence regions. Non-limiting examples of ITR to ITR sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 23. In Table 23, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT9 (SEQ ID NO: 1360)).

Table 23. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT9 (SEQ ID NO: 1360)		VOYHT10 (SEQ ID NO: 1361)		VOYHT11 (SEQ ID NO: 1362)		VOYHT12 (SEQ ID NO: 1363)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1380	141	1380	141	1380	141	1380	141
MCS	1384	10	1384	10	1384	10	1384	10
Filler	1396	1512	1397	363	1397	363	1397	363
CMV enhancer	1408	382	1408	382	1408	382	1408	382
CBA Promoter	1410	260	1410	260	1410	260	1410	260
SV40 Intron	1417	172	1417	172	1417	172	1417	172
Modulatory Polynucleotide	1262	163	1262	163	1250	158	1347	163
MCS	TCGAG	5	TCGAG	5	TCGAG	5	TCGAG	5
Rabbit globin PolyA Signal	1420	127	1420	127	1420	127	1420	127
Filler	1404	1519	1405	357	1405	357	1405	357

3' ITR	1382	141	1382	141	1382	141	1382	141

[00539] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1360 (VOYHT9) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and two filler sequence regions.

[00540] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1361 (VOYHT10) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and two filler sequence regions.

[00541] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1362 (VOYHT11) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and two filler sequence regions.

[00542] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1363 (VOYHT12) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, a rabbit globin polyadenylation signal sequence region, and two filler sequence regions.

[00543] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, an enhancer sequence region, a promoter sequence region, an intron sequence region, a modulatory polynucleotide region, and a polyadenylation signal sequence region.

[00544] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation

signal sequence region. Non-limiting examples of ITR to ITR sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 24. In Table 24, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT13 (SEQ ID NO: 1364)).

Table 24. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT13 (SEQ ID NO: 1364)		VOYHT14 (SEQ ID NO: 1365)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1380	141	1380	141
MCS	1384	10	1384	10
CMV enhancer	1408	382	1408	382
CBA Promoter	1410	260	1410	260
SV40 Intron	1417	172	1417	172
Modulatory Polynucleotide	1262	163	1249	158
MCS	TCGAG	5	TCGAG	5
Rabbit globin PolyA Signal	1420	127	1420	127
3' ITR	1382	141	1382	141

[00545] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1364 (VOYHT13) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00546] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1365 (VOYHT14) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two multiple cloning site (MCS) sequence regions, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00547] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, an enhancer sequence region, a promoter sequence region, an intron sequence region, a modulatory polynucleotide region, and a polyadenylation signal sequence region.

[00548] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide

region, and a rabbit globin polyadenylation signal sequence region. Non-limiting examples of ITR to ITR sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Tables 25-29. In Tables 25-29, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT15 (SEQ ID NO: 1366)).

Table 25. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT15 (SEQ ID NO: 1366)		VOYHT16 (SEQ ID NO: 1367)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1381	105	1381	105
CMV enhancer	1408	382	1408	382
CBA Promoter	1410	260	1410	260
SV40 Intron	1417	172	1417	172
Modulatory Polynucleotide	1259	260	1249	158
Rabbit globin PolyA Signal	1420	127	1420	127
3' ITR	1383	130	1383	130

Table 26. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT35 (SEQ ID NO: 1388)		VOYHT36 (SEQ ID NO: 1426)		VOYHT37 (SEQ ID NO: 1427)		VOYHT38 (SEQ ID NO: 1428)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1381	105	1381	105	1381	105	1381	105
CMV enhancer	1408	382	1408	382	1408	382	1408	382
CBA Promoter	1410	260	1410	260	1410	260	1410	260
SV40 Intron	1417	172	1417	172	1417	172	1417	172
Modulatory Polynucleotide	1255	158	1248	158	1231	158	1219	158
Rabbit globin PolyA Signal	1420	127	1420	127	1420	127	1420	127
3' ITR	1383	130	1383	130	1383	130	1383	130

Table 27. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT39 (SEQ ID NO: 1429)		VOYHT40 (SEQ ID NO: 1430)		VOYHT41 (SEQ ID NO: 1431)		VOYHT42 (SEQ ID NO: 1432)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1381	105	1381	105	1381	105	1381	105
CMV enhancer	1408	382	1408	382	1408	382	1408	382
CBA Promoter	1410	260	1410	260	1410	260	1410	260
SV40 Intron	1417	172	1417	172	1417	172	1417	172
Modulatory Polynucleotide	1207	158	1250	158	1251	158	1252	158

Rabbit globin PolyA Signal	1420	127	1420	127	1420	127	1420	127
3' ITR	1383	130	1383	130	1383	130	1383	130

Table 28. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT43 (SEQ ID NO: 1433)		VOYHT44 (SEQ ID NO: 1434)		VOYHT45 (SEQ ID NO: 1435)		VOYHT46 (SEQ ID NO: 1436)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1381	105	1381	105	1381	105	1381	105
CMV enhancer	1408	382	1408	382	1408	382	1408	382
CBA Promoter	1410	260	1410	260	1410	260	1410	260
SV40 Intron	1417	172	1417	172	1417	172	1417	172
Modulatory Polynucleotide	1253	260	1194	260	1223	260	1211	260
Rabbit globin PolyA Signal	1420	127	1420	127	1420	127	1420	127
3' ITR	1383	130	1383	130	1383	130	1383	130

Table 29. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT47 (SEQ ID NO: 1437)		VOYHT48 (SEQ ID NO: 1438)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1381	105	1381	105
CMV enhancer	1408	382	1408	382
CBA Promoter	1410	260	1410	260
SV40 Intron	1417	172	1417	172
Modulatory Polynucleotide	1262	163	1347	163
Rabbit globin PolyA Signal	1420	127	1420	127
3' ITR	1383	130	1383	130

[00549] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1366 (VOYHT15) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00550] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1367 (VOYHT16) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00551] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1388 (VOYHT35) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00552] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1426 (VOYHT36) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00553] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1427 (VOYHT37) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00554] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1428 (VOYHT38) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00555] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1429 (VOYHT39) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00556] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1430 (VOYHT40) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00557] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1431 (VOYHT41) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40

intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00558] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1432 (VOYHT42) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00559] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1433 (VOYHT43) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00560] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1434 (VOYHT44) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00561] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1435 (VOYHT45) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00562] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1436 (VOYHT46) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00563] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1437 (VOYHT47) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00564] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1438 (VOYHT48) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a CMV enhancer sequence region, a CBA promoter sequence region, an SV40 intron sequence region, a modulatory polynucleotide region, and a rabbit globin polyadenylation signal sequence region.

[00565] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a MCS sequence region, an enhancer sequence region, a promoter sequence region, two exon sequence regions, two intron sequence regions, a modulatory polynucleotide region, a polyadenylation signal sequence region, and a filler sequence region.

[00566] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a MCS sequence region, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin intron 2 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region. A non-limiting example of an ITR to ITR sequence for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 30. In Table 30, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT17 (SEQ ID NO: 1368)).

Table 30. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT17 (SEQ ID NO: 1368)	
	Region SEQ ID NO	Region length
5' ITR	1380	141
MCS	1387	18
CMV enhancer	1409	303
CMV Promoter	1412	204
Ie1 exon1	1415	134
Ie1 intron1	1418	32
hbglobin intron2	1419	347
hbglobin exon3	1416	53
Modulatory Polynucleotide	1262	163
hGH PolyA Signal	1422	477
Filler	1406	2403
3' ITR	1382	141

[00567] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1368 (VOYHT17) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a MCS sequence region, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin intron 2 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region.

[00568] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a MCS sequence region, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin intron 2 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region. A non-limiting example of an ITR to ITR sequence for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 31. In Table 31, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT19 (SEQ ID NO: 1370)).

Table 31. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT19 (SEQ ID NO: 1370)	
	Region SEQ ID NO	Region length
5' ITR	1380	141
Filler	1392	2405
CMV enhancer	1409	303
CMV Promoter	1412	204
Ie1 exon1	1415	134
Ie1 intron1	1418	32
hbglobin intron2	1419	347
hbglobin exon3	1416	53
Modulatory Polynucleotide	1262	163
hGH PolyA Signal	1389	14
MCS	1422	477
3' ITR	1382	141

[00569] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1370 (VOYHT19) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a MCS sequence region, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon

3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region.

[00570] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, an enhancer sequence region, a promoter sequence region, two exon sequence regions, two intron sequence regions, a modulatory polynucleotide region, a polyadenylation signal sequence region, and a filler sequence region.

[00571] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region. A non-limiting example of an ITR to ITR sequence for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 32. In Table 32, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT18 (SEQ ID NO: 1369)).

Table 32. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT18 (SEQ ID NO: 1369)	
	Region SEQ ID NO	Region length
5' ITR	1380	141
MCS	1387	18
CMV enhancer	1409	303
CMV Promoter	1412	204
Ie1 exon1	1415	134
Ie1 intron1	1418	32
hbglobin intron2	1419	347
hbglobin exon3	1416	53
Modulatory Polynucleotide	1262	163
MCS	1389	14
hGH PolyA Signal	1422	477
Filler	1407	105
3' ITR	1382	141

[00572] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1369 (VOYHT18) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR

sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region.

[00573] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region. A non-limiting example of an ITR to ITR sequence for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 33. In Table 33, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT20 (SEQ ID NO: 1371)).

Table 33. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT20 (SEQ ID NO: 1371)	
	Region SEQ ID NO	Region length
5' ITR	1380	141
MCS	1385	121
Filler	1394	103
CMV enhancer	1409	303
CMV Promoter	1412	204
Ie1 exon1	1415	134
Ie1 intron1	1418	32
hbglobin intron2	1419	347
hbglobin exon3	1416	53
Modulatory Polynucleotide	1262	163
MCS	1389	14
hGH PolyA Signal	1422	477
3' ITR	1382	141

[00574] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1371 (VOYHT20) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin

exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region.

[00575] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region. Non-limiting examples of ITR to ITR sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 34. In Table 34, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT21 (SEQ ID NO: 1372)).

Table 34. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT21 (SEQ ID NO: 1372)		VOYHT22 (SEQ ID NO: 1373)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1380	141	1380	141
MCS	1387	18	1387	18
CMV enhancer	1409	303	1409	303
CMV Promoter	1412	204	1412	204
Ie1 exon1	1415	134	1415	134
Ie1 intron1	1418	32	1418	32
Filler	1398	2395	1399	97
hbglobin intron2	1419	347	1419	347
hbglobin exon3	1416	53	1416	53
Modulatory Polynucleotide	1262	163	1262	163
MCS	1389	14	1389	14
hGH PolyA Signal	1422	477	1422	477
3' ITR	1382	141	1382	141

[00576] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1372 (VOYHT21) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region.

[00577] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1373 (VOYHT22) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and a filler sequence region.

[00578] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a MCS sequence region, an enhancer sequence region, a promoter sequence region, two exon sequence regions, two intron sequence regions, a modulatory polynucleotide region, a polyadenylation signal sequence region, and two filler sequence regions.

[00579] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a MCS sequence region, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and two filler sequence regions. A non-limiting example of an ITR to ITR sequence for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 35. In Table 35, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT23 (SEQ ID NO: 1374)).

Table 35. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT23 (SEQ ID NO: 1374)	
	Region SEQ ID NO	Region length
5' ITR	1380	141
Filler	1393	1203
CMV enhancer	1409	303
CMV Promoter	1412	204
Ie1 exon1	1415	134
Ie1 intron1	1418	32
hbglobin intron2	1419	347
hbglobin exon3	1416	53
Modulatory Polynucleotide	1262	163
MCS	1389	14

hGH PolyA Signal	1422	477
Filler	1402	1209
3' ITR	1382	141

[00580] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1374 (VOYHT23) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a MCS sequence region, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and two filler sequence regions.

[00581] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, an enhancer sequence region, a promoter sequence region, two exon sequence regions, two intron sequence regions, a modulatory polynucleotide region, a polyadenylation signal sequence region, and two filler sequence regions.

[00582] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and two filler sequence regions. A non-limiting example of an ITR to ITR sequence for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 36. In Table 36, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT24 (SEQ ID NO: 1375)).

Table 36. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT24 (SEQ ID NO: 1375)	
	Region SEQ ID NO	Region length
5' ITR	1380	141
MCS	1386	73
Filler	1395	55
CMV enhancer	1409	303
CMV Promoter	1412	204
Ie1 exon1	1415	134
Ie1 intron1	1418	32

hbglobin intron2	1419	347
hbglobin exon3	1416	53
Modulatory Polynucleotide	1262	163
MCS	1389	14
hGH PolyA Signal	1423	476
Filler	1403	56
3' ITR	1382	141

[00583] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1375 (VOYHT24) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, a human growth hormone (hGH) polyadenylation signal sequence region, and two filler sequence regions.

[00584] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, an enhancer sequence region, a promoter sequence region, two exon sequence regions, two intron sequence regions, a modulatory polynucleotide region, and a polyadenylation signal sequence region.

[00585] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, and a human growth hormone (hGH) polyadenylation signal sequence region. Non-limiting examples of an ITR to ITR sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 37. In Table 37, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT25 (SEQ ID NO: 1376)).

Table 37. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT25 (SEQ ID NO: 1376)		VOYHT26 (SEQ ID NO: 1377)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1380	141	1380	141
MCS	1387	18	1387	18
CMV enhancer	1409	303	1409	303

CMV Promoter	1412	204	1412	204
Ie1 exon1	1415	134	1415	134
Ie1 intron1	1418	32	1418	32
hbglobin intron2	1419	347	1419	347
hbglobin exon3	1416	53	1416	53
Modulatory Polynucleotide	1249	158	1262	163
MCS	1389	14	1389	14
hGH PolyA Signal	1422	477	1422	477
3' ITR	1382	141	1382	141

[00586] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1376 (VOYHT25) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, and a human growth hormone (hGH) polyadenylation signal sequence region.

[00587] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1377 (VOYHT26) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, two MCS sequence regions, a CMV enhancer sequence region, a CMV promoter sequence region, two exon sequence regions (ie1 exon 1 and human beta globin (hbglobin) exon 3 or fragments thereof), two intron sequence regions (ie1 intron 1 and hbglobin exon 3 or fragments thereof), a modulatory polynucleotide region, and a human growth hormone (hGH) polyadenylation signal sequence region.

[00588] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, a promoter sequence region, and a modulatory polynucleotide region.

[00589] In one embodiment, the AAV particle viral genome comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, an H1 promoter sequence region, and a modulatory polynucleotide region. Non-limiting examples of an ITR to ITR sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 38. In Table 38, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name and sequence identifier of the ITR to ITR sequence (e.g., VOYHT27 (SEQ ID NO: 1378)).

Table 38. Sequence Regions in ITR to ITR Sequences

Sequence Regions	VOYHT27 (SEQ ID NO: 1378)		VOYHT28 (SEQ ID NO: 1379)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	1381	105	1381	105
H1 Promoter	1413	219	1413	219
Modulatory Polynucleotide	1259	260	1249	158
3' ITR	1383	130	1383	130

[00590] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1378 (VOYHT27) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, an H1 promoter sequence region, and a modulatory polynucleotide region.

[00591] In one embodiment, the AAV particle viral genome comprises SEQ ID NO: 1379 (VOYHT28) which comprises a 5' inverted terminal repeat (ITR) sequence region and a 3' ITR sequence region, an H1 promoter sequence region, and a modulatory polynucleotide region.

[00592] In one embodiment, the AAV particle viral genome comprises one or two promoter sequence regions, a modulatory polynucleotide sequence region, and a bovine growth hormone (bGH) polyadenylation signal sequence region.

[00593] In one embodiment, the AAV particle viral genome comprises a two promoter sequence regions, a modulatory polynucleotide region, and a polyadenylation signal sequence region.

[00594] In one embodiment, the AAV particle viral genome comprises a CMV and T7 promoter sequence region, a modulatory polynucleotide region, and a bGH polyadenylation signal sequence region. Non-limiting examples of sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 39. In Table 39, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name of the sequence (e.g., VOYHT29).

Table 39. Sequence Regions

Sequence Regions	VOYHT29		VOYHT30		VOYHT31		VOYHT32	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
CMV Promoter	1411	588	1411	588	1411	588	1411	588
T7 promoter	1414	17	1414	17	1414	17	1414	17
Modulatory Polynucleotide	1249	158	1259	260	1255	158	1253	260
bGH PolyA Signal	1421	225	1421	225	1421	225	1421	225

[00595] In one embodiment, the AAV particle viral genome comprises a CMV promoter sequence region (SEQ ID NO: 1411), a T7 promoter sequence region (SEQ ID NO: 1414), a modulatory polynucleotide sequence region (SEQ ID NO: 1249), and a bGH polyadenylation signal sequence region (SEQ ID NO: 1421).

[00596] In one embodiment, the AAV particle viral genome comprises a CMV promoter sequence region (SEQ ID NO: 1411), a T7 promoter sequence region (SEQ ID NO: 1414), a modulatory polynucleotide sequence region (SEQ ID NO: 1259), and a bGH polyadenylation signal sequence region (SEQ ID NO: 1421).

[00597] In one embodiment, the AAV particle viral genome comprises a CMV promoter sequence region (SEQ ID NO: 1411), a T7 promoter sequence region (SEQ ID NO: 1414), a modulatory polynucleotide sequence region (SEQ ID NO: 1255), and a bGH polyadenylation signal sequence region (SEQ ID NO: 1421).

[00598] In one embodiment, the AAV particle viral genome comprises a CMV promoter sequence region (SEQ ID NO: 1411), a T7 promoter sequence region (SEQ ID NO: 1414), a modulatory polynucleotide sequence region (SEQ ID NO: 1253), and a bGH polyadenylation signal sequence region (SEQ ID NO: 1421).

[00599] In one embodiment, the AAV particle viral genome comprises one or two promoter sequence regions, and a modulatory polynucleotide sequence region.

[00600] In one embodiment, the AAV particle viral genome comprises a CMV and T7 promoter sequence region, and a modulatory polynucleotide region. Non-limiting examples of sequences for use in the AAV particles of the present invention having all of the sequence modules above are described in Table 40. In Table 40, the sequence identifier or sequence of the sequence region (Region SEQ ID NO) and the length of the sequence region (Region length) are described as well as the name of the sequence (e.g., VOYHT33).

Table 40. Sequence Regions

Sequence Regions	VOYHT33		VOYHT34	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
CMV Promoter	GTTG	4	-	-
H1 Promoter	1413	219	1413	219
Modulatory Polynucleotide	1249	158	1259	260

[00601] In one embodiment, the AAV particle viral genome comprises a CMV promoter sequence region (Sequence: GTTG), a H1 promoter sequence region (SEQ ID NO: 1413), and a modulatory polynucleotide sequence region (SEQ ID NO: 1249).

[00602] In one embodiment, the AAV particle viral genome comprises a H1 promoter sequence region (SEQ ID NO: 1413), and a modulatory polynucleotide sequence region (SEQ ID NO: 1259).

[00603] AAV particles may be modified to enhance the efficiency of delivery. Such modified AAV particles comprising the nucleic acid sequence encoding the siRNA molecules of the present invention can be packaged efficiently and can be used to successfully infect the target cells at high frequency and with minimal toxicity.

[00604] In some embodiments, the AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be a human serotype AAV particle. Such human AAV particle may be derived from any known serotype, e.g., from any one of serotypes AAV1-AAV11. As non-limiting examples, AAV particles may be vectors comprising an AAV1-derived genome in an AAV1-derived capsid; vectors comprising an AAV2-derived genome in an AAV2-derived capsid; vectors comprising an AAV4-derived genome in an AAV4 derived capsid; vectors comprising an AAV6-derived genome in an AAV6 derived capsid or vectors comprising an AAV9-derived genome in an AAV9 derived capsid.

[00605] In other embodiments, the AAV particle comprising a nucleic acid sequence for encoding siRNA molecules of the present invention may be a pseudotyped hybrid or chimeric AAV particle which contains sequences and/or components originating from at least two different AAV serotypes. Pseudotyped AAV particles may be vectors comprising an AAV genome derived from one AAV serotype and a capsid protein derived at least in part from a different AAV serotype. As non-limiting examples, such pseudotyped AAV particles may be vectors comprising an AAV2-derived genome in an AAV1-derived capsid; or vectors comprising an AAV2-derived genome in an AAV6-derived capsid; or vectors comprising an AAV2-derived genome in an AAV4-derived capsid; or an AAV2-derived genome in an AAV9-derived capsid. In like fashion, the present invention contemplates any hybrid or chimeric AAV particle.

[00606] In other embodiments, AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be used to deliver siRNA molecules to the central nervous system (e.g., U.S. Pat. No. 6,180,613; the contents of which is herein incorporated by reference in its entirety).

[00607] In some aspects, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may further comprise a modified capsid including peptides from non-viral origin. In other aspects, the AAV particle may contain a CNS specific

chimeric capsid to facilitate the delivery of encoded siRNA duplexes into the brain and the spinal cord. For example, an alignment of cap nucleotide sequences from AAV variants exhibiting CNS tropism may be constructed to identify variable region (VR) sequence and structure.

Viral production

[00608] The present disclosure provides a method for the generation of parvoviral particles, *e.g.* AAV particles, by viral genome replication in a viral replication cell comprising contacting the viral replication cell with an AAV polynucleotide or AAV genome.

[00609] 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, 5) harvesting and purifying the viral particle comprising a parvoviral genome.

[00610] In one embodiment, the present invention 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.

Cells

[00611] The present disclosure provides a cell comprising an AAV polynucleotide and/or AAV genome.

[00612] Viral production disclosed herein describes processes and methods for producing AAV particles that contact a target cell to deliver a payload construct, *e.g.* a recombinant viral construct, which comprises a polynucleotide sequence encoding a payload molecule.

[00613] In one embodiment, the AAV particles may be produced in a viral replication cell that comprises an insect cell.

[00614] Growing conditions for insect cells in culture, and production of heterologous products in insect cells in culture are well-known in the art, *see* U.S. Pat. No. 6,204,059, the contents of which are herein incorporated by reference in their entirety.

[00615] Any insect cell which allows for replication of parvovirus and which can be maintained in culture can be used in accordance with the present invention. Cell lines may be used from *Spodoptera frugiperda,* including, but not limited to the Sf9 or Sf21 cell lines, *Drosophila* cell lines, or mosquito cell lines, such as *Aedes albopictus* derived cell lines. Use of insect cells for expression of heterologous proteins is well documented, as are methods of introducing nucleic acids, such as vectors, *e.g.*, insect-cell compatible vectors, into such cells and methods of maintaining such cells in culture. *See*, for example, 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); and Samulski *et al.*, U.S. Pat. No. 6,204,059, the contents of each of which is herein incorporated by reference in its entirety.

[00616] The viral replication cell may be selected from any biological organism, including prokaryotic (*e.g.*, bacterial) cells, and eukaryotic cells, including, insect cells, yeast cells and mammalian cells. Viral replication cells may comprise mammalian cells such as A549, WEH1, 3T3, 10T1/2, BHK, MDCK, COS 1, COS 7, BSC 1, BSC 40, BMT 10, VERO. W138, HeLa, HEK293, Saos, C2C12, L cells, HT1080, HepG2 and primary fibroblast, hepatocyte and myoblast cells derived from mammals. Viral replication cells comprise cells derived from mammalian species including, but not limited to, human, monkey, mouse, rat, rabbit, and hamster or cell type, including but not limited to fibroblast, hepatocyte, tumor cell, cell line transformed cell, etc.

Small scale production of AAV Particles

[00617] Viral production disclosed herein describes processes and methods for producing AAV particles that contact a target cell to deliver a payload, *e.g.* a recombinant viral construct, which comprises a polynucleotide sequence encoding a payload.

[00618] In one embodiment, the AAV particles may be produced in a viral replication cell that comprises a mammalian cell.

[00619] 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. 6,156,303, 5,387,484, 5,741,683, 5,691,176, and 5,688,676; U.S. patent application 2002/0081721, and International Patent Applications WO

00/47757, WO 00/24916, and WO 96/17947, the contents of each of which are herein incorporated by reference in their entireties.

[00620] In one embodiment, AAV particles are produced in mammalian-cells wherein all three VP proteins are expressed at a stoichiometry approaching 1:1:10 (VP1:VP2:VP3). The regulatory mechanisms that allow this controlled level of expression include the production of two mRNAs, one for VP1, and the other for VP2 and VP3, produced by differential splicing.

[00621] In another embodiment, AAV particles are produced in mammalian cells using a triple transfection method wherein a payload construct, parvoviral Rep and parvoviral Cap and a helper construct are comprised within three different constructs. The triple transfection method of the three components of AAV particle production may be utilized to produce small lots of virus for assays including transduction efficiency, target tissue (tropism) evaluation, and stability.

Baculovirus

[00622] Particle production disclosed herein describes processes and methods for producing AAV particles that contact a target cell to deliver a payload construct which comprises a polynucleotide sequence encoding a payload.

[00623] Briefly, the viral construct vector and the AAV payload construct vector are each incorporated by a transposon donor/acceptor system into a bacmid, also known as a baculovirus plasmid, by standard molecular biology techniques known and performed by a person skilled in the art. Transfection of separate viral replication cell populations produces two baculoviruses, one that comprises the viral construct expression vector, and another that comprises the AAV payload construct expression vector. The two baculoviruses may be used to infect a single viral replication cell population for production of AAV particles.

[00624] Baculovirus expression vectors for producing viral particles in insect cells, including but not limited to *Spodoptera frugiperda* (Sf9) cells, provide high titers of viral particle product. Recombinant baculovirus encoding the viral construct expression vector and AAV payload construct expression vector initiates a productive infection of viral replicating cells. Infectious baculovirus particles released from the primary infection secondarily infect additional cells in the culture, exponentially infecting the entire cell culture population in a number of infection cycles that is a function of the initial multiplicity of infection, *see* Urabe, M. *et al.*, J Virol. 2006 Feb; 80 (4):1874-85, the contents of which are herein incorporated by reference in their entirety.

[00625] Production of AAV particles with baculovirus in an insect cell system may address known baculovirus genetic and physical instability. In one embodiment, the production system

addresses baculovirus instability over multiple passages by utilizing a titerless infected-cells preservation and scale-up system. Small scale seed cultures of viral producing cells are transfected with viral expression constructs encoding the structural, non-structural, components of the viral particle. Baculovirus-infected viral producing cells are harvested into aliquots that may be cryopreserved in liquid nitrogen; the aliquots retain viability and infectivity for infection of large scale viral producing cell culture Wasilko DJ *et al.*, Protein Expr Purif. 2009 Jun; 65(2):122-32, the contents of which are herein incorporated by reference in their entirety.

[00626] A genetically stable baculovirus may be used to produce source of the one or more of the components for producing AAV particles in invertebrate cells. In one embodiment, defective baculovirus expression vectors may be maintained episomally in insect cells. In such an embodiment the bacmid vector is engineered with replication control elements, including but not limited to promoters, enhancers, and/or cell-cycle regulated replication elements.

[00627] In one embodiment, baculoviruses may be engineered with a (non-) selectable marker for recombination into the chitinase/cathepsin locus. The chia/v-cath locus is non-essential for propagating baculovirus in tissue culture, and the V-cath (EC 3.4.22.50) is a cysteine endoprotease that is most active on Arg-Arg dipeptide containing substrates. The Arg-Arg dipeptide is present in densovirus and parvovirus capsid structural proteins but infrequently occurs in dependovirus VP1.

[00628] In one embodiment, stable viral replication cells permissive for baculovirus infection are engineered with at least one stable integrated copy of any of the elements necessary for AAV replication and viral particle production including, but not limited to, the entire AAV genome, Rep and Cap genes, Rep genes, Cap genes, each Rep protein as a separate transcription cassette, each VP protein as a separate transcription cassette, the AAP (assembly activation protein), or at least one of the baculovirus helper genes with native or non-native promoters.

Large-scale production

[00629] In some embodiments, AAV particle production may be modified to increase the scale of production. Large scale viral production methods according to the present disclosure may include any of those taught in US Patent Nos. 5,756,283, 6,258,595, 6,261,551, 6,270,996, 6,281,010, 6,365,394, 6,475,769, 6,482,634, 6,485,966, 6,943,019, 6,953,690, 7,022,519, 7,238,526, 7,291,498 and 7,491,508 or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597, the contents of each of which are herein incorporated by reference in their entirety. Methods of increasing viral particle production scale typically

comprise increasing the number of viral replication cells. In some embodiments, viral replication cells comprise adherent cells. To increase the scale of viral particle production by adherent viral replication cells, larger cell culture surfaces are required. In some cases, large-scale production methods comprise the use of roller bottles to increase cell culture surfaces. Other cell culture substrates with increased surface areas are known in the art. Examples of additional adherent cell culture products with increased surface areas include, but are not limited to CELLSTACK®, CELLCUBE® (Corning Corp., Corning, NY) and NUNC™ CELL FACTORY™ (Thermo Scientific, Waltham, MA.) In some cases, large-scale adherent cell surfaces may comprise from about 1,000 cm^2 to about 100,000 cm^2. In some cases, large-scale adherent cell cultures may comprise from about 10^7 to about 10^9 cells, from about 10^8 to about 10^{10} cells, from about 10^9 to about 10^{12} cells or at least 10^{12} cells. In some cases, large-scale adherent cultures may produce from about 10^9 to about 10^{12}, from about 10^{10} to about 10^{13}, from about 10^{11} to about 10^{14}, from about 10^{12} to about 10^{15} or at least 10^{15} viral particles.

[00630] In some embodiments, large-scale viral production methods of the present disclosure may comprise the use of suspension cell cultures. Suspension cell culture allows for significantly increased numbers of cells. Typically, the number of adherent cells that can be grown on about 10-50 cm^2 of surface area can be grown in about 1 cm^3 volume in suspension.

[00631] Transfection of replication cells in large-scale culture formats may be carried out according to any methods known in the art. For large-scale adherent cell cultures, transfection methods may include, but are not limited to the use of inorganic compounds (*e.g.* calcium phosphate), organic compounds [*e.g.* polyethyleneimine (PEI)] or the use of non-chemical methods (*e.g.* electroporation.) With cells grown in suspension, transfection methods may include, but are not limited to the use of calcium phosphate and the use of PEI. In some cases, transfection of large scale suspension cultures may be carried out according to the section entitled "Transfection Procedure" described in Feng, L. *et al.*, 2008. Biotechnol Appl. Biochem. 50:121-32, the contents of which are herein incorporated by reference in their entirety. According to such embodiments, PEI-DNA complexes may be formed for introduction of plasmids to be transfected. In some cases, cells being transfected with PEI-DNA complexes may be 'shocked' prior to transfection. This comprises lowering cell culture temperatures to 4°C for a period of about 1 hour. In some cases, cell cultures may be shocked for a period of from about 10 minutes to about 5 hours. In some cases, cell cultures may be shocked at a temperature of from about 0°C to about 20°C.

[00632] In some cases, transfections may include one or more vectors for expression of an RNA effector molecule to reduce expression of nucleic acids from one or more AAV payload construct. Such methods may enhance the production of viral particles by reducing cellular resources wasted on expressing payload constructs. In some cases, such methods may be carried according to those taught in US Publication No. US2014/0099666, the contents of which are herein incorporated by reference in their entirety.

Bioreactors

[00633] In some embodiments, cell culture bioreactors may be used for large scale viral production. In some cases, bioreactors comprise stirred tank reactors. Such reactors generally comprise a vessel, typically cylindrical in shape, with a stirrer (*e.g.* impeller.) In some embodiments, such bioreactor vessels may be placed within a water jacket to control vessel temperature and/or to minimize effects from ambient temperature changes. Bioreactor vessel volume may range in size from about 500 ml to about 2 L, from about 1 L to about 5 L, from about 2.5 L to about 20 L, from about 10 L to about 50 L, from about 25 L to about 100 L, from about 75 L to about 500 L, from about 250 L to about 2,000 L, from about 1,000 L to about 10,000 L, from about 5,000 L to about 50,000 L or at least 50,000 L. Vessel bottoms may be rounded or flat. In some cases, animal cell cultures may be maintained in bioreactors with rounded vessel bottoms.

[00634] In some cases, bioreactor vessels may be warmed through the use of a thermocirculator. Thermocirculators pump heated water around water jackets. In some cases, heated water may be pumped through pipes (*e.g.* coiled pipes) that are present within bioreactor vessels. In some cases, warm air may be circulated around bioreactors, including, but not limited to air space directly above culture medium. Additionally, pH and CO_2 levels may be maintained to optimize cell viability.

[00635] In some cases, bioreactors may comprise hollow-fiber reactors. Hollow-fiber bioreactors may support the culture of both anchorage dependent and anchorage independent cells. Further bioreactors may include, but are not limited to packed-bed or fixed-bed bioreactors. Such bioreactors may comprise vessels with glass beads for adherent cell attachment. Further packed-bed reactors may comprise ceramic beads.

[00636] In some cases, viral particles are produced through the use of a disposable bioreactor. In some embodiments, such bioreactors may include WAVE™ disposable bioreactors.

[00637] In some embodiments, AAV particle production in animal cell bioreactor cultures may be carried out according to the methods taught in US Patent Nos. 5,064764, 6,194,191,

6,566,118, 8,137,948 or US Patent Application No. US2011/0229971, the contents of each of which are herein incorporated by reference in their entirety.

Cell Lysis

[00638] Cells of the invention, including, but not limited to viral production cells, may be subjected to cell lysis according to any methods known in the art. Cell lysis may be carried out to obtain one or more agents (*e.g.* viral particles) present within any cells of the invention. In some embodiments, cell lysis may be carried out according to any of the methods listed in US Patent Nos. 7,326,555, 7,579,181, 7,048,920, 6,410,300, 6,436,394, 7,732,129, 7,510,875, 7,445,930, 6,726,907, 6,194,191, 7,125,706, 6,995,006, 6,676,935, 7,968,333, 5,756,283, 6,258,595, 6,261,551, 6,270,996, 6,281,010, 6,365,394, 6,475,769, 6,482,634, 6,485,966, 6,943,019, 6,953,690, 7,022,519, 7,238,526, 7,291,498 and 7,491,508 or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597, the contents of each of which are herein incorporated by reference in their entirety. Cell lysis methods may be chemical or mechanical. Chemical cell lysis typically comprises contacting one or more cells with one or more lysis agent. Mechanical lysis typically comprises subjecting one or more cells to one or more lysis condition and/or one or more lysis force.

[00639] In some embodiments, chemical lysis may be used to lyse cells. As used herein, the term "lysis agent" refers to any agent that may aid in the disruption of a cell. In some cases, lysis agents are introduced in solutions, termed lysis solutions or lysis buffers. As used herein, the term "lysis solution" refers to a solution (typically aqueous) comprising one or more lysis agent. In addition to lysis agents, lysis solutions may include one or more buffering agents, solubilizing agents, surfactants, preservatives, cryoprotectants, enzymes, enzyme inhibitors and/or chelators. Lysis buffers are lysis solutions comprising one or more buffering agent. Additional components of lysis solutions may include one or more solubilizing agent. As used herein, the term "solubilizing agent" refers to a compound that enhances the solubility of one or more components of a solution and/or the solubility of one or more entities to which solutions are applied. In some cases, solubilizing agents enhance protein solubility. In some cases, solubilizing agents are selected based on their ability to enhance protein solubility while maintaining protein conformation and/or activity.

[00640] Exemplary lysis agents may include any of those described in US Patent Nos. 8,685,734, 7,901,921, 7,732,129, 7,223,585, 7,125,706, 8,236,495, 8,110,351, 7,419,956, 7,300,797, 6,699,706 and 6,143,567, the contents of each of which are herein incorporated by

reference in their entirety. In some cases, lysis agents may be selected from lysis salts, amphoteric agents, cationic agents, ionic detergents and non-ionic detergents. Lysis salts may include, but are not limited to sodium chloride (NaCl) and potassium chloride (KCl.) Further lysis salts may include any of those described in US Patent Nos. 8,614,101, 7,326,555, 7,579,181, 7,048,920, 6,410,300, 6,436,394, 7,732,129, 7,510,875, 7,445,930, 6,726,907, 6,194,191, 7,125,706, 6,995,006, 6,676,935 and 7,968,333, the contents of each of which are herein incorporated by reference in their entirety. Concentrations of salts may be increased or decreased to obtain an effective concentration for rupture of cell membranes. Amphoteric agents, as referred to herein, are compounds capable of reacting as an acid or a base. Amphoteric agents may include, but are not limited to lysophosphatidylcholine, 3-((3-Cholamidopropyl) dimethylammonium)-1-propanesulfonate (CHAPS), ZWITTERGENT® and the like. Cationic agents may include, but are not limited to cetyltrimethylammonium bromide (C (16) TAB) and Benzalkonium chloride. Lysis agents comprising detergents may include ionic detergents or non-ionic detergents. Detergents may function to break apart or dissolve cell structures including, but not limited to cell membranes, cell walls, lipids, carbohydrates, lipoproteins and glycoproteins. Exemplary ionic detergents include any of those taught in US Patent Nos. 7,625,570 and 6,593,123 or US Publication No. US2014/0087361, the contents of each of which are herein incorporated by reference in their entirety. Some ionic detergents may include, but are not limited to sodium dodecyl sulfate (SDS), cholate and deoxycholate. In some cases, ionic detergents may be included in lysis solutions as a solubilizing agent. Non-ionic detergents may include, but are not limited to octylglucoside, digitonin, lubrol, C12E8, TWEEN®-20, TWEEN®-80, Triton X-100 and Noniodet P-40. Non-ionic detergents are typically weaker lysis agents, but may be included as solubilizing agents for solubilizing cellular and/or viral proteins. Further lysis agents may include enzymes and urea. In some cases, one or more lysis agents may be combined in a lysis solution in order to enhance one or more of cell lysis and protein solubility. In some cases, enzyme inhibitors may be included in lysis solutions in order to prevent proteolysis that may be triggered by cell membrane disruption.

[00641] In some embodiments, mechanical cell lysis is carried out. Mechanical cell lysis methods may include the use of one or more lysis condition and/or one or more lysis force. As used herein, the term "lysis condition" refers to a state or circumstance that promotes cellular disruption. Lysis conditions may comprise certain temperatures, pressures, osmotic purity, salinity and the like. In some cases, lysis conditions comprise increased or decreased temperatures. According to some embodiments, lysis conditions comprise changes in

temperature to promote cellular disruption. Cell lysis carried out according to such embodiments may include freeze-thaw lysis. As used herein, the term "freeze-thaw lysis" refers to cellular lysis in which a cell solution is subjected to one or more freeze-thaw cycle. According to freeze-thaw lysis methods, cells in solution are frozen to induce a mechanical disruption of cellular membranes caused by the formation and expansion of ice crystals. Cell solutions used according freeze-thaw lysis methods, may further comprise one or more lysis agents, solubilizing agents, buffering agents, cryoprotectants, surfactants, preservatives, enzymes, enzyme inhibitors and/or chelators. Once cell solutions subjected to freezing are thawed, such components may enhance the recovery of desired cellular products. In some cases, one or more cryoprotectants are included in cell solutions undergoing freeze-thaw lysis. As used herein, the term "cryoprotectant" refers to an agent used to protect one or more substance from damage due to freezing. Cryoprotectants may include any of those taught in US Publication No. US2013/0323302 or US Patent Nos. 6,503,888, 6,180,613, 7,888,096, 7,091,030, the contents of each of which are herein incorporated by reference in their entirety. In some cases, cryoprotectants may include, but are not limited to dimethyl sulfoxide, 1,2-propanediol, 2,3-butanediol, formamide, glycerol, ethylene glycol, 1,3-propanediol and n-dimethyl formamide, polyvinylpyrrolidone, hydroxyethyl starch, agarose, dextrans, inositol, glucose, hydroxyethylstarch, lactose, sorbitol, methyl glucose, sucrose and urea. In some embodiments, freeze-thaw lysis may be carried out according to any of the methods described in US Patent No. 7,704,721, the contents of which are herein incorporated by reference in their entirety.

[00642] As used herein, the term "lysis force" refers to a physical activity used to disrupt a cell. Lysis forces may include, but are not limited to mechanical forces, sonic forces, gravitational forces, optical forces, electrical forces and the like. Cell lysis carried out by mechanical force is referred to herein as "mechanical lysis." Mechanical forces that may be used according to mechanical lysis may include high shear fluid forces. According to such methods of mechanical lysis, a microfluidizer may be used. Microfluidizers typically comprise an inlet reservoir where cell solutions may be applied. Cell solutions may then be pumped into an interaction chamber via a pump (*e.g.* high-pressure pump) at high speed and/or pressure to produce shear fluid forces. Resulting lysates may then be collected in one or more output reservoir. Pump speed and/or pressure may be adjusted to modulate cell lysis and enhance recovery of products (*e.g.* viral particles.) Other mechanical lysis methods may include physical disruption of cells by scraping.

[00643] Cell lysis methods may be selected based on the cell culture format of cells to be lysed. For example, with adherent cell cultures, some chemical and mechanical lysis methods may be used. Such mechanical lysis methods may include freeze-thaw lysis or scraping. In another example, chemical lysis of adherent cell cultures may be carried out through incubation with lysis solutions comprising surfactant, such as Triton-X-100. In some cases, cell lysates generated from adherent cell cultures may be treated with one more nuclease to lower the viscosity of the lysates caused by liberated DNA.

[00644] In one embodiment, a method for harvesting AAV particles without lysis may be used for efficient and scalable AAV particle production. In a non-limiting example, AAV particles may be produced by culturing an AAV particle lacking a heparin binding site, thereby allowing the AAV particle to pass into the supernatant, in a cell culture, collecting supernatant from the culture; and isolating the AAV particle from the supernatant, as described in US Patent Application 20090275107, the contents of which are incorporated herein by reference in their entirety.

Clarification

[00645] Cell lysates comprising viral particles may be subjected to clarification. Clarification refers to initial steps taken in purification of viral particles from cell lysates. Clarification serves to prepare lysates for further purification by removing larger, insoluble debris. Clarification steps may include, but are not limited to centrifugation and filtration. During clarification, centrifugation may be carried out at low speeds to remove larger debris only. Similarly, filtration may be carried out using filters with larger pore sizes so that only larger debris is removed. In some cases, tangential flow filtration may be used during clarification. Objectives of viral clarification include high throughput processing of cell lysates and to optimize ultimate viral recovery. Advantages of including a clarification step include scalability for processing of larger volumes of lysate. In some embodiments, clarification may be carried out according to any of the methods presented in US Patent Nos. 8,524,446, 5,756,283, 6,258,595, 6,261,551, 6,270,996, 6,281,010, 6,365,394, 6,475,769, 6,482,634, 6,485,966, 6,943,019, 6,953,690, 7,022,519, 7,238,526, 7,291,498, 7,491,508, US Publication Nos. US2013/0045186, US2011/0263027, US2011/0151434, US2003/0138772, and International Publication Nos. WO2002012455, WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597, the contents of each of which are herein incorporated by reference in their entirety.

[00646] Methods of cell lysate clarification by filtration are well understood in the art and may be carried out according to a variety of available methods including, but not limited to passive filtration and flow filtration. Filters used may comprise a variety of materials and pore sizes. For example, cell lysate filters may comprise pore sizes of from about 1 μM to about 5 μM, from about 0.5 μM to about 2 μM, from about 0.1 μM to about 1 μM, from about 0.05 μM to about 0.05 μM and from about 0.001 μM to about 0.1 μM. Exemplary pore sizes for cell lysate filters may include, but are not limited to, 2.0, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.95, 0.9, 0.85, 0.8, 0.75, 0.7, 0.65, 0.6, 0.55, 0.5, 0.45, 0.4, 0.35, 0.3, 0.25, 0.2, 0.15, 0.1, 0.05, 0.22, 0.21, 0.20, 0.19, 0.18, 0.17, 0.16, 0.15, 0.14, 0.13, 0.12, 0.11, 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, 0.01, 0.02, 0.019, 0.018, 0.017, 0.016, 0.015, 0.014, 0.013, 0.012, 0.011, 0.01, 0.009, 0.008, 0.007, 0.006, 0.005, 0.004, 0.003, 0.002, 0.001 and 0.001 μM. In one embodiment, clarification may comprise filtration through a filter with 2.0 μM pore size to remove large debris, followed by passage through a filter with 0.45 μM pore size to remove intact cells.

[00647] Filter materials may be composed of a variety of materials. Such materials may include, but are not limited to polymeric materials and metal materials (e.g. sintered metal and pored aluminum.) Exemplary materials may include, but are not limited to nylon, cellulose materials (e.g. cellulose acetate), polyvinylidene fluoride (PVDF), polyethersulfone, polyamide, polysulfone, polypropylene, and polyethylene terephthalate. In some cases, filters useful for clarification of cell lysates may include, but are not limited to ULTIPLEAT PROFILE™ filters (Pall Corporation, Port Washington, NY), SUPOR™ membrane filters (Pall Corporation, Port Washington, NY)

[00648] In some cases, flow filtration may be carried out to increase filtration speed and/or effectiveness. In some cases, flow filtration may comprise vacuum filtration. According to such methods, a vacuum is created on the side of the filter opposite that of cell lysate to be filtered. In some cases, cell lysates may be passed through filters by centrifugal forces. In some cases, a pump is used to force cell lysate through clarification filters. Flow rate of cell lysate through one or more filters may be modulated by adjusting one of channel size and/or fluid pressure.

[00649] According to some embodiments, cell lysates may be clarified by centrifugation. Centrifugation may be used to pellet insoluble particles in the lysate. During clarification, centrifugation strength [expressed in terms of gravitational units (g), which represents multiples of standard gravitational force] may be lower than in subsequent purification steps. In some cases, centrifugation may be carried out on cell lysates at from about 200 g to about 800 g, from

about 500 g to about 1500 g, from about 1000 g to about 5000 g, from about 1200 g to about 10000 g or from about 8000 g to about 15000 g. In some embodiments, cell lysate centrifugation is carried out at 8000 g for 15 minutes. In some cases, density gradient centrifugation may be carried out in order to partition particulates in the cell lysate by sedimentation rate. Gradients used according to methods of the present disclosure may include, but are not limited to cesium chloride gradients and iodixanol step gradients.

Purification: Chromatography

[00650] In some cases, AAV particles may be purified from clarified cell lysates by one or more methods of chromatography. Chromatography refers to any number of methods known in the art for separating out one or more elements from a mixture. Such methods may include, but are not limited to ion exchange chromatography (*e.g.* cation exchange chromatography and anion exchange chromatography), immunoaffinity chromatography and size-exclusion chromatography. In some embodiments, methods of viral chromatography may include any of those taught in US Patent Nos. 5,756,283, 6,258,595, 6,261,551, 6,270,996, 6,281,010, 6,365,394, 6,475,769, 6,482,634, 6,485,966, 6,943,019, 6,953,690, 7,022,519, 7,238,526, 7,291,498 and 7,491,508 or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597, the contents of each of which are herein incorporated by reference in their entirety.

[00651] In some embodiments, ion exchange chromatography may be used to isolate viral particles. Ion exchange chromatography is used to bind viral particles based on charge-charge interactions between capsid proteins and charged sites present on a stationary phase, typically a column through which viral preparations (*e.g.* clarified lysates) are passed. After application of viral preparations, bound viral particles may then be eluted by applying an elution solution to disrupt the charge-charge interactions. Elution solutions may be optimized by adjusting salt concentration and/or pH to enhance recovery of bound viral particles. Depending on the charge of viral capsids being isolated, cation or anion exchange chromatography methods may be selected. Methods of ion exchange chromatography may include, but are not limited to any of those taught in US Patent Nos. 7,419,817, 6,143,548, 7,094,604, 6,593,123, 7,015,026 and 8,137,948, the contents of each of which are herein incorporated by reference in their entirety.

[00652] In some embodiments, immunoaffinity chromatography may be used. Immunoaffinity chromatography is a form of chromatography that utilizes one or more immune compounds (*e.g.* antibodies or antibody-related structures) to retain viral particles. Immune compounds may bind

specifically to one or more structures on viral particle surfaces, including, but not limited to one or more viral coat protein. In some cases, immune compounds may be specific for a particular viral variant. In some cases, immune compounds may bind to multiple viral variants. In some embodiments, immune compounds may include recombinant single-chain antibodies. Such recombinant single chain antibodies may include those described in Smith, R.H. *et al.*, 2009. Mol. Ther. 17(11):1888-96, the contents of which are herein incorporated by reference in their entirety. Such immune compounds are capable of binding to several AAV capsid variants, including, but not limited to AAV1, AAV2, AAV6 and AAV8.

[00653] In some embodiments, size-exclusion chromatography (SEC) may be used. SEC may comprise the use of a gel to separate particles according to size. In viral particle purification, SEC filtration is sometimes referred to as "polishing." In some cases, SEC may be carried out to generate a final product that is near-homogenous. Such final products may in some cases be used in pre-clinical studies and/or clinical studies (Kotin, R.M. 2011. Human Molecular Genetics. 20(1):R2-R6, the contents of which are herein incorporated by reference in their entirety.) In some cases, SEC may be carried out according to any of the methods taught in US Patent Nos. 6,143,548, 7,015,026, 8,476,418, 6,410,300, 8,476,418, 7,419,817, 7,094,604, 6,593,123, and 8,137,948, the contents of each of which are herein incorporated by reference in their entirety.

[00654] In one embodiment, the compositions comprising at least one AAV particle may be isolated or purified using the methods described in US Patent No. US 6146874, the contents of which are herein incorporated by reference in its entirety.

[00655] In one embodiment, the compositions comprising at least one AAV particle may be isolated or purified using the methods described in US Patent No. US 6660514, the contents of which are herein incorporated by reference in its entirety.

[00656] In one embodiment, the compositions comprising at least one AAV particle may be isolated or purified using the methods described in US Patent No. US 8283151, the contents of which are herein incorporated by reference in its entirety.

[00657] In one embodiment, the compositions comprising at least one AAV particle may be isolated or purified using the methods described in US Patent No. US 8524446, the contents of which are herein incorporated by reference in its entirety.

II. FORMULATION AND DELIVERY

Pharmaceutical compositions and formulation

[00658] In addition to the pharmaceutical compositions (AAV particles comprising a modulatory polynucleotide sequence encoding the siRNA molecules), provided herein are

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, and/or rats; and/or birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

[00659] In some embodiments, compositions are administered to humans, human patients or subjects. For the purposes of the present disclosure, the phrase "active ingredient" generally refers either to the synthetic siRNA duplexes, the modulatory polynucleotide encoding the siRNA duplex, or the AAV particle comprising a modulatory polynucleotide encoding the siRNA duplex described herein.

[00660] Formulations of the 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.

[00661] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered.

[00662] The AAV particles comprising the modulatory polynucleotide sequence encoding the siRNA molecules of the present invention can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection or transduction; (3) permit the sustained or delayed release; or (4) alter the biodistribution (e.g., target the AAV particle to specific tissues or cell types such as brain and neurons).

[00663] Formulations of the present invention can include, without limitation, saline, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with AAV particles (e.g., for transplantation into a subject), nanoparticle

mimics and combinations thereof. Further, the AAV particles of the present invention may be formulated using self-assembled nucleic acid nanoparticles.

[00664] Formulations of the 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 associating the active ingredient with an excipient and/or one or more other accessory ingredients.

[00665] 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.

[00666] Relative amounts of the active ingredient, the 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 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1% and 100%, e.g., between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

[00667] 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.

[00668] Excipients, which, as used herein, includes, but is 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.

[00669] 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.

[00670] In some embodiments, the formulations may comprise at least one inactive ingredient. As used herein, the term "inactive ingredient" refers to one or more inactive agents included in formulations. In some embodiments, all, none or some of the inactive ingredients which may be used in the formulations of the present invention may be approved by the US Food and Drug Administration (FDA).

[00671] Formulations of vectors comprising the nucleic acid sequence for the siRNA molecules of the present invention may include cations or anions. In one embodiment, the formulations include metal cations such as, but not limited to, Zn2+, Ca2+, Cu2+, Mg+ and combinations thereof.

[00672] As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form (e.g., by reacting the free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, acetic acid, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzene sulfonic acid, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts,

and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, *Pharmaceutical Salts: Properties, Selection, and Use*, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge et al., *Journal of Pharmaceutical Science*, 66, 1-19 (1977); the content of each of which is incorporated herein by reference in their entirety.

[00673] The term "pharmaceutically acceptable solvate," as used herein, means a compound of the invention wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N,N'*-dimethylformamide (DMF), *N,N'*-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a "hydrate."

[00674] According to the present invention, the AAV particle comprising the modulatory polynucleotide sequence encoding for the siRNA molecules 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 siRNA molecules to the brain blood barrier endothelium may be used to formulate the siRNA duplexes targeting the HTT gene.

Inactive Ingredients

[00675] In some embodiments, formulations may comprise at least one excipient which is an inactive ingredient. As used herein, the term "inactive ingredient" refers to one or more inactive agents 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).

[00676] Formulations of AAV particles described herein may include cations or anions. In one embodiment, the formulations include metal cations such as, but not limited to, Zn2+, Ca2+, Cu2+, Mg+ and combinations thereof. As a non-limiting example, formulations may include polymers and compositions described herein complexed with a metal cation (*See e.g.*, U.S. Pat. Nos. 6,265,389 and 6,555,525, each of which is herein incorporated by reference in its entirety).

Delivery

[00677] In one embodiment, the AAV particles described herein may be administered or delivered using the methods for the delivery of AAV virions described in European Patent Application No. EP1857552, the contents of which are herein incorporated by reference in its entirety.

[00678] In one embodiment, the AAV particles described herein may be administered or delivered using the methods for delivering proteins using AAV vectors described in European Patent Application No. EP2678433, the contents of which are herein incorporated by reference in its entirety.

[00679] In one embodiment, the AAV particle described herein may be administered or delivered using the methods for delivering DNA molecules using AAV vectors described in US Patent No. US 5,858,351, the contents of which are herein incorporated by reference in its entirety.

[00680] In one embodiment, the AAV particle described herein may be administered or delivered using the methods for delivering DNA to the bloodstream described in US Patent No. US 6,211,163, the contents of which are herein incorporated by reference in its entirety.

[00681] In one embodiment, the AAV particle described herein may be administered or delivered using the methods for delivering AAV virions described in US Patent No. US 6,325,998, the contents of which are herein incorporated by reference in its entirety.

[00682] In one embodiment, the AAV particle described herein may be administered or delivered using the methods for delivering a payload to the central nervous system described in US Patent No. US 7,588,757, the contents of which are herein incorporated by reference in its entirety.

[00683] In one embodiment, the AAV particle described herein may be administered or delivered using the methods for delivering a payload described in US Patent No. US 8283151, the contents of which are herein incorporated by reference in its entirety.

[00684] In one embodiment, the AAV particle described herein may be administered or delivered using the methods for delivering a payload using a glutamic acid decarboxylase (GAD) delivery vector described in International Patent Publication No. WO2001089583, the contents of which are herein incorporated by reference in its entirety.

[00685] In one embodiment, the AAV particle described herein may be administered or delivered using the methods for delivering a payload to neural cells described in International Patent Publication No. WO2012057363, the contents of which are herein incorporated by reference in its entirety.

Delivery to Cells

[00686] The present disclosure provides a method of delivering to a cell or tissue any of the above-described AAV polynucleotides or AAV genomes, comprising contacting the cell or tissue with said AAV polynucleotide or AAV genomes or contacting the cell or tissue with a particle comprising said AAV polynucleotide or AAV genome, or contacting the cell or tissue with any of the described compositions, including pharmaceutical compositions. The method of delivering the AAV polynucleotide or AAV genome to a cell or tissue can be accomplished *in vitro, ex vivo*, or *in vivo*.

Introduction into cells- Synthetic dsRNA

[00687] To ensure the chemical and biological stability of siRNA molecules (e.g., siRNA duplexes and dsRNA), it is important to deliver siRNA molecules inside the target cells. In some embodiments, the cells may include, but are not limited to, cells of mammalian origin, cells of human origins, embryonic stem cells, induced pluripotent stem cells, neural stem cells, and neural progenitor cells.

[00688] Nucleic acids, including siRNA, carry a net negative charge on the sugar-phosphate backbone under normal physiological conditions. In order to enter the cell, a siRNA molecule must come into contact with a lipid bilayer of the cell membrane, whose head groups are also negatively charged.

[00689] The siRNA duplexes can be complexed with a carrier that allows them to traverse cell membranes such as package particles to facilitate cellular uptake of the siRNA. The package particles may include, but are not limited to, liposomes, nanoparticles, cationic lipids, polyethylenimine derivatives, dendrimers, carbon nanotubes and the combination of carbon-made nanoparticles with dendrimers. Lipids may be cationic lipids and/or neutral lipids. In

addition to well established lipophilic complexes between siRNA molecules and cationic carriers, siRNA molecules can be conjugated to a hydrophobic moiety, such as cholesterol (e.g., U.S. Patent Publication No. 20110110937; the content of which is herein incorporated by reference in its entirety). This delivery method holds a potential of improving *in vitro* cellular uptake and *in vivo* pharmacological properties of siRNA molecules. The siRNA molecules of the present invention may also be conjugated to certain cationic cell-penetrating peptides (CPPs), such as MPG, transportan or penetratin covalently or non-covalently (e.g., U.S. Patent Publication No. 20110086425; the content of which is herein incorporated by reference in its entirety).

Introduction into cells- AAV particles

[00690] The siRNA molecules (e.g., siRNA duplexes) of the present invention may be introduced into cells using any of a variety of approaches such as, but not limited to, AAV particles. These AAV particles are engineered and optimized to facilitate the entry of siRNA molecule into cells that are not readily amendable to transfection. Also, some synthetic AAV particles possess an ability to integrate the shRNA into the cell genome, thereby leading to stable siRNA expression and long-term knockdown of a target gene. 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 virus.

[00691] In some embodiments, the siRNA molecules of the present invention are introduced into a cell by contacting the cell with an AAV particle comprising a modulatory polynucleotide sequence encoding a siRNA molecule, and a lipophilic carrier. In other embodiments, the siRNA molecule is introduced into a cell by transfecting or infecting the cell with an AAV particle comprising a nucleic acid sequence capable of producing the siRNA molecule when transcribed in the cell. In some embodiments, the siRNA molecule is introduced into a cell by injecting into the cell an AAV particle comprising a nucleic acid sequence capable of producing the siRNA molecule when transcribed in the cell.

[00692] In some embodiments, prior to transfection, an AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be transfected into cells.

[00693] In other embodiments, the AAV particles comprising the nucleic acid sequence encoding the siRNA molecules of the present invention may be delivered into cells by electroporation (e.g. U.S. Patent Publication No. 20050014264; the content of which is herein incorporated by reference in its entirety).

[00694] Other methods for introducing AAV particles comprising the nucleic acid sequence encoding the siRNA molecules described herein may include photochemical internalization as described in U. S. Patent publication No. 20120264807; the content of which is herein incorporated by reference in its entirety.

[00695] In some embodiments, the formulations described herein may contain at least one AAV particle comprising the nucleic acid sequence encoding the siRNA molecules described herein. In one embodiment, the siRNA molecules may target the HTT gene at one target site. In another embodiment, the formulation comprises a plurality of AAV particles, each AAV particle comprising a nucleic acid sequence encoding a siRNA molecule targeting the HTT gene at a different target site. The HTT may be targeted at 2, 3, 4, 5 or more than 5 sites.

[00696] In one embodiment, the AAV particles from any relevant species, such as, but not limited to, human, dog, mouse, rat or monkey may be introduced into cells.

[00697] In one embodiment, the AAV particles may be introduced into cells which are relevant to the disease to be treated. As a non-limiting example, the disease is HD and the target cells are neurons and astrocytes. As another non-limiting example, the disease is HD and the target cells are medium spiny neurons, cortical neurons and astrocytes.

[00698] In one embodiment, the AAV particles may be introduced into cells which have a high level of endogenous expression of the target sequence.

[00699] In another embodiment, the AAV particles may be introduced into cells which have a low level of endogenous expression of the target sequence.

[00700] In one embodiment, the cells may be those which have a high efficiency of AAV transduction.

Delivery to Subjects

[00701] The present disclosure additionally provides a method of delivering to a subject, including a mammalian subject, any of the above-described AAV polynucleotides or AAV genomes comprising administering to the subject said AAV polynucleotide or AAV genome, or administering to the subject a particle comprising said AAV polynucleotide or AAV genome, or administering to the subject any of the described compositions, including pharmaceutical compositions.

[00702] The pharmaceutical compositions of AAV particles described herein may be characterized by one or more of bioavailability, therapeutic window and/or volume of distribution.

III. ADMINISTRATION AND DOSING

Administration

[00703] The AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered by any route which results in a therapeutically effective outcome. These include, but are not limited to, within the parenchyma of an organ such as, but not limited to, a brain (e.g., intraparenchymal), corpus striatum (intrastriatal), enteral (into the intestine), gastroenteral, epidural, oral (by way of the mouth), transdermal, peridural, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), subpial (under the pia), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intraarterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraganglionic (into the ganglion), intraperitoneal, (infusion or injection into the peritoneum), intravesical infusion, intravitreal, (through the eye), intracavernous injection (into a pathologic cavity) intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), in ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis, infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracornal, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corporus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within

the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration which is then covered by a dressing which occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis or spinal.

[00704] In specific embodiments, compositions of AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered in a way which facilitates the vectors or siRNA molecule to enter the central nervous system and penetrate into medium spiny and/or cortical neurons and/or astrocytes.

[00705] In some embodiments, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered by intramuscular injection.

[00706] In one embodiment, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered via intraparenchymal injection.

[00707] In one embodiment, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered via intraparenchymal injection and intrathecal injection.

[00708] In one embodiment, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered via intrastriatal injection.

[00709] In one embodiment, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered via intrastriatal injection and another route of administration described herein.

[00710] In some embodiments, AAV particles that express siRNA duplexes of the present invention may be administered to a subject by peripheral injections (e.g., intravenous) and/or intranasal delivery. It was disclosed in the art that the peripheral administration of AAV particles for siRNA duplexes can be transported to the central nervous system, for example, to the neurons (e.g., U. S. Patent Publication Nos. 20100240739; and 20100130594; the content of each of which is incorporated herein by reference in their entirety).

[00711] In other embodiments, compositions comprising at least one AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered to a subject by intracranial delivery (See, e.g., U. S. Pat. No. 8,119,611; the content of which is incorporated herein by reference in its entirety).

[00712] The AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered in any suitable form, either as a liquid solution or suspension, as a solid form suitable for liquid solution or suspension in a liquid solution. The siRNA duplexes may be formulated with any appropriate and pharmaceutically acceptable excipient.

[00713] The AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may be administered in a "therapeutically effective" amount, i.e., an amount that is sufficient to alleviate and/or prevent at least one symptom associated with the disease, or provide improvement in the condition of the subject.

[00714] In one embodiment, the AAV particle may be administered to the CNS in a therapeutically effective amount to improve function and/or survival for a subject with Huntington's Disease (HD). As a non-limiting example, the vector may be administered by direct infusion into the striatum.

[00715] In one embodiment, the AAV particle may be administered to a subject (e.g., to the CNS of a subject via intrathecal administration) in a therapeutically effective amount for the siRNA duplexes or dsRNA to target the medium spiny neurons, cortical neurons and/or astrocytes. As a non-limiting example, the siRNA duplexes or dsRNA may reduce the expression of HTT protein or mRNA. As another non-limiting example, the siRNA duplexes or dsRNA can suppress HTT and reduce HTT mediated toxicity. The reduction of HTT protein and/or mRNA as well as HTT mediated toxicity may be accomplished with almost no enhanced inflammation.

[00716] In one embodiment, the AAV particle may be administered to a subject (e.g., to the CNS of a subject) in a therapeutically effective amount to slow the functional decline of a subject (e.g., determined using a known evaluation method such as the unified Huntington's

disease rating scale (UHDRS)). As a non-limiting example, the vector may be administered via intraparenchymal injection.

[00717] In one embodiment, the AAV particle may be administered to the cisterna magna in a therapeutically effective amount to transduce medium spiny neurons, cortical neurons and/or astrocytes. As a non-limiting example, the vector may be administered intrathecally.

[00718] In one embodiment, the AAV particle may be administered using intrathecal infusion in a therapeutically effective amount to transduce medium spiny neurons, cortical neurons and/or astrocytes. As a non-limiting example, the vector may be administered intrathecally.

[00719] In one embodiment, the AAV particle may be administered to the cisterna magna in a therapeutically effective amount to transduce medium spiny neurons, cortical neurons and/or astrocytes. As a non-limiting example, the vector may be administered by intraparenchymal injection.

[00720] In one embodiment, the AAV particle comprising a modulatory polynucleotide may be formulated. As a non-limiting example the baricity and/or osmolality of the formulation may be optimized to ensure optimal drug distribution in the central nervous system or a region or component of the central nervous system.

[00721] In one embodiment, the AAV particle comprising a modulatory polynucleotide may be delivered to a subject via a single route administration.

[00722] In one embodiment, the AAV particle comprising a modulatory polynucleotide may be delivered to a subject via a multi-site route of administration. A subject may be administered the AAV particle comprising a modulatory polynucleotide at 2, 3, 4, 5 or more than 5 sites.

[00723] In one embodiment, a subject may be administered the AAV particle comprising a modulatory polynucleotide described herein using a bolus injection.

[00724] In one embodiment, a subject may be administered the AAV particle comprising a modulatory polynucleotide described herein using sustained delivery over a period of minutes, hours or days. The infusion rate may be changed depending on the subject, distribution, formulation or another delivery parameter.

[00725] In one embodiment, the AAV particle described herein is administered via putamen and caudate infusion. As a non-limiting example, the dual infusion provides a broad striatal distribution as well as a frontal and temporal cortical distribution.

[00726] In one embodiment, the AAV particle is AAV-DJ8 which is administered via unilateral putamen infusion. As a non-limiting example, the distribution of the administered AAV-DJ8 is similar to the distribution of AAV1 delivered via unilateral putamen infusion.

[00727] In one embodiment, the AAV particle described herein is administered via intrathecal (IT) infusion at C1. The infusion may be for 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more than 15 hours.

[00728] In one embodiment, the selection of subjects for administration of the AAV particle described herein and/or the effectiveness of the dose, route of administration and/or volume of administration may be evaluated using imaging of the perivascular spaces (PVS) which are also known as Virchow-Robin spaces. PVS surround the arterioles and venules as they perforate brain parenchyma and are filled with cerebrospinal fluid (CSF)/interstitial fluid. PVS are common in the midbrain, basal ganglia, and centrum semiovale. While not wishing to be bound by theory, PVS may play a role in the normal clearance of metabolites and have been associated with worse cognition and several disease states including Parkinson's disease. PVS are usually are normal in size but they can increase in size in a number of disease states. Potter et al. (Cerebrovasc Dis. 2015 Jan; 39(4): 224–231; the contents of which are herein incorporated by reference in its entirety) developed a grading method where they studied a full range of PVS and rated basal ganglia, centrum semiovale and midbrain PVS. They used the frequency and range of PVS used by Mac and Lullich et al. (J Neurol Neurosurg Psychiatry. 2004 Nov;75(11):1519-23; the contents of which are herein incorporated by reference in its entirety) and Potter et al. gave 5 ratings to basal ganglia and centrum semiovale PVS: 0 (none), 1 (1-10), 2 (11-20), 3 (21-40) and 4 (>40) and 2 ratings to midbrain PVS: 0 (non visible) or 1 (visible). The user guide for the rating system by Potter et al. can be found at: www.sbirc.ed.ac.uk/documents/epvs-rating-scale-user-guide.pdf.

Dosing

[00729] The pharmaceutical compositions of the present invention may be administered to a subject using any amount effective for reducing, preventing and/or treating a HTT associated disorder (*e.g.*, Huntington' Disease (HD)). The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like.

[00730] The compositions of the present invention are typically formulated in unit dosage form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutic effectiveness for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the

specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the siRNA duplexes employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[00731] In one embodiment, the age and sex of a subject may be used to determine the dose of the compositions of the present invention. As a non-limiting example, a subject who is older may receive a larger dose (e.g., 5-10%, 10-20%, 15-30% ,20-50%, 25-50% or at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more than 90% more) of the composition as compared to a younger subject. As another non-limiting example, a subject who is younger may receive a larger dose (e.g., 5-10%, 10-20%, 15-30%, 20-50%, 25-50% or at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more than 90% more) of the composition as compared to an older subject. As yet another non-limiting example, a subject who is female may receive a larger dose (e.g., 5-10%, 10-20%, 15-30% ,20-50%, 25-50% or at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more than 90% more) of the composition as compared to a male subject. As yet another non-limiting example, a subject who is male may receive a larger dose (e.g., 5-10%, 10-20%, 15-30% ,20-50%, 25-50% or at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more than 90% more) of the composition as compared to a female subject

[00732] In some specific embodiments, the doses of AAV particles for delivering siRNA duplexes of the present invention may be adapted depending on the disease condition, the subject and the treatment strategy.

[00733] In one embodiment, delivery of the compositions in accordance with the present invention to cells comprises a rate of delivery defined by [VG/hour = mL/hour * VG/mL] wherein VG is viral genomes, VG/mL is composition concentration, and mL/hour is rate of prolonged delivery.

[00734] In one embodiment, delivery of compositions in accordance with the present invention to cells may comprise a total concentration per subject between about $1x10^6$ VG and about $1x10^{16}$ VG. In some embodiments, delivery may comprise a composition concentration of about $1x10^6$, $2x10^6$, $3x10^6$, $4x10^6$, $5x10^6$, $6x10^6$, $7x10^6$, $8x10^6$, $9x10^6$, $1x10^7$, $2x10^7$, $3x10^7$, $4x10^7$, $5x10^7$, $6x10^7$, $7x10^7$, $8x10^7$, $9x10^7$, $1x10^8$, $2x10^8$, $3x10^8$, $4x10^8$, $5x10^8$, $6x10^8$, $7x10^8$, $8x10^8$, $9x10^8$, $1x10^9$, $2x10^9$, $3x10^9$, $4x10^9$, $5x10^9$, $6x10^9$, $7x10^9$, $8x10^9$, $9x10^9$, $1x10^{10}$, $2x10^{10}$, $3x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $1.1x10^{11}$, $1.2x10^{11}$, $1.3x10^{11}$, $1.4x10^{11}$, $1.5x10^{11}$, $1.6x10^{11}$, $1.7x10^{11}$, $1.8x10^{11}$, $1.9x10^{11}$, $2x10^{11}$, $2.1x10^{11}$, $2.2x10^{11}$, $2.3x10^{11}$, $2.4x10^{11}$,

$2.5x10^{11}$, $2.6x10^{11}$, $2.7x10^{11}$, $2.8x10^{11}$, $2.9x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $7.1x10^{11}$, $7.2x10^{11}$, $7.3x10^{11}$, $7.4x10^{11}$, $7.5x10^{11}$, $7.6x10^{11}$, $7.7x10^{11}$, $7.8x10^{11}$, $7.9x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$, $1.1\ x10^{12}$, $1.2x10^{12}$, $1.3x10^{12}$, $1.4x10^{12}$, $1.5x10^{12}$, $1.6x10^{12}$, $1.7x10^{12}$, $1.8x10^{12}$, $1.9x10^{12}$, $2x10^{12}$, $2.1x10^{12}$, $2.2x10^{12}$, $2.3x10^{12}$, $2.4x10^{12}$, $2.5x10^{12}$, $2.6x10^{12}$, $2.7x10^{12}$, $2.8x10^{12}$, $2.9x10^{12}$, $3x10^{12}$, $3.1x10^{12}$, $3.2x10^{12}$, $3.3x10^{12}$, $3.4x10^{12}$, $3.5x10^{12}$, $3.6x10^{12}$, $3.7x10^{12}$, $3.8x10^{12}$, $3.9x10^{12}$, $4x10^{12}$, $4.1x10^{12}$, $4.2x10^{12}$, $4.3x10^{12}$, $4.4x10^{12}$, $4.5x10^{12}$,$4.6x10^{12}$, $4.7x10^{12}$, $4.8x10^{12}$, $4.9x10^{12}$, $5x10^{12}$, $6x10^{12}$, $6.1x10^{12}$, $6.2x10^{12}$, $6.3x10^{12}$, $6.4x10^{12}$, $6.5x10^{12}$, $6.6x10^{12}$, $6.7x10^{12}$, $6.8x10^{12}$, $6.9x10^{12}$, $7x10^{12}$, $8x10^{12}$, $8.1x10^{12}$, $8.2x10^{12}$, $8.3x10^{12}$, $8.4x10^{12}$, $8.5x10^{12}$, $8.6x10^{12}$, $8.7x10^{12}$, $8.8\ x10^{12}$, $8.9x10^{12}$, $9x10^{12}$, $1x10^{13}$, $1.1x10^{13}$, $1.2x10^{13}$, $1.3x10^{13}$, $1.4x10^{13}$, $1.5x10^{13}$, $1.6x10^{13}$, $1.7x10^{13}$, $1.8x10^{13}$, $1.9x10^{13}$, $2x10^{13}$, $3x10^{13}$, $4x10^{13}$, $5x10^{13}$, $6x10^{13}$, $6.7x10^{13}$, $7x10^{13}$, $8x10^{13}$, $9x10^{13}$, $1x10^{14}$, $2x10^{14}$, $3x10^{14}$, $4x10^{14}$, $5x10^{14}$, $6x10^{14}$, $7x10^{14}$, $8x10^{14}$, $9x10^{14}$, $1x10^{15}$, $2x10^{15}$, $3x10^{15}$, $4x10^{15}$, $5x10^{15}$, $6x10^{15}$, $7x10^{15}$, $8x10^{15}$, $9x10^{15}$, or $1x10^{16}$ VG/subject.

[00735] In one embodiment, delivery of compositions in accordance with the present invention to cells may comprise a total concentration per subject between about $1x10^{6}$ VG/kg and about $1x10^{16}$ VG/kg. In some embodiments, delivery may comprise a composition concentration of about $1x10^{6}$, $2x10^{6}$, $3x10^{6}$, $4x10^{6}$, $5x10^{6}$, $6x10^{6}$, $7x10^{6}$, $8x10^{6}$, $9x10^{6}$, $1x10^{7}$, $2x10^{7}$, $3x10^{7}$, $4x10^{7}$, $5x10^{7}$, $6x10^{7}$, $7x10^{7}$, $8x10^{7}$, $9x10^{7}$, $1x10^{8}$, $2x10^{8}$, $3x10^{8}$, $4x10^{8}$, $5x10^{8}$, $6x10^{8}$, $7x10^{8}$, $8x10^{8}$, $9x10^{8}$, $1x10^{9}$, $2x10^{9}$, $3x10^{9}$, $4x10^{9}$, $5x10^{9}$, $6x10^{9}$, $7x10^{9}$, $8x10^{9}$, $9x10^{9}$, $1x10^{10}$, $2x10^{10}$, $3x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $1.1x10^{11}$, $1.2x10^{11}$, $1.3x10^{11}$, $1.4x10^{11}$, $1.5x10^{11}$, $1.6x10^{11}$, $1.7x10^{11}$, $1.8x10^{11}$, $1.9x10^{11}$, $2x10^{11}$, $2.1x10^{11}$, $2.2x10^{11}$, $2.3x10^{11}$, $2.4x10^{11}$, $2.5x10^{11}$, $2.6x10^{11}$, $2.7x10^{11}$, $2.8x10^{11}$, $2.9x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $7.1x10^{11}$, $7.2x10^{11}$, $7.3x10^{11}$, $7.4x10^{11}$, $7.5x10^{11}$, $7.6x10^{11}$, $7.7x10^{11}$, $7.8x10^{11}$, $7.9x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$, $1.1\ x10^{12}$, $1.2x10^{12}$, $1.3x10^{12}$, $1.4x10^{12}$, $1.5x10^{12}$, $1.6x10^{12}$, $1.7x10^{12}$, $1.8x10^{12}$, $1.9x10^{12}$, $2x10^{12}$, $2.1x10^{12}$, $2.2x10^{12}$, $2.3x10^{12}$, $2.4x10^{12}$, $2.5x10^{12}$, $2.6x10^{12}$, $2.7x10^{12}$, $2.8x10^{12}$, $2.9x10^{12}$, $3x10^{12}$, $3.1x10^{12}$, $3.2x10^{12}$, $3.3x10^{12}$, $3.4x10^{12}$, $3.5x10^{12}$, $3.6x10^{12}$, $3.7x10^{12}$, $3.8x10^{12}$, $3.9x10^{12}$, $4x10^{12}$, $4.1x10^{12}$, $4.2x10^{12}$, $4.3x10^{12}$, $4.4x10^{12}$, $4.5x10^{12}$,$4.6x10^{12}$, $4.7x10^{12}$, $4.8x10^{12}$, $4.9x10^{12}$, $5x10^{12}$, $6x10^{12}$, $6.1x10^{12}$, $6.2x10^{12}$, $6.3x10^{12}$, $6.4x10^{12}$, $6.5x10^{12}$, $6.6x10^{12}$, $6.7x10^{12}$, $6.8x10^{12}$, $6.9x10^{12}$, $7x10^{12}$, $8x10^{12}$, $8.1x10^{12}$, $8.2x10^{12}$, $8.3x10^{12}$, $8.4x10^{12}$, $8.5x10^{12}$, $8.6x10^{12}$, $8.7x10^{12}$, $8.8\ x10^{12}$, $8.9x10^{12}$, $9x10^{12}$, $1x10^{13}$, $1.1x10^{13}$, $1.2x10^{13}$, $1.3x10^{13}$, $1.4x10^{13}$, $1.5x10^{13}$, $1.6x10^{13}$, $1.7x10^{13}$, $1.8x10^{13}$, $1.9x10^{13}$, $2x10^{13}$, $3x10^{13}$, $4x10^{13}$, $5x10^{13}$, $6x10^{13}$, $6.7x10^{13}$, $7x10^{13}$, $8x10^{13}$, $9x10^{13}$, $1x10^{14}$, $2x10^{14}$, $3x10^{14}$, $4x10^{14}$, $5x10^{14}$, $6x10^{14}$, $7x10^{14}$, $8x10^{14}$, $9x10^{14}$, $1x10^{15}$, $2x10^{15}$, $3x10^{15}$, $4x10^{15}$, $5x10^{15}$, $6x10^{15}$, $7x10^{15}$, $8x10^{15}$, $9x10^{15}$, or $1x10^{16}$ VG/kg.

[00736] In one embodiment, about 10^{5} to 10^{6} viral genome (unit) may be administered per dose.

[00737] In one embodiment, delivery of the compositions in accordance with the present invention to cells may comprise a total concentration between about $1x10^6$ VG/mL and about $1x10^{16}$ VG/mL. In some embodiments, delivery may comprise a composition concentration of about $1x10^6$, $2x10^6$, $3x10^6$, $4x10^6$, $5x10^6$, $6x10^6$, $7x10^6$, $8x10^6$, $9x10^6$, $1x10^7$, $2x10^7$, $3x10^7$, $4x10^7$, $5x10^7$, $6x10^7$, $7x10^7$, $8x10^7$, $9x10^7$, $1x10^8$, $2x10^8$, $3x10^8$, $4x10^8$, $5x10^8$, $6x10^8$, $7x10^8$, $8x10^8$, $9x10^8$, $1x10^9$, $2x10^9$, $3x10^9$, $4x10^9$, $5x10^9$, $6x10^9$, $7x10^9$, $8x10^9$, $9x10^9$, $1x10^{10}$, $2x10^{10}$, $3x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $1.1x10^{11}$, $1.2x10^{11}$, $1.3x10^{11}$, $1.4x10^{11}$, $1.5x10^{11}$, $1.6x10^{11}$, $1.7x10^{11}$, $1.8x10^{11}$, $1.9x10^{11}$, $2x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$, $1.1x10^{12}$, $1.2x10^{12}$, $1.3x10^{12}$, $1.4x10^{12}$, $1.5x10^{12}$, $1.6x10^{12}$, $1.7x10^{12}$, $1.8x10^{12}$, $1.9x10^{12}$, $2x10^{12}$, $2.1x10^{12}$, $2.2x10^{12}$, $2.3x10^{12}$, $2.4x10^{12}$, $2.5x10^{12}$, $2.6x10^{12}$, $2.7x10^{12}$, $2.8x10^{12}$, $2.9x10^{12}$, $3x10^{12}$, $3.1x10^{12}$, $3.2x10^{12}$, $3.3x10^{12}$, $3.4x10^{12}$, $3.5x10^{12}$, $3.6x10^{12}$, $3.7x10^{12}$, $3.8x10^{12}$, $3.9x10^{12}$, $4x10^{12}$, $4.1x10^{12}$, $4.2x10^{12}$, $4.3x10^{12}$, $4.4x10^{12}$, $4.5x10^{12}$, $4.6x10^{12}$, $4.7x10^{12}$, $4.8x10^{12}$, $4.9x10^{12}$, $5x10^{12}$, $6x10^{12}$, $6.1x10^{12}$, $6.2x10^{12}$, $6.3x10^{12}$, $6.4x10^{12}$, $6.5x10^{12}$, $6.6x10^{12}$, $6.7x10^{12}$, $6.8x10^{12}$, $6.9x10^{12}$, $7x10^{12}$, $8x10^{12}$, $9x10^{12}$, $1x10^{13}$, $1.1x10^{13}$, $1.2x10^{13}$, $1.3x10^{13}$, $1.4x10^{13}$, $1.5x10^{13}$, $1.6x10^{13}$, $1.7x10^{13}$, $1.8x10^{13}$, $1.9x10^{13}$, $2x10^{13}$, $3x10^{13}$, $4x10^{13}$, $5x10^{13}$, $6x10^{13}$, $6.7x10^{13}$, $7x10^{13}$, $8x10^{13}$, $9x10^{13}$, $1x10^{14}$, $2x10^{14}$, $3x10^{14}$, $4x10^{14}$, $5x10^{14}$, $6x10^{14}$, $7x10^{14}$, $8x10^{14}$, $9x10^{14}$, $1x10^{15}$, $2x10^{15}$, $3x10^{15}$, $4x10^{15}$, $5x10^{15}$, $6x10^{15}$, $7x10^{15}$, $8x10^{15}$, $9x10^{15}$, or $1x10^{16}$ VG/mL.

[00738] In certain embodiments, the desired siRNA duplex dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses, e.g., two or more administrations of the single unit dose. As used herein, a "single unit dose" is a dose of any modulatory polynucleotide therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event. As used herein, a "total daily dose" is an amount given or prescribed in a 24 hour period. It may be administered as a single unit dose. In one embodiment, the AAV particles comprising the modulatory polynucleotides of the present invention are administered to a subject in split doses. They may be formulated in buffer only or in a formulation described herein.

[00739] In one embodiment, the dose, concentration and/or volume of the composition described herein may be adjusted depending on the contribution of the caudate or putamen to cortical and subcortical distribution after administration. The administration may be

intracerebroventricular, intraputamenal, intrathalamic, intraparenchymal, subpial, and/or intrathecal administration.

[00740] In one embodiment, the dose, concentration and/or volume of the composition described herein may be adjusted depending on the cortical and neuraxial distribution following administration by intracerebroventricular, intraputamenal, intrathalamic, intraparenchymal, subpial, and/or intrathecal delivery.

IV. METHODS AND USES OF THE COMPOSITIONS OF THE INVENTION

Huntington's Disease (HD)

[00741] Huntington's Disease (HD) is a monogenic fatal neurodegenerative disease characterized by progressive chorea, neuropsychiatric and cognitive dysfunction. Huntington's disease is known to be caused by an autosomal dominant triplet (CAG) repeat expansion in the huntingtin (HTT) gene, which encodes poly-glutamine at the N-terminus of the HTT protein. This repeat expansion results in a toxic gain of function of HTT and ultimately leads to striatal neurodegeneration which progresses to widespread brain atrophy. Medium spiny neurons of the striatum appear to be especially vulnerable in HD with up to 95% loss, whereas interneurons are largely spared.

[00742] Huntington's Disease has a profound impact on quality of life. Symptoms typically appear between the ages of 35-44 and life expectancy subsequent to onset is 10-25 years. In a small percentage of the HD population (~6%), disease onset occurs prior to the age of 21 with appearance of an akinetic-rigid syndrome. These cases tend to progress faster than those of the later onset variety and have been classified as juvenile or Westphal variant HD. It is estimated that approximately 35,000-70,000 patients are currently suffering from HD in the US and Europe. Currently, only symptomatic relief and supportive therapies are available for treatment of HD, with a cure yet to be identified. Ultimately, individuals with HD succumb to pneumonia, heart failure or other complications such as physical injury from falls.

[00743] While not wishing to be bound by theory, the function of the wild type HTT protein may serve as a scaffold to coordinate complexes of other proteins. HTT is a very large protein (67 exons, 3144 amino acids, ~350kDa) that undergoes extensive post-translational modification and has numerous sites for interaction with other proteins, particularly at its N-terminus (coincidently the region that carries the repeats in HD). HTT localizes primarily to the cytoplasm but has been shown to shuttle into the nucleus where it may regulate gene transcription. It has also been suggested that HTT has a role in vesicular transport and regulating RNA trafficking.

[00744] As a non-limiting example, the HTT protein sequence is SEQ ID NO: 1424 (NCBI NP_002102.4) and the HTT nucleic acid sequence is SEQ ID NO: 1425 (NCBI NM_002111.7).

[00745] The mechanisms by which CAG-expanded HTT disrupts normal HTT function and results in neurotoxicity were initially thought to be a disease of haploinsufficiency, this theory was disproven when terminal deletion of the HTT gene in man did not lead to development of HD, suggesting that fully expressed HTT protein is not critical to survival. However, conditional knockout of HTT in mouse led to neurodegeneration, indicating that some amount of HTT is necessary for cell survival. Huntingtin protein is expressed in all cells, though its concentration is highest in the brain where large aggregates of abnormal HTT are found in neuronal nuclei. In the brains of HD patients, HTT aggregates into abnormal nuclear inclusions. It is now believed that it is this process of misfolding and aggregating along with the associated protein intermediates (i.e. the soluble species and toxic N-terminal fragments) that result in neurotoxicity. In fact, HD belongs to a family of nine additional human genetic disorders all of which are characterized by CAG-expanded genes and resultant polyglutamine (poly-Q) protein products with subsequent formation of intraneuronal aggregates. Interestingly, in all of these diseases the length of the expansion correlates with both age of onset and rate of disease progression, with longer expansions linked to greater severity of disease.

[00746] Hypotheses on the molecular mechanisms underlying the neurotoxicity of CAG-expanded HTT and its resultant aggregates have been wide ranging, but include, caspase activation, dysregulation of transcriptional pathways, increased production of reactive oxygen species, mitochondrial dysfunction, disrupted axonal transport and/or inhibition of protein degradation systems within the cell. CAG-expanded HTT may not only have a toxic gain of function, but also exert a dominant negative effect by interfering with the normal function of other cellular proteins and processes. HTT has also been implicated in non-cell autonomous neurotoxicity, whereby a cell hosting HTT spreads the HTT to other neurons nearby.

[00747] In one embodiment, a subject has fully penetrant HD where the HTT gene has 41 or more CAG repeats (e.g., 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 or more than 90 CAG repeats).

[00748] In one embodiment, a subject has incomplete penetrance where the HTT gene has between 36 and 40 CAG repeats (e.g., 36, 37, 38, 39 and 40 CAG repeats).

[00749] Symptoms of HD may include features attributed to CNS degeneration such as, but are not limited to, chorea, dystonia, bradykinesia, incoordination, irritability and depression,

problem solving difficulties, reduction in the ability of a person to function in their normal day to day life, diminished speech, and difficulty swallowing, , as well as features not attributed to CNS degeneration such as, but not limited to, weight loss, muscle wasting, metabolic dysfunction and endocrine disturbances.

[00750] Model systems for studying Huntington's Disease which may be used with the modulatory polynucleotides and AAV particles described herein include, but are not limited to, cell models (e.g., primary neurons and induced pluripotent stem cells), invertebrate models (e.g., *drosophila* or *caenorhabditis elegans*), mouse models (e.g., YAC128 mouse model; R6/2 mouse model; BAC, YAC and knock-in mouse model), rat models (e.g., BAC) and large mammal models (e.g., pigs, sheep or monkeys).

[00751] Studies in animal models of HD have suggested that phenotypic reversal is feasible, for example, subsequent to gene shut off in regulated-expression models. In a mouse model allowing shut off of expression of a 94-polyglutamine repeat HTT protein, not only was the clinical syndrome reversed but also the intracellular aggregates were resolved. Further, animal models in which silencing of HTT was tested, demonstrated promising results with the therapy being both well tolerated and showing potential therapeutic benefit.

[00752] Such siRNA mediated HTT expression inhibition may be used for treating HD. According to the present invention, methods for treating and/or ameliorating HD in a patient comprises administering to the patient an effective amount of AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention into cells. The administration of the AAV particles comprising such a nucleic acid sequence will encode the siRNA molecules which cause the inhibition/silence of HTT gene expression.

[00753] In one embodiment, the AAV particles described herein may be used to reduce the amount of HTT in a subject in need thereof and thus provides a therapeutic benefit as described herein.

[00754] In certain aspects, the symptoms of HD include behavioral difficulties and symptoms such as, but not limited to, apathy or lack of initiative, dysphoria, irritability, agitation or anxiety, poor self-care, poor judgment, inflexibility, disinhibition, depression, suicidal ideation euphoria, aggression, delusions, compulsions, hypersexuality, hallucinations, speech deterioration, slurred speech, difficulty swallowing, weight loss, cognitive dysfunction which impairs executive functions (e.g., organizing, planning, checking or adapting alternatives, and delays in the acquisition of new motor skills), unsteady gait and involuntary movements (chorea). In other aspects, the composition of the present invention is applied to one or both of the brain and the

spinal cord. In one embodiment, the survival of the subject is prolonged by treating any of the symptoms of HD described herein.

[00755] Disclosed in the present invention are methods for treating Huntington's Disease (HD) associated with HTT protein in a subject in need of treatment. The method optionally comprises administering to the subject a therapeutically effective amount of a composition comprising at least AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present invention. As a non-limiting example, the siRNA molecules can silence HTT gene expression, inhibit HTT protein production, and reduce one or more symptoms of HD in the subject such that HD is therapeutically treated.

Methods of treatment of Huntington's Disease

[00756] The present invention provides AAV particles comprising modulatory polynucleotides encoding siRNA molecules targeting the HTT gene, and methods for their design and manufacture. While not wishing to be bound by a single theory of operability, the invention provides modulatory polynucleotides, including siRNAs, that interfere with HTT expression, including HTT mutant and/or wild-type HTT gene expression. Particularly, the present invention employs viral genomes such as adeno-associated viral (AAV) viral genomes comprising modulatory polynucleotide sequences encoding the siRNA molecules of the present invention. The AAV vectors comprising the modulatory polynucleotides encoding the siRNA molecules of the present invention may increase the delivery of active agents into neurons of interest such as medium spiny neurons of the striatum and cortical neurons. The siRNA duplexes or encoded dsRNA targeting the HTT gene may be able to inhibit HTT gene expression (e.g., mRNA level) significantly inside cells; therefore, reducing HTT expression induced stress inside the cells such as aggregation of protein and formation of inclusions, increased free radicals, mitochondrial dysfunction and RNA metabolism.

[00757] Provided in the present invention are methods for introducing the AAV particles comprising a modulatory polynucleotide sequence encoding the siRNA molecules of the present invention into cells, the method comprising introducing into said cells any of the AAV particles in an amount sufficient for degradation of target HTT mRNA to occur, thereby activating target-specific RNAi in the cells. In some aspects, the cells may be stem cells, neurons such as medium spiny or cortical neurons, muscle cells and glial cells such as astrocytes.

[00758] In some embodiments, the present invention provides methods for treating or ameliorating Huntington's Disease (HD) by administering to a subject in need thereof a therapeutically effective amount of a plasmid or AAV vector described herein.

[00759] In some embodiments, the AAV particles comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be used to treat and/or ameliorate for HD.

[00760] In one embodiment, the AAV particles comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be used to reduce the cognitive and/or motor decline of a subject with HD, where the amount of decline is determined by a standard evaluation system such as, but not limited to, Unified Huntington's Disease Ratings Scale (UHDRS) and subscores, and cognitive testing.

[00761] In one embodiment, the AAV particles comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be used to reduce the decline of functional capacity and activities of daily living as measured by a standard evaluation system such as, but not limited to, the total functional capacity (TFC) scale.

[00762] In some embodiments, the present invention provides methods for treating, or ameliorating Huntington's Disease associated with HTT gene and/or HTT protein in a subject in need of treatment, the method comprising administering to the subject a pharmaceutically effective amount of AAV particles comprising modulatory polynucleotides encoding at least one siRNA duplex targeting the HTT gene, inhibiting HTT gene expression and protein production, and ameliorating symptoms of HD in the subject.

[00763] In one embodiment, the AAV vectors of the present invention may be used as a method of treating Huntington's disease in a subject in need of treatment. Any method known in the art for defining a subject in need of treatment may be used to identify said subject(s). A subject may have a clinical diagnosis of Huntington's disease, or may be pre-symptomatic. Any known method for diagnosing HD may be utilized, including, but not limited to, cognitive assessments and/or neurological or neuropsychiatric examinations, motor tests, sensory tests, psychiatric evaluations, brain imaging, family history and/or genetic testing.

[00764] In one embodiment, HD subject selection is determined with the use of the Prognostic Index for Huntington's Disease, or a derivative thereof (Long JD et al., *Movement Disorders,* 2017, 32(2), 256-263, the contents of which are herein incorporated by reference in their entirety). This prognostic index uses four components to predict probability of motor diagnosis, (1) total motor score (TMS) from the Unified Huntington's Disease Rating Scale (UHDRS), (2) Symbol Digit Modality Test (SDMT), (3) base-line age, and (4) cytosine-adenine-guanine (CAG) expansion.

[00765] In one embodiment, the prognostic index for Huntington's Disease is calculated with the following formula: $PI_{HD} = 51 \times TMS+ (-34) \times SDMT + 7 \times Age \times (CAG-34)$, wherein larger values for PI_{HD} indicate greater risk of diagnosis or onset of symptoms.

[00766] In another embodiment, the prognostic index for Huntington's Disease is calculated with the following normalized formula that gives standard deviation units to be interpreted in the context of 50% 10-year survival: $PIN_{HD} = (PI_{HD} - 883)/1044$, wherein $PIN_{HD} < 0$ indicates greater than 50% 10-year survival, and $PIN_{HD} > 0$ suggests less than 50% 10-year survival.

[00767] In one embodiment, the prognostic index may be used to identify subjects whom will develop symptoms of HD within several years, but that do not yet have clinically diagnosable symptoms. Further, these asymptomatic patients may be selected for and receive treatment using the AAV vectors and compositions of the present invention during the asymptomatic period.

[00768] In one embodiment, the AAV particles may be administered to a subject who has undergone biomarker assessment. Potential biomarkers in blood for premanifest and early progression of HD include, but are not limited to, 8-OhdG oxidative stress marker, metabolic markers (e.g., creatine kinase, branched-chain amino acids), cholesterol metabolites (e.g., 24-OH cholesterol), immune and inflammatory proteins (e.g., clusterin, complement components, interleukins 6 and 8), gene expression changes (e.g., transcriptomic markers), endocrine markers (e.g., cortisol, ghrelin and leptin), BDNF, adenosine 2A receptors. Potential biomarkers for brain imaging for premanifest and early progression of HD include, but are not limited to, striatal volume, subcortical white-matter volume, cortical thickness, whole brain and ventricular volumes, functional imaging (e.g., functional MRI), PET (e.g., with fluorodeoxyglucose), and magnetic resonance spectroscopy (e.g., lactate). Potential biomarkers for quantitative clinical tools for premanifest and early progression of HD include, but are not limited to, quantitative motor assessments, motor physiological assessments (e.g., transcranial magnetic stimulation), and quantitative eye movement measurements. Non-limiting examples of quantitative clinical biomarker assessments include tongue force variability, metronome-guided tapping, grip force, oculomotor assessments and cognitive tests. Non-limiting examples of multicenter observational studies include PREDICT-HD and TRACK-HD. A subject may have symptoms of HD, diagnosed with HD or may be asymptomatic for HD.

[00769] In one embodiment, the AAV particles may be administered to a subject who has undergone biomarker assessment using neuroimaging. A subject may have symptoms of HD, diagnosed with HD or may be asymptomatic for HD.

[00770] In one embodiment, the AAV particles may be administered to a subject who is asymptomatic for HD. A subject may be asymptomatic but may have undergone predictive genetic testing or biomarker assessment to determine if they are at risk for HD and/or a subject may have a family member (e.g., mother, father, brother, sister, aunt, uncle, grandparent) who has been diagnosed with HD.

[00771] In one embodiment, the AAV particles may be administered to a subject who is in the early stages of HD. In the early stage a subject has subtle changes in coordination, some involuntary movements (chorea), changes in mood such as irritability and depression, problem solving difficulties, reduction in the ability of a person to function in their normal day to day life.

[00772] In one embodiment, the AAV particles may be administered to a subject who is in the middle stages of HD. In the middle stage a subject has an increase in the movement disorder, diminished speech, difficulty swallowing, and ordinary activities will become harder to do. At this stage a subject may have occupational and physical therapists to help maintain control of voluntary movements and a subject may have a speech language pathologist.

[00773] In one embodiment, the AAV particles may be administered to a subject who is in the late stages of HD. In the late stage, a subject with HD is almost completely or completely dependent on others for care as the subject can no longer walk and is unable to speak. A subject can generally still comprehend language and is aware of family and friends but choking is a major concern.

[00774] In one embodiment, the AAV particles may be used to treat a subject who has the juvenile form of HD which is the onset of HD before the age of 20 years and as early as 2 years.

[00775] In one embodiment, the AAV particles may be used to treat a subject with HD who has fully penetrant HD where the HTT gene has 41 or more CAG repeats (e.g., 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 or more than 90 CAG repeats).

[00776] In one embodiment, the AAV particles may be used to treat a subject with HD who has incomplete penetrance where the HTT gene has between 36 and 40 CAG repeats (e.g., 36, 37, 38, 39 and 40 CAG repeats).

[00777] In some embodiments, the composition comprising the AAV particles comprising modulatory polynucleotides encoding the siRNA molecules of the present invention is administered to the central nervous system of the subject. In other embodiments, the composition comprising the AAV particles comprising modulatory polynucleotides encoding the siRNA

molecules of the present invention is administered to a tissue of a subject (e.g., brain of the subject).

[00778] In one embodiment, the AAV particles comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be delivered into specific types of targeted cells, including, but not limited to, neurons including medium spiny or cortical neurons; glial cells including oligodendrocytes, astrocytes and microglia; and/or other cells surrounding neurons such as T cells.

[00779] In one embodiment, the AAV particles comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be delivered to neurons in the striatum and/or neurons of the cortex.

[00780] In some embodiments, the composition of the present invention for treating HD is administered to the subject in need intravenously, intramuscularly, subcutaneously, intraperitoneally, intraparenchymally, subpially, intrathecally and/or intraventricularly, allowing the siRNA molecules or vectors comprising the siRNA molecules to pass through one or both the blood-brain barrier and the blood spinal cord barrier, or directly access the brain and/or spinal cord. In some aspects, the method includes administering (e.g., intraparenchymal administration, subpial administration, intraventricular administration and/or intrathecal administration) directly to the central nervous system (CNS) of a subject (using, e.g., an infusion pump and/or a delivery scaffold) a therapeutically effective amount of a composition comprising AAV particles encoding the nucleic acid sequence for the siRNA molecules of the present invention. The vectors may be used to silence or suppress HTT gene expression, and/or reducing one or more symptoms of HD in the subject such that HD is therapeutically treated.

[00781] In some embodiments, the siRNA molecules or the AAV vectors comprising such siRNA molecules may be introduced directly into the central nervous system of the subject, for example, by infusion to the white matter a subject. While not wishing to be bound by theory, distribution via direct white matter infusion may be independent of axonal transport mechanisms which may be impaired in subjects with Huntington's Disease which means white matter infusion may allow for more transport of the AAV vectors.

[00782] In one embodiment, the composition comprising the AAV particles comprising modulatory polynucleotides encoding the siRNA molecules of the present invention is administered to the central nervous system of the subject via intraparenchymal injection.

[00783] In one embodiment, the AAV particle composition comprising modulatory polynucleotides encoding the siRNA molecules of the present invention is administered to the central nervous system of the subject via intraparenchymal injection and intrathecal injection.

[00784] In one embodiment, the AAV particle composition comprising modulatory polynucleotides encoding the siRNA molecules of the present invention is administered to the central nervous system of the subject via intraparenchymal injection and intracerebroventricular injection.

[00785] In some embodiments, the composition of the present invention for treating HD is administered to the subject in need by intraparenchymal administration.

[00786] In some embodiments, the AAV particle composition comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be introduced directly into the central nervous system of the subject, for example, by infusion into the putamen.

[00787] In some embodiments, the AAV particle composition comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be introduced directly into the central nervous system of the subject, for example, by infusion into the thalamus of a subject. While not wishing to be bound by theory, the thalamus is an area of the brain which is relatively spared in subjects with Huntington's Disease which means it may allow for more widespread cortical transduction via axonal transport of the AAV vectors.

[00788] In some embodiments, the AAV particle composition comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be introduced indirectly into the central nervous system of the subject, for example, by intravenous administration.

Modulate HTT Expression

[00789] In one embodiment, administration of the AAV particles to a subject will reduce the expression of HTT in a subject and the reduction of expression of the HTT will reduce the effects of HD in a subject.

[00790] In one embodiment, the encoded dsRNA once expressed and contacts a cell expressing HTT protein, inhibits the expression of HTT protein by at least 10%, at least 20%, at least 25%, at least 30%, at least 35% or at least 40% or more, such as when assayed by a method as described herein.

[00791] In one embodiment, administration of the AAV particles comprising a modulatory polynucleotide sequence encoding a siRNA of the invention, to a subject may lower HTT (e.g., mutant HTT, wild-type HTT and/or mutant and wild-type HTT) in a subject. In one embodiment,

administration of the AAV particles to a subject may lower wild-type HTT in a subject. In yet another embodiment, administration of the AAV particles to a subject may lower both mutant HTT and wild-type HTT in a subject. The mutant and/or wild-type HTT may be lowered by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. The mutant HTT may be lowered by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. The wild-type HTT may be lowered by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. The mutant and wild-type HTT may be lowered by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. As a non-limiting example, the AAV particles may lower the expression of HTT by at least 50% in the medium spiny neurons. As a non-limiting example, the vectors, e.g., AAV vectors may lower the expression of HTT by at

least 40% in the medium spiny neurons. As a non-limiting example, the AAV particles may lower the expression of HTT by at least 40% in the medium spiny neurons of the putamen. As a non-limiting example, AAV particles may lower the expression of HTT by at least 30% in the medium spiny neurons of the putamen. As yet another non-limiting example, the AAV particles may lower the expression of HTT in the putamen and cortex by at least 40%. As yet another non-limiting example, the AAV particles may lower the expression of HTT in the putamen and cortex by at least 30%. As yet another non-limiting example, the AAV particles may lower the expression of HTT in the putamen by at least 30%. As yet another non-limiting example, the AAV particles may lower the expression of HTT in the putamen by at least 30% and cortex by at least 15%.

[00792] In one embodiment, the AAV particles may be used to reduce the expression of HTT protein by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. As a non-limiting example, the expression of HTT protein expression may be reduced by 50-90%. As a non-limiting example, the expression of HTT protein expression may be reduced by 30-70%.

[00793] In one embodiment, the siRNA duplexes or encoded dsRNA may be used to reduce the expression of HTT mRNA by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. As a non-limiting example, the expression of HTT mRNA may be reduced 50-90%.

[00794] In one embodiment, the AAV particles may be used to decrease HTT protein in a subject. The decrease may independently be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%. As a non-limiting example, a subject may have a 50% decrease of HTT protein. As a non-limiting example, a subject may have a decrease of 70% of HTT protein and a decrease of 10% of wild type HTT protein. As a non-limiting example, the decrease of HTT in the medium spiny neurons of the putamen may be about 40%. As a non-limiting example, the decrease of HTT in the putamen and cortex may be about 40%. As a non-limiting example, the decrease of HTT in the medium spiny neurons of the putamen may be between 40%-70%. As a non-limiting example, the decrease of HTT in the putamen and cortex may be between 40%-70%.

[00795] In one embodiment, the AAV particles may be used to decrease wild type HTT protein in a subject. The decrease may independently be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%,

20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%. As a non-limiting example, a subject may have a 50% decrease of wild type HTT protein. As a non-limiting example, the decrease of wild type HTT in the medium spiny neurons of the putamen may be about 40%. As a non-limiting example, the decrease of wild type HTT in the putamen and cortex may be about 40%. As a non-limiting example, the decrease of wild type HTT in the medium spiny neurons of the putamen may be between 40%-70%. As a non-limiting example, the decrease of wild type HTT in the putamen and cortex may be between 40%-70%.

[00796] In one embodiment, the AAV particles may be used to decrease mutant HTT protein in a subject. The decrease may independently be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-

90%, 80-95%, or 90-95%. As a non-limiting example, a subject may have a 50% decrease of mutant HTT protein. As a non-limiting example, the decrease of mutant HTT in the medium spiny neurons of the putamen may be about 40%. As a non-limiting example, the decrease of mutant HTT in the putamen and cortex may be about 40%. As a non-limiting example, the decrease of mutant HTT in the medium spiny neurons of the putamen may be between 40%-70%. As a non-limiting example, the decrease of mutant HTT in the putamen and cortex may be between 40%-70%.

[00797] In some embodiments, the present invention provides methods for inhibiting/silencing HTT gene expression in a cell. Accordingly, the siRNA duplexes or encoded dsRNA can be used to substantially inhibit HTT gene expression in a cell, in particular in a neuron. In some aspects, the inhibition of HTT gene expression refers to an inhibition by at least about 20%, such as by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. Accordingly, the protein product of the targeted gene may be inhibited by at least about 20%, preferably by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[00798] In some embodiments, the present invention provides methods for inhibiting/silencing HTT gene expression in a cell, in particular in a medium spiny neuron. In some aspects, the inhibition of HTT gene expression refers to an inhibition by at least about 20%, such as by at

least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. Accordingly, the protein product of the targeted gene may be inhibited by at least about 20%, preferably by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[00799] In some embodiments, the present invention provides methods for inhibiting/silencing HTT gene expression in a cell, in particular in an astrocyte. In some aspects, the inhibition of HTT gene expression refers to an inhibition by at least about 20%, such as by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. Accordingly, the protein product of the targeted gene may be inhibited by at least about 20%, preferably by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[00800] In one embodiment, the siRNA duplexes or encoded dsRNA may be used to reduce the expression of HTT protein and/or mRNA in at least one region of the CNS such as, but not limited to the midbrain. The expression of HTT protein and/or mRNA is reduced by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in at least one region of the CNS. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 50-90%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 30-70%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 40-70%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 50-70%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 50-60%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 50%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 51%. As a non-limiting example, the

expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 52%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 53%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 54%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 55%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 56%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 57%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 58%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 59%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 60%.

[00801] In one embodiment, the siRNA duplexes or encoded dsRNA may be used to reduce the expression of HTT protein and/or mRNA in at least one region of the CNS such as, but not limited to the forebrain. The expression of HTT protein and/or mRNA is reduced by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in at least one region of the CNS. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 50-90%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 30-70%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 40-70%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 50-70%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 50-60%. As a

non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 50%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 51%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 52%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 53%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 54%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 55%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 56%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 57%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 58%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 59%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum and/or cortex is reduced by 60%.

[00802] In one embodiment, the siRNA duplexes or encoded dsRNA may be used to reduce the expression of HTT protein and/or mRNA in the striatum. The expression of HTT protein and/or mRNA is reduced by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 30-70%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by at least 30%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 40-70%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 50-70%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 50-60%. As a non-limiting example, the

expression of HTT protein and mRNA in the striatum is reduced by 50%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 51%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 52%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 53%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 54%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 55%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 56%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 57%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 58%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 59%. As a non-limiting example, the expression of HTT protein and mRNA in the striatum is reduced by 60%.

[00803] In some embodiments, the AAV particles comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be used to suppress HTT protein in neurons and/or astrocytes of the striatum and/or the cortex. As a non-limiting example, the suppression of HTT protein is in medium spiny neurons of the striatum and/or neurons of the cortex.

[00804] In some embodiments, the AAV particles comprising modulatory polynucleotides encoding the siRNA molecules of the present invention may be used to suppress HTT protein in neurons and/or astrocytes of the striatum and/or the cortex and reduce associated neuronal toxicity. The suppression of HTT protein in the neurons and/or astrocytes of the striatum and/or the cortex may be, independently, suppressed by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-

55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%. The reduction of associated neuronal toxicity may be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[00805] In one embodiment, the siRNA duplexes or encoded dsRNA may be used to reduce the expression of HTT protein and/or mRNA in the cortex. The expression of HTT protein and/or mRNA is reduced by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 40-50%. As a non-limiting example, the

expression of HTT protein and mRNA in the cortex is reduced by 30-70%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by at least 30%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 40-70%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 50-70%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 50-60%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 50%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 51%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 52%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 53%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 54%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 55%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 56%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 57%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 58%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 59%. As a non-limiting example, the expression of HTT protein and mRNA in the cortex is reduced by 60%.

[00806] In one embodiment, the siRNA duplexes or encoded dsRNA may be used to reduce the expression of HTT protein and/or mRNA in the motor cortex. The expression of HTT protein and/or mRNA is reduced by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 30-70%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by at

least 30%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 40-70%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 50-70%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 50-60%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 50%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 51%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 52%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 53%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 54%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 55%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 56%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 57%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 58%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 59%. As a non-limiting example, the expression of HTT protein and mRNA in the motor cortex is reduced by 60%.

[00807] In one embodiment, the siRNA duplexes or encoded dsRNA may be used to reduce the expression of HTT protein and/or mRNA in the somatosensory cortex. The expression of HTT protein and/or mRNA is reduced by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 30-70%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by at least 30%. As a non-limiting example, the expression of

HTT protein and mRNA in the somatosensory cortex is reduced by 40-70%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 50-70%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 50-60%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 50%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 51%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 52%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 53%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 54%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 55%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 56%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 57%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 58%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 59%. As a non-limiting example, the expression of HTT protein and mRNA in the somatosensory cortex is reduced by 60%.

[00808] In one embodiment, the siRNA duplexes or encoded dsRNA may be used to reduce the expression of HTT protein and/or mRNA in the temporal cortex. The expression of HTT protein and/or mRNA is reduced by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 30-70%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal

cortex is reduced by at least 30%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 40-70%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 40-50%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 50-70%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 50-60%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 50%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 51%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 52%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 53%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 54%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 55%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 56%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 57%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 58%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 59%. As a non-limiting example, the expression of HTT protein and mRNA in the temporal cortex is reduced by 60%.

[00809] In one embodiment, the siRNA duplexes or encoded dsRNA may be used to reduce the expression of HTT protein and/or mRNA in the putamen. The expression of HTT protein and/or mRNA is reduced by at least about 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%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 55-60%, 55-70%, 55-80%, 55-90%, 55-95%, 55-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in at least one region of the CNS. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 40-70%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 40-50%. As a non-limiting

example, the expression of HTT protein and mRNA in the putamen is reduced by 50-70%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 50-60%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 50%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 51%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 52%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 53%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 54%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 55%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 56%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 57%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 58%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 59%. As a non-limiting example, the expression of HTT protein and mRNA in the putamen is reduced by 60%.

Solo and Combination Therapy

[00810] In some embodiments, the present composition is administered as a solo therapeutic or combination therapeutics for the treatment of HD.

[00811] In some embodiments, the pharmaceutical composition of the present invention is used as a solo therapy. In other embodiments, the pharmaceutical composition of the present invention is used in combination therapy. The combination therapy may be in combination with one or more neuroprotective agents such as small molecule compounds, growth factors and hormones which have been tested for their neuroprotective effect on neuron degeneration.

[00812] The AAV particles encoding siRNA duplexes targeting the HTT gene may be used in combination with one or more other therapeutic agents. By "in combination with," it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent.

[00813] Therapeutic agents that may be used in combination with the AAV particles encoding the nucleic acid sequence for the siRNA molecules of the present invention can be small molecule compounds which are antioxidants, anti-inflammatory agents, anti-apoptosis agents,

calcium regulators, antiglutamatergic agents, structural protein inhibitors, compounds involved in muscle function, and compounds involved in metal ion regulation.

[00814] Compounds tested for treating HD which may be used in combination with the vectors described herein include, but are not limited to, dopamine-depleting agents (e.g., tetrabenazine for chorea), benzodiazepines (e.g., clonazepam for myoclonus, chorea, dystonia, rigidity, and/or spasticity), anticonvulsants (e.g., sodium valproate and levetiracetam for myoclonus), amino acid precursors of dopamine (e.g., levodopa for rigidity which is particularly associate with juvenile HD or young adult-onset parkinsonian phenotype), skeletal muscle relaxants (e.g., baclofen, tizanidine for rigidity and/or spasticity), inhibitors for acetycholine release at the neuromuscular junction to cause muscle paralysis (e.g., botulinum toxin for bruxism and/or dystonia), atypical neuroleptics (e.g., olanzapine and quetiapine for psychosis and/or irritability, risperidone, sulpiride and haloperidol for psychosis, chorea and/or irritability, clozapine for treatment-resistant psychosis, aripiprazole for psychosis with prominent negative symptoms), agents to increase ATP/cellular energetics (e.g., creatine), selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram, fluoxetine, paroxetine, sertraline, mirtazapine, venlafaxine for depression, anxiety, obsessive compulsive behavior and/or irritability), hypnotics (e.g., xopiclone and/or zolpidem for altered sleep-wake cycle), anticonvulsants (e.g., sodium valproate and carbamazepine for mania or hypomania) and mood stabilizers (e.g., lithium for mania or hypomania).

[00815] Neurotrophic factors may be used in combination therapy with the AAV particles encoding the nucleic acid sequence for the siRNA molecules of the present invention for treating HD. Generally, a neurotrophic factor is defined as a substance that promotes survival, growth, differentiation, proliferation and /or maturation of a neuron, or stimulates increased activity of a neuron. In some embodiments, the present methods further comprise delivery of one or more trophic factors into the subject in need of treatment. Trophic factors may include, but are not limited to, IGF-I, GDNF, BDNF, CTNF, VEGF, Colivelin, Xaliproden, Thyrotrophin-releasing hormone and ADNF, and variants thereof.

[00816] In one aspect, the AAV particles comprising modulatory polynucleotides encoding the siRNA duplex targeting the HTT gene may be co-administered with AAV vectors expressing neurotrophic factors such as AAV-IGF-I (See e.g., Vincent et al., *Neuromolecular medicine*, 2004, 6, 79-85; the content of which is incorporated herein by reference in its entirety) and AAV-GDNF (See e.g., Wang et al., *J Neurosci.*, 2002, 22, 6920-6928; the content of which is incorporated herein by reference in its entirety).

V. DEFINITIONS

[00817] Unless stated otherwise, the following terms and phrases have the meanings described below. The definitions are not meant to be limiting in nature and serve to provide a clearer understanding of certain aspects of the present invention.

[00818] As used herein, the term "nucleic acid", "polynucleotide" and 'oligonucleotide" refer to any nucleic acid polymers composed of either polydeoxyribonucleotides (containing 2-deoxy-D-ribose), or polyribonucleotides (containing D-ribose), or any other type of polynucleotide which is an N glycoside of a purine or pyrimidine base, or modified purine or pyrimidine bases. There is no intended distinction in length between the term "nucleic acid", "polynucleotide" and "oligonucleotide", and these terms will be used interchangeably. These terms refer only to the primary structure of the molecule. Thus, these terms include double- and single-stranded DNA, as well as double- and single stranded RNA.

[00819] As used herein, the term "RNA" or "RNA molecule" or "ribonucleic acid molecule" refers to a polymer of ribonucleotides; the term "DNA" or "DNA molecule" or "deoxyribonucleic acid molecule" refers to a polymer of deoxyribonucleotides. DNA and RNA can be synthesized naturally, e.g., by DNA replication and transcription of DNA, respectively; or be chemically synthesized. DNA and RNA can be single-stranded (i.e., ssRNA or ssDNA, respectively) or multi-stranded (e.g., double stranded, i.e., dsRNA and dsDNA, respectively). The term "mRNA" or "messenger RNA", as used herein, refers to a single stranded RNA that encodes the amino acid sequence of one or more polypeptide chains.

[00820] As used herein, the term "RNA interfering" or "RNAi" refers to a sequence specific regulatory mechanism mediated by RNA molecules which results in the inhibition or interfering or "silencing" of the expression of a corresponding protein-coding gene. RNAi has been observed in many types of organisms, including plants, animals and fungi. RNAi occurs in cells naturally to remove foreign RNAs (e.g., viral RNAs). Natural RNAi proceeds via fragments cleaved from free dsRNA which direct the degradative mechanism to other similar RNA sequences. RNAi is controlled by the RNA-induced silencing complex (RISC) and is initiated by short/small dsRNA molecules in cell cytoplasm, where they interact with the catalytic RISC component argonaute. The dsRNA molecules can be introduced into cells exogenously. Exogenous dsRNA initiates RNAi by activating the ribonuclease protein Dicer, which binds and cleaves dsRNAs to produce double-stranded fragments of 21-25 base pairs with a few unpaired overhang bases on each end. These short double stranded fragments are called small interfering RNAs (siRNAs).

[00821] As used herein, the terms "short interfering RNA," "small interfering RNA" or "siRNA" refer to an RNA molecule (or RNA analog) comprising between about 5-60 nucleotides (or nucleotide analogs) which is capable of directing or mediating RNAi. Preferably, a siRNA molecule comprises between about 15-30 nucleotides or nucleotide analogs, such as between about 16-25 nucleotides (or nucleotide analogs), between about 18-23 nucleotides (or nucleotide analogs), between about 19-22 nucleotides (or nucleotide analogs) (e.g., 19, 20, 21 or 22 nucleotides or nucleotide analogs), between about 19-25 nucleotides (or nucleotide analogs), and between about 19-24 nucleotides (or nucleotide analogs). The term "short" siRNA refers to a siRNA comprising 5-23 nucleotides, preferably 21 nucleotides (or nucleotide analogs), for example, 19, 20, 21 or 22 nucleotides. The term "long" siRNA refers to a siRNA comprising 24-60 nucleotides, preferably about 24-25 nucleotides, for example, 23, 24, 25 or 26 nucleotides. Short siRNAs may, in some instances, include fewer than 19 nucleotides, e.g., 16, 17 or 18 nucleotides, or as few as 5 nucleotides, provided that the shorter siRNA retains the ability to mediate RNAi. Likewise, long siRNAs may, in some instances, include more than 26 nucleotides, e.g., 27, 28, 29, 30, 35, 40, 45, 50, 55, or even 60 nucleotides, provided that the longer siRNA retains the ability to mediate RNAi or translational repression absent further processing, e.g., enzymatic processing, to a short siRNA. siRNAs can be single stranded RNA molecules (ss-siRNAs) or double stranded RNA molecules (ds-siRNAs) comprising a sense strand and an antisense strand which hybridized to form a duplex structure called siRNA duplex.

[00822] As used herein, the term "the antisense strand" or "the first strand" or "the guide strand" of a siRNA molecule refers to a strand that is substantially complementary to a section of about 10-50 nucleotides, e.g., about 15-30, 16-25, 18-23 or 19-22 nucleotides of the mRNA of the gene targeted for silencing. The antisense strand or first strand has sequence sufficiently complementary to the desired target mRNA sequence to direct target-specific silencing, e.g., complementarity sufficient to trigger the destruction of the desired target mRNA by the RNAi machinery or process.

[00823] As used herein, the term "the sense strand" or "the second strand" or "the passenger strand" of a siRNA molecule refers to a strand that is complementary to the antisense strand or first strand. The antisense and sense strands of a siRNA molecule are hybridized to form a duplex structure. As used herein, a "siRNA duplex" includes a siRNA strand having sufficient complementarity to a section of about 10-50 nucleotides of the mRNA of the gene targeted for silencing and a siRNA strand having sufficient complementarity to form a duplex with the other siRNA strand.

[00824] As used herein, the term "complementary" refers to the ability of polynucleotides to form base pairs with one another. Base pairs are typically formed by hydrogen bonds between nucleotide units in antiparallel polynucleotide strands. Complementary polynucleotide strands can form base pair in the Watson-Crick manner (e.g., A to T, A to U, C to G), or in any other manner that allows for the formation of duplexes. As persons skilled in the art are aware, when using RNA as opposed to DNA, uracil rather than thymine is the base that is considered to be complementary to adenosine. However, when a U is denoted in the context of the present invention, the ability to substitute a T is implied, unless otherwise stated. Perfect complementarity or 100% complementarity refers to the situation in which each nucleotide unit of one polynucleotide strand can form hydrogen bond with a nucleotide unit of a second polynucleotide strand. Less than perfect complementarity refers to the situation in which some, but not all, nucleotide units of two strands can form hydrogen bond with each other. For example, for two 20-mers, if only two base pairs on each strand can form hydrogen bond with each other, the polynucleotide strands exhibit 10% complementarity. In the same example, if 18 base pairs on each strand can form hydrogen bonds with each other, the polynucleotide strands exhibit 90% complementarity.

[00825] As used herein, the term "substantially complementary" means that the siRNA has a sequence (e.g., in the antisense strand) which is sufficient to bind the desired target mRNA, and to trigger the RNA silencing of the target mRNA.

[00826] As used herein, "targeting" means the process of design and selection of nucleic acid sequence that will hybridize to a target nucleic acid and induce a desired effect.

[00827] The term "gene expression" refers to the process by which a nucleic acid sequence undergoes successful transcription and in most instances translation to produce a protein or peptide. For clarity, when reference is made to measurement of "gene expression", this should be understood to mean that measurements may be of the nucleic acid product of transcription, e.g., RNA or mRNA or of the amino acid product of translation, e.g., polypeptides or peptides. Methods of measuring the amount or levels of RNA, mRNA, polypeptides and peptides are well known in the art.

[00828] As used herein, the term "mutation" refers to any changing of the structure of a gene, resulting in a variant (also called "mutant") form that may be transmitted to subsequent generations. Mutations in a gene may be caused by the alternation of single base in DNA, or the deletion, insertion, or rearrangement of larger sections of genes or chromosomes.

[00829] As used herein, the term "vector" means any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule such as the siRNA molecule of the invention. A "viral genome" or "vector genome" or "viral vector" refers to a sequence which comprises one or more polynucleotide regions encoding or comprising a molecule of interest, e.g., a transgene, a polynucleotide encoding a polypeptide or multi-polypeptide or a modulatory nucleic acid such as small interfering RNA (siRNA). Viral genomes are commonly used to deliver genetic materials into cells. Viral genomes are often modified for specific applications. Types of viral genome sequence include retroviral viral genome sequences, lentiviral viral genome sequences, adenoviral viral genome sequences and adeno-associated viral genome sequences.

[00830] The term "adeno-associated virus" or "AAV" as used herein refers to any vector which comprises or derives from components of an adeno-associated vector and is suitable to infect mammalian cells, preferably human cells. The term AAV vector typically designates an AAV type viral particle or virion comprising a payload. The AAV vector may be derived from various serotypes, including combinations of serotypes (i.e., "pseudotyped" AAV) or from various genomes (e.g., single stranded or self-complementary). In addition, the AAV vector may be replication defective and/or targeted.

[00831] As used herein, the phrase "inhibit expression of a gene" means to cause a reduction in the amount of an expression product of the gene. The expression product can be a RNA molecule transcribed from the gene (*e.g.*, an mRNA) or a polypeptide translated from an mRNA transcribed from the gene. Typically a reduction in the level of an mRNA results in a reduction in the level of a polypeptide translated therefrom. The level of expression may be determined using standard techniques for measuring mRNA or protein.

[00832] As used herein, the term "*in vitro*" refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, in a Petri dish, *etc.*, rather than within an organism (*e.g.*, animal, plant, or microbe).

[00833] As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, animal, plant, or microbe or cell or tissue thereof).

[00834] As used herein, the term "modified" refers to a changed state or structure of a molecule of the invention. Molecules may be modified in many ways including chemically, structurally, and functionally.

[00835] As used herein, the term "synthetic" means produced, prepared, and/or manufactured by the hand of man. Synthesis of polynucleotides or polypeptides or other molecules of the present invention may be chemical or enzymatic.

[00836] As used herein, the term "transfection" refers to methods to introduce exogenous nucleic acids into a cell. Methods of transfection include, but are not limited to, chemical methods, physical treatments and cationic lipids or mixtures. The list of agents that can be transfected into a cell is large and includes, but is not limited to, siRNA, sense and/or anti-sense sequences, DNA encoding one or more genes and organized into an expression plasmid, proteins, protein fragments, and more.

[00837] As used herein, "off target" refers to any unintended effect on any one or more target, gene, or cellular transcript.

[00838] As used herein, the phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00839] As used herein, the term "effective amount" of an agent is that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as such, an "effective amount" depends upon the context in which it is being applied. For example, in the context of administering an agent that treats HD, an effective amount of an agent is, for example, an amount sufficient to achieve treatment, as defined herein, of HD, as compared to the response obtained without administration of the agent.

[00840] As used herein, the term "therapeutically effective amount" means an amount of an agent to be delivered (*e.g.*, nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, *etc.*) that is sufficient, when administered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[00841] As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the invention may be administered, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates such as chimpanzees and other apes and monkey species, and humans) and/or plants.

[00842] As used herein, the term "preventing" or "prevention" refers to delaying or forestalling the onset, development or progression of a condition or disease for a period of time, including weeks, months, or years.

[00843] The term "treatment" or "treating," as used herein, refers to the application of one or more specific procedures used for the cure or amelioration of a disease. In certain embodiments, the specific procedure is the administration of one or more pharmaceutical agents. In the context of the present invention, the specific procedure is the administration of one or more siRNA molecules.

[00844] As used herein, the term "amelioration" or "ameliorating" refers to a lessening of severity of at least one indicator of a condition or disease. For example, in the context of neurodegeneration disorder, amelioration includes the reduction of neuron loss.

[00845] As used herein, the term "administering" refers to providing a pharmaceutical agent or composition to a subject.

[00846] As used herein, the term "neurodegeneration" refers to a pathologic state which results in neural cell death. A large number of neurological disorders share neurodegeneration as a common pathological state. For example, Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS) all cause chronic neurodegeneration, which is characterized by a slow, progressive neural cell death over a period of several years, whereas acute neurodegeneration is characterized by a sudden onset of neural cell death as a result of ischemia, such as stroke, or trauma, such as traumatic brain injury, or as a result of axonal transection by demyelination or trauma caused, for example, by spinal cord injury or multiple sclerosis. In some neurological disorders, mainly one type of neuronal cell is degenerative, for example, medium spiny neuron degeneration in early HD.

VI. EQUIVALENTS AND SCOPE

[00847] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[00848] In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context.

The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

[00849] It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

[00850] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00851] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (e.g., any antibiotic, therapeutic or active ingredient; any method of production; any method of use; etc.) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[00852] It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit of the invention in its broader aspects.

[00853] While the present invention has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the invention.

VII. EXAMPLES

Example 1. *In Vivo* YAC128 Mouse Study of HTT Suppression, Guide to Passenger Ratio and Precision of 5' End Processing after Treatment with AAV1-miRNA Vectors Produced in Mammalian Cells

[00854] Based on *in vitro* suppression of HTT with plasmid transfection and with infection of AAV packaged AAV-miRNA expression vectors, selected AAV-miRNA expression vectors were packaged in AAV1 and evaluated in vivo in YAC128 mice, to quantify HTT mRNA suppression, and to assess guide to passenger strand ratio and the precision of 5' end processing by deep sequencing. The AAV-miRNA transgene genomes were packaged in AAV1 with a CBA promoter (AAV1.CBA.iHtt), and then, the vectors were produced by triple transfection in HEK293 or HEK293T cells, purified and formulated in phosphate buffered saline (PBS) with 0.001% F-68. The vectors were administered to YAC128 mice 7-12 weeks of age via bilateral intrastriatal infusion at a dose of approximately 1E10 to 3E10 vg in 5 uL over 10 minutes per hemisphere. A control group was treated with vehicle (PBS with 0.001% F-68). Each group comprised 4 females and 4 males. Approximately 28 days following test article administration, striatum tissue punches were collected and snap-frozen for later analysis.

[00855] Striatum tissue samples were then homogenized and total RNAs were purified. The relative expression of HTT was determined by qRT-PCR. Housekeeping genes for normalization included mouse XPNPEP1 (X-Prolyl Aminopeptidase 1) and mouse HPRT (hypoxanthine-guanine phosphoribosyltransferase). HTT mRNA was normalized to housekeeping gene expression, and then further normalized to the vehicle group. The total dose (vg/ mouse), and constructs are shown in Table 41. The results are shown in Tables 42 and 43.

Table 41. Construct and Total Dose

ITR to ITR Sequence Name (SEQ ID NO)	Modulatory Polynucleotide Construct Name	Modulatory Polynucleotide SEQ ID NO	Total Dose (vg/mouse)
VOYHT43 (SEQ ID NO: 1433)	VOYHTmiR-127.016	1253	6E10
VOYHT15 (SEQ ID NO: 1366)	VOYHTmiR-127.579	1259	6E10
VOYHT38 (SEQ ID NO: 1428)	VOYHTmiR-104.907	1219	4.91E10
VOYHT37 (SEQ ID NO: 1427)	VOYHTmiR-104.425	1231	6E10
VOYHT42 (SEQ ID NO: 1432)	VOYHTmiR-116.016	1252	3.57E10
VOYHT46 (SEQ ID NO: 1436)	VOYHTmiR-127.257	1211	6E10
VOYHT44 (SEQ ID NO: 1434)	VOYHTmiR-127.218	1194	6E10
VOYHT39 (SEQ ID NO: 1429)	VOYHTmiR-104.257	1207	6E10
VOYHT36 (SEQ ID NO: 1426)	VOYHTmiR-102.016	1248	4.89E10
VOYHT16 (SEQ ID NO: 1367)	VOYHTmiR-104.016	1249	5.79E10
VOYHT35 (SEQ ID NO: 1388)	VOYHTmiR-104.579	1255	5.85E10
VOYHT48 (SEQ ID NO: 1438)	VOYHTmiR-104.579.10	1347	2.65E10
VOYHT40 (SEQ ID NO: 1430)	VOYHTmiR-109.016	1250	5.91E10
VOYHT41 (SEQ ID NO: 1431)	VOYHTmiR-114.016	1251	3.76E10
VOYHT45 (SEQ ID NO: 1435)	VOYHTmiR-127.907	1223	4.71E10
VOYHT47 (SEQ ID NO: 1437)	VOYHTmiR-104.579.3	1262	3.15E10
Vehicle	N/A	-	-

Table 42. HTT mRNA Suppression in YAC128 Mouse Striatum after Intrastriatal Infusion

ITR to ITR Sequence Name	Modulatory Polynucleotide Construct Name	Modulatory Polynucleotide SEQ ID NO	Relative HTT mRNA Level (%) (normalized to	Relative HTT mRNA Level (%) (normalized to

			XPNPEP1) – mean ± standard deviation	HPRT) – mean ± standard deviation
VOYHT43	VOYHTmiR-127.016	1253	63 ± 8	68 ± 9
VOYHT44	VOYHTmiR-127.218	1194	85 ± 19	86 ± 22
VOYHT46	VOYHTmiR-127.257	1211	76 ± 13	78 ± 8
VOYHT42	VOYHTmiR-116.016	1252	99 ± 11	106 ± 18
VOYHT15	VOYHTmiR-127.579	1259	74 ± 6	77 ± 10
VOYHT37	VOYHTmiR-104.425	1231	83 ± 4	86 ± 7
VOYHT39	VOYHTmiR-104.257	1207	91 ± 7	96 ± 10
VOYHT38	VOYHTmiR-104.907	1219	103 ± 18	102 ± 14
Vehicle	N/A	-	100 ± 15	100 ± 14

Table 43. HTT mRNA Suppression in YAC128 Mouse Striatum after Intrastriatal Infusion

ITR to ITR Sequence Name	Modulatory Polynucleotide Construct Name	Modulatory Polynucleotide SEQ ID NO	Relative HTT mRNA Level (%) (normalized to XPNPEP1) – mean ± standard deviation	Relative HTT mRNA Level (%) (normalized to HPRT) – mean ± standard deviation
VOYHT47	VOYHTmiR-104.579.3	1262	67 ± 19	63 ± 18
VOYHT48	VOYHTmiR-104.579.10	1347	70 ± 10	69 ± 10
VOYHT36	VOYHTmiR-102.016	1248	92 ± 12	91 ± 12
VOYHT16	VOYHTmiR-104.016	1249	73 ± 10	68 ± 7
VOYHT41	VOYHTmiR-114.016	1251	93 ± 9	88 ± 16
VOYHT45	VOYHTmiR-127.907	1223	87 ± 14	83 ± 10
VOYHT40	VOYHTmiR-109.016	1250	79 ± 7	76 ± 6
VOYHT35	VOYHTmiR-104.579	1255	94 ± 16	96 ± 13
Vehicle	N/A	-	100 ± 6	100 ± 8

[00856] In YAC128 mouse striatum, VOYHT43 (VOYHTmiR-127.016), VOYHT46 (VOYHTmiR-127.257), VOYHT15 (VOYHTmiR-127.579), VOYHT47 (VOYHTmiR-104.579.3), VOYHT48 (VOYHTmiR-104.579.10), VOYHT16 (VOYHTmiR-104.016) and VOYHT40 (VOYHTmiR-109.016) caused about 20 to 40% silencing of HTT mRNA at about 28 days after intrastriatal infusion of 1E10 to 3E10 vg per striatum.

[00857] Striatum tissue samples were also evaluated for pri-miRNA processing by deep sequencing to assess guide:passenger strand ratio, abundance of guide and passenger strands relative to the total endogenous pool of miRNAs, and precision of processing at the 5'-end of the guide strand. The results are shown in Table 44.

Table 44. Deep Sequencing of YAC128 Mouse Striatal Samples after Intrastriatal Infusion

ITR to ITR Sequence Name	Modulatory Polynucleotide Construct Name	Modulatory Polynucleotide SEQ ID NO	Abundance Relative to Endogenous miRNA Pool (%)	Guide/ Passenger Ratio	% N (Guide)
VOYHT43	VOYHTmiR-127.016	1253	58.13	422.9	91.5
VOYHT44	VOYHTmiR-127.218	1194	1.49	2.44	96.2
VOYHT46	VOYHTmiR-127.257	1211	9.66	0.04	85.7
VOYHT42	VOYHTmiR-116.016	1252	3.09	207.8	95.9
VOYHT15	VOYHTmiR-127.579	1259	0.05	24.28	83.2
VOYHT37	VOYHTmiR-104.425	1231	0.12	0.32	92.7
VOYHT39	VOYHTmiR-104.257	1207	0.07	0.38	97.1

VOYHT38	VOYHTmiR-104.907	1219	6.45	2384	96.4
VOYHT47	VOYHTmiR-104.579.3	1262	0.21	40	86.8
VOYHT48	VOYHTmiR-104.579.10	1347	0.76	83	89.8
VOYHT36	VOYHTmiR-102.016	1248	3.06	494	86.4
VOYHT16	VOYHTmiR-104.016	1249	5.41	629	86.8
VOYHT41	VOYHTmiR-114.016	1251	1.7	256	85.8
VOYHT45	VOYHTmiR-127.907	1223	51.29	163	82.9
VOYHT40	VOYHTmiR-109.016	1250	1.75	135	87.1
VOYHT35	VOYHTmiR-104.579	1255	0.01	19	84.9

[00858] VOYHT43, VOYHT15, VOYHT46, VOYHT48, VOYHT40, and VOYHT47 were shown to have good Htt mRNA knockdown as compared to the other constructs. VOYHT37, VOYHT46, VOYHT44, and VOYHT39 were considered to have a low guide to passenger strand ratio (G:P ratio) as they had a ratio of less than 4. VOYHT43 and VOYHT45 had abundance relative to total miRNA reads which was greater than 10% and considered too high for additional studies. VOYHT48, VOYHT40 and VOYHT47 were selected for additional studies.

Example 2. AAV-miRNA Expression Vectors

[00859] The constructs comprising the pri-miRNA cassettes containing guide strands targeting HTT and passenger strands were engineered into AAV-miRNA expression vectors (either ss or sc). The AAV-miRNA expression vector construct from ITR to ITR, recited 5' to 3', comprises a mutant or wild type ITR, a promoter (either a CMV (which includes an SV40 intron or a human betaglobin intron), U6, H1, CBA (which includes a CMVie enhancer, a CB promoter and an SV40 intron or a human betaglobin intron), or CAG promoter (which includes a CMVie enhancer, a CB promoter, and a rabbit betaglobin intron or a human betaglobin intron), the pri-miRNA cassette containing guide strand sequence targeting HTT and passenger strand sequence, a rabbit globin polyA or human growth hormone polyA and wild type ITR. In vitro and in vivo studies are performed to evaluate the pharmacological activity of the AAV-miRNA expression vectors.

Example 3. *In Vivo* YAC128 Mouse Study of HTT Suppression, Guide to Passenger Strand Ratio and Precision of Processing after Treatment with AAV-miRNA Vectors Produced with the Baculo / Sf9 System

[00860] Three constructs comprising the pri-miRNA cassettes containing guide strands targeting HTT and passenger strands were engineered into scAAV-miRNA expression vectors designed for baculo/Sf9 production. The scAAV-miRNA expression construct from ITR to ITR, recited 5' to 3', comprised a wild type ITR, a CBA promoter (which includes a CMVie enhancer, a CB promoter and an SV40 intron), the pri-miRNA cassette containing guide strand sequence targeting HTT and passenger strand sequence, a rabbit globin polyA, a stuffer sequence, and

wild type ITR. The vectors were produced in the baculo/Sf9 system, purified and formulated in phosphate buffered saline (PBS) with 0.001% F-68, and then administered to YAC128 mice 7-12 weeks of age via bilateral intrastriatal infusion of 5 µL vector at 0.5 µL/min, with a vector concentration of 3.6×10^{12} vg/mL; the total dose was 3.6×10^{10} vg. A control group was treated with vehicle (PBS with 0.001% F-68). Each group comprised 4 females and 4 males. Approximately 28 days following test article administration, striatum tissue punches were collected and snap-frozen. Striatum tissue samples were homogenized and total RNAs were purified, and the relative expression of HTT mRNA was determined by qRT-PCR. The housekeeping gene for normalization was mouse XPNPEP1 (X-Prolyl Aminopeptidase 1). HTT mRNA was normalized to housekeeping gene expression, and then further normalized to the vehicle group. The HTT mRNA results are shown in Table 45.

Table 45. HTT mRNA Suppression in YAC128 Mouse Striatum after Intrastriatal Infusion

ITR to ITR Sequence Name	Modulatory Polynucleotide Construct Name	Modulatory Polynucleotide SEQ ID NO	Relative HTT mRNA Level (%) (normalized to XPNPEP1) – mean ± standard deviation
VOYHT1	VOYHTmiR-104.579.3	1262	56 ± 14
VOYHT3	VOYHTmiR-109.016	1250	58 ± 15
VOYHT4	VOYHTmiR-104.579.10	1347	57 ± 15
Vehicle	N/A	-	100 ± 23

[00861] In YAC128 mouse striatum, VOYHT1 (VOYHTmiR-104.579.3), VOYHT4 (VOYHTmiR-104.579.10), and VOYHT3 (VOYHTmiR-109.016) caused about 42% to 44% silencing of HTT mRNA at about 28 days after intrastriatal infusion of 1.8×10^{10} vg per striatum.

Example 4. In Vivo Study in Non-Human Primates

Study Design

[00862] A study in rhesus monkeys was conducted to evaluate HTT suppression, precision, and efficiency of pri-miRNA processing, tolerability, and distribution of vector genomes within the CNS. Selected constructs comprising the pri-miRNA cassettes containing guide strands targeting HTT and passenger strands were engineered into scAAV-miRNA expression vectors designed for baculo/Sf9 production. The scAAV-miRNA expression construct from ITR to ITR, recited 5' to 3', comprised a wild type ITR, a CBA promoter (which includes a CMVie enhancer, a CB promoter and an SV40 intron), the pri-miRNA cassette containing guide strand sequence targeting HTT and passenger strand sequence, a rabbit globin polyA, a stuffer sequence, and wild type ITR. The vectors were produced in the baculo/Sf9 system, purified and formulated in phosphate buffered saline (PBS) with 0.001% F-68.

[00863] Four groups of rhesus monkeys received vehicle (n=3) or one of three vectors (n=6 per group) as bilateral intraputamenal infusions of 100 µL/side at 3 – 5 µL/min. Gadoteridol (2 mM; ProHance) was co-infused. For animals receiving a vector, the same vector was infused on both sides, with the right side receiving a concentration of 9×10^{11} vg/mL and the left side receiving a concentration of 2.7×10^{12} vg/mL. The total dose of vector administered was 9×10^{10} vg (low dose) or 2.7×10^{11} vg (high dose) per putamen, or 3.6×10^{11} vg per animal. All animals were euthanized after five weeks. The study design is shown in Table 46.

Table 46. Study Design

Group	N	ITR to ITR Sequence Name (SEQ ID NO)	Titer (vg/ml)		Dosing Sites
			Left (High Dose)	Right (Low Dose)	
1	6	VOYHT1 (SEQ ID NO: 1352)	2.7E12	0.9E12	Bilateral putamen infusion via posterior trajectory 100 ul per side
2	6	VOYHT3 (SEQ ID NO: 1354)	2.7E12	0.9E12	
3	6	VOYHT4 (SEQ ID NO: 1355)	2.7E12	0.9E12	
Control	3		-	-	

HTT mRNA Analysis

[00864] HTT mRNA suppression was evaluated in 2 mm tissue punches from the putamen, using branched DNA (bDNA) for quantifying HTT mRNA levels. For each group receiving vector, a total of 60 punches were evaluated per dose of vector (10 punches per putamen, 6 animals per dose of vector). From the vehicle group, 10 punches per putamen were taken from each of 3 animals. HTT mRNA was normalized to the geometric mean of housekeeping genes TATA-box binding protein (TBP), alanyl-tRNA synthetase (AARS) and X-prolyl aminopeptidase 1 (XPNPEP1), and then further normalized to the vehicle group. The HTT mRNA results are shown in Tables 47 and 48.

Table 47. HTT mRNA Suppression in Non-Human Primate Putamen after Intraputamenal Infusion at the High Dose

Group	N	Titer (vg/ml)	Relative HTT mRNA Level (%) (normalized to geometric mean of TBP, AARS and XPNPEP1) – mean ± standard deviation
		Left (High Dose)	
1	6	2.7E12	46 ± 11
2	6	2.7E12	65 ± 9
3	6	2.7E12	46 ± 10
Control	3	-	100 ± 5

Table 48. HTT mRNA Suppression in Non-Human Primate Putamen after Intraputamenal Infusion at the Low Dose

Group	N	Titer (vg/ml)	Relative HTT mRNA Level (%) (normalized to geometric mean of TBP, AARS and XPNPEP1) – mean ± standard deviation
		Right (Low Dose)	
1	6	0.9E12	60 ± 6
2	6	0.9E12	76 ± 8

3	6	0.9E12	62 ± 13
Control	3	-	100 ± 5

Vector Genome Quantitation

[00865] From the same 2 mm tissue punches from the putamen (with high and low dose treatments) that were used for quantifying HTT mRNA levels by bDNA, a portion of the tissue lysate was used for vector genome copy (VG) determination by droplet digital PCR. For Group 1 (VOYHT1) and Group 3 (VOYHT4), approximately 50% HTT mRNA suppression was achieved with approximately 10 VG copies per diploid cell. For Group 2 (VOYHT3), approximately 50% HTT mRNA suppression was achieved with approximately 400 VG copies per diploid cell. The results are shown in Table 49 (high dose, 2.7E12 vg/mL) and Table 50 (low dose, 0.9E12 vg/mL).

Table 49. Vector Genome Copy Number and HTT mRNA Suppression in Non-Human Primate Putamen after Intraputamenal Infusion at the High Dose

	Group 1		Group 2		Group 3	
Tissue Punch No.	Vector Genome Copies/Diploid Cell	Relative HTT mRNA Level (%)	Vector Genome Copies/Diploid Cell	Relative HTT mRNA Level (%)	Vector Genome Copies/Diploid Cell	Relative HTT mRNA Level (%)
1	7.17	50.8	22.52	73.9	2.46	91.7
2	13.35	53.3	5.56	93.4	1123.54	25.7
3	8.4	55.5	7.85	84.8	28.28	61.3
4	6.19	58.7	6.89	85.7	3.06	54.2
5	33.58	49.3	29.35	69.7	126.02	29.4
6	110.19	46.6	0.38	102.9	232.98	35.1
7	312.01	33.5	1408.59	28.5	59.23	78.7
8	645.36	38.3	410.37	62.7	2101.49	29.3
9	112.5	41.2	188.99	64.3	652.06	32.9
10	210.8	47.9	413.03	56.7	297.66	33.6
11	697.33	31.7	1106.15	34.7	305.33	25.9
12	590.33	40.1	2.51	96.5	1167.46	38.9
13	40.5	52.1	277.83	54.6	1.66	80.2
14	9.58	36.2	94.19	74	304.93	47.5
15	476.2	27.8	2.81	80	2.56	69.1
16	1803.57	30.2	960.38	25.2	26.54	52.9
17	4.55	52	7.98	83.3	72.32	27.5
18	1.52	74.9	0.6	94.9	593.8	30.6
19	977.99	24.4	1908.77	29.5	89.84	81.8
20	140.01	35.6	1252.94	34.1	536.51	31.3
21	1340	29.9	146.95	65.8	158.23	59.9
22	2208.66	31.5	1672.46	25.8	282.82	38
23	185.63	37.7	279.26	62.2	1493.92	21.8

24	31.98	69.1	1.6	89.3	598.55	31.8
25	793.55	34.2	547.85	64.1	2.27	84.7
26	2.84	83.8	657.52	48.3	35.32	97.9
27	1377.78	26.1	23.98	86.2	0.79	101
28	861.05	33.2	1479.57	19.5	48.26	75.7
29	5.98	67.9	2.41	96.9	233.81	42.7
30	1.17	93.6	0.86	97.8	56.44	67.2
31	40.1	40.5	16.7	93.1	73.5	39.2
32	1216.3	27.4	3.8	97.9	1321.9	28.6
33	1.8	75.9	43.5	66.3	8.3	47.8
34	0.9	87.7	4.6	96.7	162.7	29.4
35	81.3	38.7	1665.9	23.1	24.1	43.1
36	192.1	44.1	642.7	35.5	505.4	40.3
37	1142.9	23.9	43.3	88.8	1181.3	23.1
38	2046.4	25.1	23.1	104.3	2.3	96.8
39	1.7	89.4	1854.5	25.9	957.4	27.4
40	0.4	89.2	1.6	100.8	1240	23.5
41	1082.2	26.1	437.9	48.9	85.3	71.3
42	291.8	47.7	833	42.7	366.2	44.4
43	1327.27	25.5	698.46	59.4	1378.13	24.7
44	1450	24.8	478.32	80.4	614.11	37.6
45	327.71	55.8	1610.13	24.4	1121.75	26.3
46	1.29	88.7	167.05	81.2	1496.89	29.7
47	1455.07	24.8	1653.33	22.7	1133.25	22.9
48	1029.21	37.2	1205.39	31.3	1251.79	31.2
49	870.1	24.1	35.66	92.9	983.7	28.4
50	98.26	35.9	56.33	89.8	1869.84	24.9
51	422.46	39.4	192.11	54	176.41	53.9
52	28.19	84.4	468.19	67.6	750.01	21.9
53	79	42.7	2196.15	20.5	639.03	25.4
54	629.63	29.6	1355.84	27.3	719.08	30.3
55	1296.5	24.2	1.7	103.7	1076.8	38.5
56	336.7	43	515.7	84.1	29.8	94.8
57	210.7	53.7	1348.7	31	155.6	67.3
58	1.3	93.2	78.7	87.7	1268.3	23.1
59	1832.3	26.1	398.1	60	1303.2	33.4
60	538.5	39.5	660.2	46.2	698.2	37

Table 50. Vector Genome Copy Number and HTT mRNA Suppression in Non-Human Primate Putamen after Intraputamenal Infusion at the Low Dose

	Group 1		Group 2		Group 3	
Tissue Punch No.	Vector Genome Copies/Diploid Cell	Relative HTT mRNA Level (%)	Vector Genome Copies/Diploid Cell	Relative HTT mRNA Level (%)	Vector Genome Copies/Diploid Cell	Relative HTT mRNA Level (%)

61	27.8	74.5	7.5	93.4	0.3	108.2
62	270.4	49.2	0.8	107.1	5.8	68.3
63	0.5	88	4.9	89.9	58.5	73.1
64	20.4	64	2.3	99.6	73.7	47.8
65	1.2	78.8	1.6	98.5	9.4	72.9
66	3.7	90.4	1	101.8	56.6	55.1
67	369.6	31.2	746.5	34.2	1.1	115
68	1082.2	34.3	0.9	116.5	890.1	26.2
69	420.1	34.7	420.5	45.2	384.4	40.1
70	702.6	29.8	138.7	65.3	431	31.4
71	247.6	42.3	269.6	61.3	105.2	58.9
72	91.7	70.3	121.9	63.7	314.3	33.5
73	625.3	28.1	29.2	82	253.6	54.2
74	767.6	40.6	0.6	104.6	42.8	73.9
75	70	60.6	0.6	94.2	0.6	103.7
76	1081.7	26.4	2.5	101.8	45	54.8
77	5	67.3	7.8	88.9	0.4	91.3
78	0.3	91.7	0.5	103	379.2	36.7
79	646.9	28.4	405.4	65.9	143.7	82.5
80	30.5	86.9	66	105.8	318.5	46.3
81	501.8	29.5	58.4	90.1	10.5	82
82	811	34.1	171.2	69.4	81.3	59.8
83	1066.7	26.4	275.5	60.8	15.3	89.4
84	97.9	81.7	88.1	77	899.2	26.9
85	405.3	42	34.4	97.7	0.3	115.8
86	0.5	100.2	2.4	111.6	144.9	82
87	36.5	80.6	6.3	95.5	0.5	103.7
88	263.8	49.7	13.4	96.9	8.5	82.3
89	544.3	25.2	6.4	96.6	0.2	104.5
90	0.7	93.8	0.3	97	229.3	49
91	0.2	94.3	9.1	88.9	0.4	102.1
92	465.1	42.5	5.4	94.8	4.3	87.6
93	3.6	76.6	631.9	42	51.4	71.7
94	0.3	86.8	6.4	93.3	35.4	59.2
95	2	90	14.5	90.9	204.1	40.6
96	62.4	60.5	10.7	96.1	0.7	97.2
97	0.2	95.3	31.7	92.9	42.1	92.4
98	18.2	84.6	445.6	69.1	4.3	103.2
99	476.8	28.1	471.3	43.3	875.3	24.5
100	0.1	91.9	773	26.5	896.6	26.2
101	4.5	96.9	67.8	79.7	862.3	22.4
102	525.2	31.5	671	39.3	311.2	45.3
103	64.3	80.8	1077.2	28.3	593.2	43.7
104	265.4	51.1	693.7	50	190.2	67.6
105	754.9	25.4	774.7	35.1	843.5	24.2
106	67.2	79.3	1063.2	28	767.5	27

107	147.9	61	520.1	54.4	899.4	23.7
108	545.6	32.8	478.8	48.7	686.1	27.1
109	130.3	66.1	676.9	29.8	626	27.2
110	246.8	43.4	6.3	96.9	1.6	103.1
111	194.5	42.1	264.6	54.8	12.1	86.4
112	18.7	85.4	134.3	65.3	5.1	62.9
113	25.7	77	23.7	90.6	28.3	73.3
114	277.9	32.7	4.2	95.7	169.9	50.4
115	2.4	102.2	11.6	101.6	768.8	27.2
116	31.3	89.6	1062.7	44.8	14.3	99.6
117	666.6	27.2	145.4	71.9	311.3	49.8
118	0.3	93.7	213.6	80	534.6	35
119	657.8	25	463.3	46.6	414.8	33.9
120	471.8	30.6	170.8	69.4	785.8	24.2

Pri-miRNA Processing

[00866] Precision and efficiency of pri-miRNA processing were evaluated by deep sequencing of 2 mm punches from the putamen, from the high and low dose treatments, to assess guide:passenger strand ratio, abundance of guide and passenger strands relative to the total endogenous pool of miRNAs, and precision of processing at the 5'-end of the guide strand. These results are shown in Table 51.

Table 51. Deep Sequencing in Non-Human Primate Putamen after Intraputamenal Infusion

Group	Titer (vg/ml)	Abundance Relative to Endogenous miRNA Pool (%)	Guide/Passenger Ratio	% N (Guide)
1	High (2.7E12)	2.2	376	98
	Low (0.9E12)	0.35	424	97
2	High (2.7E12)	0.23	147	96
	Low (0.9E12)	0.21	136	96
3	High (2.7E12)	3.54	44	98
	Low (0.9E12)	1.53	46	97

Tolerability Results

[00867] Body weight assessments were acquired on Day -8 (i.e., 8 days prior to dosing of the first animal), Day 1, and each week thereafter until termination on Day 36±3. There was no significant change in the average body weights in each group throughout the 5 week in-life period.

[00868] Cage-side observations were performed twice daily (a.m. and p.m.) beginning on Day -8 until scheduled necropsy, to assess abnormalities including neurological signs, and signs of pain or distress, as well as changes in general health, appearance, and behavior. In addition,

beginning on Day -8, food consumption was assessed qualitatively once per day. Only decreased appetence was noted in a few animals following surgery; this is considered a common finding post-surgery. Food consumption returned to normal within the first week and remained normal for the remainder of the study.

[00869] Blood was collected on Day -8, Day 15±2, and Day 36±3 for evaluation of hematology, serum chemistry, and coagulation. Hematology assessments comprised WBC, RBC, HGB, HCT, MCV, MCH, MCHC, PLT (qualitative assessment), and absolute and relative values for NEUT, LYMPH, MONO, EOS, and BASO. Serum chemistry comprised TP, ALB, GLOB, A/G ratio, ALP ALT, AST, TBIL (direct and indirect), BUN, CREAT, Ca CHOL, GLU, Phos, TCO2, Na, K and Cl. Coagulation comprised PT, A-PTT and fibrinogen. Although some values fell outside of the normal limits, they were interpreted as physiological variations in the absence of any clinical correlation during in-life.

[00870] At necropsy, no abnormalities in gross pathology were observed.

[00871] Histopathology was conducted on the putamen including the infusion site. For all animals, a 3 mm thick coronal brain slab containing the putamen was fixed by immersion in 4% paraformaldehyde for 72 to 96 hours at room temperature and then transferred to phosphate buffered saline (PBS) for storage at approximately +4degC. The 3 mm brain slabs were then embedded in paraffin and coronally sectioned. Full coronal sections, 5 um thick, containing the infusion site in the putamen were assessed for pathology by standard hematoxylin and eosin staining. The vehicle control group was consistent with what would be expected to occur with any injection into the putamen, i.e. the reactions were typical for those associated with a needle track. In Groups 1, 2, and 3, each animal treated with one of three vectors exhibited pathology findings comprised of mild focal gliosis from the needle track, minimal to mild perivascular infiltrates and/or occasional edema most likely due to a combination of trauma from the injection and reaction to the AAV. There were no pathology findings that were considered adverse, given the absence of clinical symptoms.

Example 5. Activity of Vectors with Filler Sequences

[00872] The miRNA expression vectors encoding VOYHTmiR-104.579.3 (SEQ ID NO: 1262) or VOYHTmiR-104.016 (SEQ ID NO: 1249) were packaged in AAV1, and infected into HEK293T cells. For HEK293T, the cells were plated into 96-well plates (2.5E4 cells/well in 100 ul cell culture medium) and infected with the miRNA expression vectors. 48 hours after infection, the cells were harvested for immediate cell lysis, RNA isolation and qRT-PCR. The

MOI and the results for the vectors and the description of the vectors tested are shown in Table 52. In Table 52, SC means self-complementary vector and SS means single-stranded.

Table 52. Knockdown of HTT mRNA

No.	Modulatory Polynucleotide Name	Sequence Name	Promoter	Length of Construct (ITR to ITR)	SC or SS	Filler SEQ (Y/N)	Relative Htt mRNA Level (%) (normalized to GFP Control)		
							1E3	1E4	1E5
13	VOYHTmiR-104.579.3	VOYHT1	CBA	2301 nt	SC	Y	51	15	13
14	VOYHTmiR-104.579.3	VOYHT6	CBA	2299 nt	SC	Y	54	17	12
15	VOYHTmiR-104.579.3	VOYHT10	CBA	2307 nt	SC	Y	88	63	30
16	VOYHTmiR-104.579.3	VOYHT13	CBA	1587 nt	SC	N	47	30	12
17	VOYHTmiR-104.016	VOYHT14	CBA	1582 nt	SC	N	86	43	30
18	VOYHTmiR-104.016	VOYHT25	CMV	2198 nt	SC	N	49	41	16
19	VOYHTmiR-104.579.3	VOYHT26	CMV	2203 nt	SC	N	32	16	9
20	VOYHTmiR-104.579.3	VOYHT22	CMV	2300 nt	SC	Y	74	26	12
21	VOYHTmiR-104.579.3	VOYHT18	CMV	2308 nt	SC	Y	32	17	10
22	VOYHTmiR-104.579.3	VOYHT20	CMV	2306 nt	SC	Y	45	19	7
23	VOYHTmiR-104.579.3	VOYHT24	CMV	2314 nt	SC	Y	65	22	12
24	VOYHTmiR-104.579.3	VOYHT2	CBA	4608 nt	SS	Y	106	58	27
25	VOYHTmiR-104.579.3	VOYHT5	CBA	4606 nt	SS	Y	132	68	41
26	VOYHTmiR-104.579.3	VOYHT9	CBA	4616 nt	SS	Y	93	56	19
27	VOYHTmiR-104.579.3	VOYHT21	CMV	4598 nt	SS	Y	114	85	26
28	VOYHTmiR-104.579.3	VOYHT17	CMV	4606 nt	SS	Y	128	54	20
29	VOYHTmiR-104.579.3	VOYHT19	CMV	4608 nt	SS	Y	53	72	25
30	VOYHTmiR-104.579.10	VOYHT4	CBA	2301 nt	SS	Y	63	61	14
31	VOYHTmiR-104.579.10	VOYHT48	CBA	1352 nt		N	49	26	10

[00873] The miRNA expression vectors which were approximately 2300 nucleotides in length had a higher genome quality as compared to the vectors having approximately 1500 nucleotides or 1900 nucleotides. CBA and CMV promoters produced similar levels of knockdown *in vitro*. Self-complementary vectors produced the highest levels of knockdown *in vitro*.

Example 6. Quality Control of Vectors Produced with the Baculo / Sf9 System in Large Scale

[00874] The miRNA expression vectors of the present disclosure were produced by using a Baculo/Sf9 system on a 1L scale. A cesium chloride (CsCl) gradient analysis was used in addition to standard purification techniques to ensure a high % of full vectors. The achieved % of full vectors was at least 80%. Titers ranged from 0.9E12 to 4E13 vg/L of culture, and the vectors with a 5' or 3' filler sequence vectors presented the highest titers. The quality of the genome packaged in the vectors of the present disclosure was evaluated by using alkaline denaturing gel analysis, showing a high level of genome quality. The gel banding patterns for the 1L scale production was similar to the small scale production pattern. The purity of the vectors of the present invention was evaluated by using silver stain PAGE analysis, showing good VP1, VP2, and VP3 ratio and purity.

[00875] The miRNA expression vectors encoding VOYHTmiR-104.579.3, VOYHTmiR-104.579.10, and VOYHTmiR-109.016 were packaged in AAV1, and infected into HEK293T cells. For HEK293T, the cells were plated into 96-well plates (2.5E4 cells/well in 100 ul cell culture medium) and infected with the miRNA expression vectors. 60 hours after infection, the cells were harvested for immediate cell lysis, RNA isolation and qRT-PCR and the levels of HTT were calculated compared to a GFP transduction control. The MOI and the results for the vectors and the description of the vectors tested are shown in Table 53. In Table 53, SC means self-complementary vector.

Table 53. Knockdown of HTT mRNA

No.	Modulatory Polynucleotide Name	Sequence Name	Promoter	Length of Construct (ITR to ITR)	SC or SS	Filler SEQ (Y/N)	Relative Htt mRNA Level (%) (normalized to GFP Control)		
							1E3	1E4	1E5
14	VOYHTmiR-104.579.3	VOYHT6	CBA	2.3kb	SC	Y	81	39	16
32	VOYHTmiR-109.016	VOYHT7	CBA	2.3kb	SC	Y	74	59	27
33	VOYHTmiR-104.579.10	VOYHT8	CBA	2.3kb	SC	Y	66	35	17
13	VOYHTmiR-104.579.3	VOYHT1	CBA	2.3kb	SC	Y	81	39	15
34	VOYHTmiR-109.016	VOYHT3	CBA	2.3kb	SC	Y	75	44	21
30	VOYHTmiR-104.579.10	VOYHT4	CBA	2.3kb	SC	Y	58	31	14
15	VOYHTmiR-104.579.3	VOYHT10	CBA	2.3kb	SC	Y	77	83	24

[00876] A dose dependent knockdown was observed for most of the constructs. Self-complementary vectors produced highest levels of knockdown in vitro compared to single-stranded vectors. Vectors with 5' or 3' filler sequences presented higher levels of knockdown in vitro compared to vectors with split filler sequences.

[00877] While the present invention has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the invention.

[00878] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification,

including definitions, will control. In addition, section headings, the materials, methods, and examples are illustrative only and not intended to be limiting.

CLAIMS

We claim:

1. An AAV viral genome comprises, in order:

a) a 5' inverted terminal repeat (ITR) sequence region, wherein said 5' ITR sequence region is selected from the group consisting of SEQ ID NO: 1380 and 1381,

b) an enhancer sequence region, wherein said enhancer sequence region is selected from the group consisting of SEQ ID NO: 1408 and 1409,

c) a promoter sequence region, wherein said promoter sequence region is selected from the group consisting of SEQ ID NO: 1410-1411 and the sequence GTTG,

d) a first intron sequence region, wherein said first sequence region is selected from the group consisting of SEQ ID NO: 1417-1419,

e) a modulatory polynucleotide sequence region, wherein said modulatory polynucleotide sequence region selected from the group consisting of SEQ ID NO: 1183-1279, and 1346-1347,

f) a polyadenylation (polyA) signal sequence region, wherein said polyA signal sequence region selected from the group consisting of SEQ ID NO: 1420-1423, and

g) a 3' ITR sequence region, wherein said 3' ITR sequence region is selected from the group consisting of SEQ ID NO: 1382 and 1383.

2. The AAV viral genome of claim 1 further comprising at least one multiple cloning site (MCS) sequence region, wherein said at least one MCS sequence region is selected from the group consisting of SEQ ID NO: 1384-1390 and the sequence TCGAG.

3. The AAV viral genome of claim 2, wherein the AAV viral genome comprises one MCS sequence region.

4. The AAV viral genome of claim 2 further comprising at least one exon sequence region, wherein said at least one exon sequence region is selected from the group consisting of SEQ ID NO: 1415 and 1416.

5. The AAV viral genome of claim 4, wherein the AAV viral genome comprises one exon sequence region.

6. The AAV viral genome of claim 4, wherein the AAV viral genome comprises two exon sequence regions.

7. The AAV viral genome of claim 6, wherein the AAV viral genome comprises a second intron sequence region.

8. The AAV viral genome of claim 2, wherein the AAV viral genome comprises a first MCS sequence region and a second MCS sequence region.

9. The AAV viral genome of claim 8, wherein the first MCS sequence region is located 3' to the 5' ITR sequence region and the second MCS sequence region is located 3' to the modulatory polynucleotide sequence region.

10. The AAV viral genome of claim 8 further comprising at least one exon sequence region, wherein said at least one exon sequence region is selected from the group consisting of SEQ ID NO: 1415 and 1416.

11. The AAV viral genome of claim 10, wherein the AAV viral genome comprises one exon sequence region.

12. The AAV viral genome of claim 10, wherein the AAV viral genome comprises two exon sequence regions.

13. The AAV viral genome of claim 12, wherein the AAV viral genome comprises a second intron sequence region.

14. The AAV viral genome of claim 13, wherein the first MCS sequence region is located 3' to the 5' ITR sequence region, the second MCS sequence region is located 3' to the modulatory polynucleotide sequence region, the two exon sequence regions are located 3' to the promoter region and 5' to the modulatory polynucleotide sequence region, and the second intron sequence region is located 3' to the first intron sequence region.

15. An AAV viral genome polynucleotide selected from the group consisting of SEQ ID NO: 1352-1379, 1388, and 1426-1438 or variants having at least 95% identity thereto.

16. An AAV particle comprising the AAV viral genome of any of claims 1-15.

17. The AAV particle of claim 16 comprising an AAV serotype selected from the group consisting of 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, AAV-PHP.B, 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/orAAVG2B5 and variants thereof.

18. A pharmaceutical composition comprising the AAV particle of any of claims 16-17.

19. A method for inhibiting the expression of HTT gene in a cell comprising administering to the cell the pharmaceutical composition of claim 18.

20. The method of claim 19, wherein the cell is a mammalian cell.

21. The method of claim 20, wherein the mammalian cell is a medium spiny neuron, a cortical neuron, or an astrocyte.

21. A method for treating Huntington's Disease (HD) in a subject in need of treatment, the method comprising administering to the subject a therapeutically effective amount the pharmaceutical composition of claim 18.

22. The method of claim 21, wherein the expression of HTT is inhibited or suppressed.

23. The method of claim 22, wherein the expression of HTT is inhibited or suppressed by about 30% to about 70%.

24. The method of claim 23, wherein the expression of HTT is inhibited or suppressed by about 50% to about 90%.

25. A method for inhibiting the expression of HTT gene in a cell wherein the HTT gene causes a gain of function effect inside the cell, comprising administering the cell the pharmaceutical composition of claim 18.

26. The method of claim 25, wherein the cell is a mammalian cell.

27. The method of claim 26, wherein the mammalian cell is a medium spiny neuron, a cortical neuron, or an astrocyte.

28. A method for inhibiting the expression of the HTT gene in a region of the central nervous system of a subject comprising administering to said subject the pharmaceutical composition of claim 18.

29. The method of claim 28, wherein the region is the forebrain.

30. The method of claim 29, wherein the expression is reduced in the putamen in the forebrain.

31. The method of claim 30, wherein the expression of HTT in the putamen is reduced by 40-70%.

32. A method for treating Huntington's Disease (HD) in a subject in need of treatment, the method inhibiting the expression of the HTT gene in a region of the central nervous system of a subject comprising administering to said subject the pharmaceutical composition of claim 18.

33. The method of claim 32, wherein the region is the forebrain.

34. The method of claim 33, wherein the expression is reduced in the putamen in the forebrain.

35. The method of claim 34, wherein the expression of HTT in the putamen is reduced by 40-70%.