

REDIRECTION OF TROPISM OF AAV CAPSIDS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application 63/023,927 filed on May 13, 2020, and U.S. Provisional Application 63/122,300 filed on December 7, 2020, the entire contents of which are hereby incorporated by reference.

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 2057_1119PCT_SL, created on March 31, 2021 which is 7,087,883 bytes in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The disclosure relates to compositions, methods, and processes for the preparation, use, and/or formulation of adeno-associated virus capsid proteins, wherein the capsid proteins comprise peptides, e.g., targeting peptide inserts, for enhanced tropism to a target cell or tissue.

BACKGROUND

[0004] Gene delivery to the adult central nervous system (CNS) remains a significant challenge in gene therapy. Engineered adeno-associated virus (AAV) capsids with improved brain tropism represent an attractive solution to the limitations of CNS delivery.

[0005] AAV-derived vectors are promising tools for clinical gene transfer because of their non-pathogenic nature, their low immunogenic profile, low rate of integration into the host genome and long-term transgene expression in non-dividing cells. However, the transduction efficiency of AAV natural variants in certain organs is too low for clinical applications, and capsid neutralization by pre-existing neutralizing antibodies may prevent treatment of a large proportion of patients. For these reasons, considerable efforts have been devoted to obtaining novel capsid variants with enhanced properties. Of many approaches tested so far, significant advances have resulted from directed evolution of AAV capsids using *in vitro* or *in vivo* selection of capsid variants created by capsid sequence randomization using either error-prone PCR, shuffling of various parent serotypes, or insertion of fully randomized short peptides at defined positions.

[0006] Attempts at providing AAV capsids with improved properties, e.g., improved tropism to a target cell or tissue upon systemic administration, have met with limited success. As such, there is a need for improved methods of producing AAV capsids and resulting AAV capsids for delivery of a payload of interest to a target cell or tissue, e.g., a CNS cell or tissue, or a muscle cell or tissue.

SUMMARY OF THE DISCLOSURE

[0007] The present disclosure pertains at least in part, to compositions and methods for the production and use of an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant. In some embodiments, the AAV capsid variant has an enhanced tropism for a tissue or a cell, e.g., a CNS tissue, a CNS cell, a muscle tissue, or a muscle cell. Said tropism can be useful for delivery of a payload, e.g., a payload described herein to a cell or tissue, for the treatment of a disorder, e.g., a neurological or a neurodegenerative disorder, a muscular or a neuromuscular disorder, or a neuro-oncological disorder.

[0008] Accordingly, in one aspect, the present disclosure provides an AAV capsid polypeptide, e.g., an AAV capsid variant, comprising: the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; an amino acid sequence comprising no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the amino acid sequence is present in loop VIII. In some embodiments, the amino acid sequence is present immediately subsequent to position 586, 588, or 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises the amino acid sequence of any one of SEQ ID NOs: 3636-3647, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0009] In another aspect, the present disclosure provides an AAV capsid polypeptide, e.g., an AAV capsid variant, comprising: a parental amino acid sequence having an insert, wherein the insert comprises the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; an amino acid sequence comprising no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the parental sequence comprises an amino acid sequence comprising at least one, two, or three modifications but no more than 30, 20 or 10 modifications, e.g., substitutions, to the amino acid sequence of SEQ ID NO: 138; and/or the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the insert is present in, e.g., inserted into, loop VIII of the parental amino acid sequence. In some embodiments, the insert is present, e.g., inserted, immediately subsequent to position 586, 588, or 589 of the parental sequence. In some embodiments, the AAV capsid variant further comprises a deletion at position 587 and/or a deletion at position 588 of the parental amino acid sequence.

[0010] In another aspect, the present disclosure provides a peptide, e.g., a targeting peptide, comprising: at least the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; an

amino acid sequence comprising no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide is encoded by the nucleotide sequence of any one of SEQ ID NOs: 3660-3671, or a nucleic acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of any of SEQ ID NOs: 3660-3671. In some embodiments, the nucleotide sequence encoding the peptide comprises the nucleotide sequence of any one of SEQ ID NOs: 3660-3671, or a nucleic acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto, or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of any of SEQ ID NOs: 3660-3671.

[0011] In yet another aspect, the present disclosure provides a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, wherein the AAV capsid variant comprises the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; an amino acid sequence comprising no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the polynucleotide comprises the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0012] In yet another aspect, the present disclosure provides an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein. In some embodiments, the AAV particle comprises a nucleic acid sequence encoding a payload. In some embodiments, the AAV particle further comprises a viral genome comprising a promoter operably linked to the nucleic acid encoding the payload.

[0013] In yet another aspect, the present disclosure provides a method of making an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein. The method comprises providing a host cell comprising a viral genome and incubating the host cell under conditions suitable to enclose the viral genome in the AAV capsid variant, e.g., an AAV capsid variant described herein, thereby making the AAV particle.

[0014] In yet another aspect, the present disclosure provides a method of delivering a payload to a cell or tissue (e.g., a CNS cell, a CNS tissue, a muscle cell, or a muscle tissue). The method comprising administering an effective amount of an AAV particle comprising an AAV capsid variant described herein.

[0015] In yet another aspect, the present disclosure provides a method of treating a subject having or diagnosed with having neurological, e.g., a neurodegenerative, disorder. The method comprising administering an effective amount of an AAV particle comprising an AAV capsid variant described herein.

[0016] In yet another aspect, the present disclosure provides a method of treating a subject having or diagnosed with having a muscular disorder or a neuromuscular disorder. The method comprising administering an effective amount of an AAV particle comprising an AAV capsid variant described herein.

[0017] In yet another aspect, the present disclosure provides a method of treating a subject having or diagnosed with having a neuro-oncological disorder. The method comprising administering an effective amount of an AAV particle comprising an AAV capsid variant described herein.

[0018] The present disclosure presents an AAV capsid protein comprising a parental amino acid sequence selected from any of SEQ ID NO: 1-1724, which may have inserted therein at least one peptide selected from any member of SEQ ID NO: 1725-3622.

[0019] In certain embodiments, the inserted peptide is selected from SEQ ID NO: 1725-3622 and is inserted into the parental amino acid sequence.

[0020] In certain embodiments, the peptide is inserted at any amino acid position between amino acids 586-592, inclusive of the parental amino acid sequence. In such embodiments, the peptide may be inserted between amino acids 588-589 of the parental amino acid sequence.

[0021] In some embodiments, the parental amino acid sequence may be SEQ ID NO: 138 or SEQ ID NO: 11.

[0022] The present disclosure also presents a peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1725-3622.

[0023] In other aspects, the disclosure presents an AAV particle comprising an AAV capsid protein disclosed herein and a viral genome. In such aspects, the viral genome may comprise a nucleic acid sequence that encodes a payload. In some embodiments, the payload may be an RNAi agent, which may consist of dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, miRNA precursor, stRNA, lncRNA, piRNA, or snoRNA.

[0024] In additional aspects, the payload may be a peptide, polypeptide, antibody or antibody fragment.

[0025] The present disclosure also presents a pharmaceutical composition comprising the AAV particle and a pharmaceutically acceptable excipient, as well as a method of treating a disease in a subject by administering the pharmaceutical composition said subject.

[0026] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following enumerated embodiments.

Enumerated Embodiments

- [0027] 1. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising:
- (a) the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659;
 - (b) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or
 - (c) an amino acid sequence comprising no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659.
- [0028] 2. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising:
- (a) the amino acid sequence of any of SEQ ID NO: 3648-3659;
 - (b) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 3648-3659; or
 - (c) an amino acid sequence comprising no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 3648-3659.
- [0029] 3. The AAV capsid polypeptide, e.g., the AAV capsid variant, of embodiment 1 or 2, which comprises at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 3648-3659.
- [0030] 4. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, wherein the 3 consecutive amino acids comprise PLN.
- [0031] 5. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-4, wherein the 4 consecutive amino acids comprise PLNG (SEQ ID NO: 3678).
- [0032] 6. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, wherein the 5 consecutive amino acids comprise PLNGA (SEQ ID NO: 3679).
- [0033] 7. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, wherein the 6 consecutive amino acids comprise PLNGAV (SEQ ID NO: 3680).
- [0034] 8. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, wherein the 7 consecutive amino acids comprise PLNGAVH (SEQ ID NO: 3681).
- [0035] 9. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, wherein the 8 consecutive amino acids comprise PLNGAVHL (SEQ ID NO: 3682).
- [0036] 10. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, wherein the 9 consecutive amino acids comprise PLNGAVHLY (SEQ ID NO: 3648).

- [0037] 11. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, wherein the 3 consecutive amino acids comprise YST.
- [0038] 12. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 11, wherein the 4 consecutive amino acids comprise YSTD (SEQ ID NO: 3690).
- [0039] 13. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 11-12, wherein the 5 consecutive amino acids comprise YSTDE (SEQ ID NO: 3691) or YSTDV (SEQ ID NO: 3700).
- [0040] 14. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 11-13, wherein the 6 consecutive amino acids comprise YSTDER (SEQ ID NO: 3692) or YSTDVR (SEQ ID NO: 3701).
- [0041] 15. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, wherein the 3 consecutive amino acids comprise IVM.
- [0042] 16. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 15, wherein the 4 consecutive amino acids comprise IVMN (SEQ ID NO: 3693).
- [0043] 17. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 15-16, wherein the 5 consecutive amino acids comprise IVMNS (SEQ ID NO: 3694).
- [0044] 18. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 15-17, wherein the 6 consecutive amino acids comprise IVMNSL (SEQ ID NO: 3695).
- [0045] 19. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 15-18, wherein the 7 consecutive amino acids comprise IVMNSLK (SEQ ID NO: 3651).
- [0046] 20. The AAV capsid polypeptide, e.g., the AAV capsid variant of any one of embodiments 1-19, which comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 3648-3659.
- [0047] 21. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-10 or 20, comprising the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), optionally, wherein position 7 is H.
- [0048] 22. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 20, comprising the amino acid sequence of RDSPKGW (SEQ ID NO: 3649), or an amino acid sequence having at least one, two, or three modifications but no more than four

modifications, e.g., substitutions, relative to the amino acid sequence of RDSPKGW (SEQ ID NO: 3649).

[0049] 23. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 15-20, comprising the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), or an amino acid sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of IVMNSLK (SEQ ID NO: 3651).

[0050] 24. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 11-14, or 20, comprising the amino acid sequence of YSTDVRM (SEQ ID NO: 3650), or an amino acid sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of YSTDVRM (SEQ ID NO: 3650).

[0051] 25. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3 or 20, comprising the amino acid sequence of RESPRGL (SEQ ID NO: 3652), or a sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of RESPRGL (SEQ ID NO: 3652).

[0052] 26. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises the amino acid sequence of any of SEQ ID NO: 3648-3659.

[0053] 27. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-26, comprising:

(i) an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 3660-3671, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of any of SEQ ID NOs: 3660-3671.

[0054] 28. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-27, wherein the nucleotide sequence encoding the AAV capsid variant comprises:

(i) the nucleotide sequence of any one of SEQ ID NOs: 3660-3671, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of any of SEQ ID NOs: 3660-3671.

[0055] 29. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-10, 20-21, or 26-28, comprising an amino acid sequence encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3660, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3660.

[0056] 30. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-10, 20-21, or 26-29, wherein the nucleotide sequence encoding the AAV capsid variant comprises:

(i) the nucleotide sequence of SEQ ID NO: 3660, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3660.

[0057] 31. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 20, 22, or 26-28, comprising an amino acid sequence encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3661, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3661.

[0058] 32. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 20, 22, 26-28, or 31, wherein the nucleotide sequence encoding the AAV capsid variant comprises:

(i) the nucleotide sequence of SEQ ID NO: 3661, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3661.

[0059] 33. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 11-14, 20, 24, or 26-28, comprising an amino acid sequence encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3662, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3662.

[0060] 34. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 11-14, 20, 24, 26-28, or 33, wherein the nucleotide sequence encoding the AAV capsid variant comprises:

(i) the nucleotide sequence of SEQ ID NO: 3662, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3662.

[0061] 35. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 15-20, 23, or 26-28, comprising an amino acid sequence encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3663, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3663.

[0062] 36. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 15-20, 23, 26-28, or 35, wherein the nucleotide sequence encoding the AAV capsid variant comprises:

(i) the nucleotide sequence of SEQ ID NO: 3663, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3663.

[0063] 37. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 20, or 25-28, comprising an amino acid sequence encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3664, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3664.

[0064] 38. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 20, 25-28, or 37, wherein the nucleotide encoding the AAV capsid variant comprises:

(i) the nucleotide sequence of SEQ ID NO: 3664, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3664.

[0065] 39. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, wherein the amino acid sequence is present in loop VIII.

[0066] 40. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-10, 20-21, 26-30, or 39, wherein the amino acid sequence is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0067] 41. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 15-20, 23, 26-28, 35-36, or 39, wherein the amino acid sequence is present immediately subsequent to position 588, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0068] 42. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 11-14, 20, 22, 24-28, 31-34, 37-38, or 39 wherein the amino acid sequence is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0069] 43. The AAV capsid polypeptide, e.g., the AAV capsid variant of any one of embodiments 1-42, which comprises an amino acid residue other than "A" at position 587 and/or an amino acid residue other than "Q" at position 588, numbered according to SEQ ID NO: 138.

[0070] 44. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-10, 20-21, 26-30, 39-40, or 43, comprising the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), wherein the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0071] 45. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 20, 26-28, 39-40, or 43, comprising the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654), wherein the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0072] 46. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 15-20, 23, 26-28, 35-36, 39, or 41, comprising the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), wherein the amino acid sequence of IVMNSLK (SEQ ID NO: 3651) is present immediately subsequent to position 588, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

- [0073] 47. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 11-14, 20, 22, 24-28, 31-34, 37-38, 39, or 42, comprising the amino acid sequence of any of SEQ ID NOs: 3649, 3650, 3652, 3653, or 3655-3659, wherein the amino acid sequence of any of the aforesaid sequences is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.
- [0074] 48. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which further comprises the amino acid substitution of K449R, numbered according to SEQ ID NO: 138.
- [0075] 49. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which further comprises a modification, e.g., an insertion, substitution, and/or deletion, in loop I, II, IV and/or VI.
- [0076] 50. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 138.
- [0077] 51. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.
- [0078] 52. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises the amino acid sequence of SEQ ID NO: 138.
- [0079] 53. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.
- [0080] 54. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.
- [0081] 55. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises a VP1 protein, a VP2 protein, a VP3 protein, or a combination thereof.
- [0082] 56. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises the amino acid sequence corresponding to positions 138-

743, e.g., a VP2, of any one of SEQ ID NOs: 3636-3647, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0083] 57. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises the amino acid sequence corresponding to positions 203-743, e.g., a VP3, of any one of SEQ ID NOs: 3636-3647, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0084] 58. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises the amino acid sequence of any one of SEQ ID NOs: 3636-3647, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0085] 59. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any one of SEQ ID NOs: 3636-3647.

[0086] 60. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0087] 61. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0088] 62. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-10, 20-21, 26-30, 39-40, 43-44, or 48-61, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 3623, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0089] 63. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 15-20, 23, 26-28, 35-36, 39, 41, 46, or 48-61, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 3627, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0090] 64. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, wherein the nucleotide sequence encoding the capsid variant is codon optimized.

- [0091] 65. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of any one of embodiments 1-10, 20-21, 26-30, 39-40, 43-44, 48-62, or 64, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 3636.
- [0092] 66. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3636.
- [0093] 67. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of any one of embodiments 1-3, 20, 22, 26-28, 31-32, 39, 42, 47-61, or 64, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 3637.
- [0094] 68. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3637.
- [0095] 69. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of any one of embodiments 1-3, 11-12, 20, 24, 26-28, 33-34, 39, 42, 47-61, or 64, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 3638.
- [0096] 70. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3638.
- [0097] 71. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of any one of embodiments 1-3, 15-20, 23, 26-28, 35-36, 39, 41, 46, 48-61, or 63-64, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 3639.
- [0098] 72. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3639.
- [0099] 73. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of any one of embodiments 1-3, 20, 25-28, 37-39, 42, 47-61, or 64, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 3640.
- [0100] 74. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3640.
- [0101] 75. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3641.
- [0102] 76. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3642.
- [0103] 77. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3643.
- [0104] 78. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3644.
- [0105] 79. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3645.

- [0106] 80. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3646.
- [0107] 81. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the amino acid sequence of SEQ ID NO: 3647.
- [0108] 82. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence at least 95% identical thereto.
- [0109] 83. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising a parental amino acid sequence having an insert, e.g., a targeting peptide, wherein the insert comprises:
- (a) the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659;
 - (b) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or
 - (c) an amino acid sequence comprising no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659.
- [0110] 84. The AAV capsid polypeptide, e.g., the AAV capsid variant, of embodiment 83, wherein the parental sequence comprises:
- (i) the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; and/or
 - (ii) an amino acid sequence comprising at least one, two, or three modifications but no more than 30, 20 or 10 modifications, e.g., substitutions, to the amino acid sequence of SEQ ID NO: 138.
- [0111] 85. The AAV capsid polypeptide, e.g., the AAV capsid variant, of embodiment 83 or 84, wherein the parental sequence further comprises a substitution at position K449, e.g., a K449R substitution.
- [0112] 86. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-85, wherein the parental sequence comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.
- [0113] 87. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-86, wherein the nucleotide sequence encoding the parental sequence comprises the nucleotide sequence of SEQ ID NO: 137, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.
- [0114] 88. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-87, wherein the parental sequence comprises:

(i) the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; and/or

(ii) an amino acid sequence comprising at least one, two, or three modifications but no more than 30, 20 or 10 modifications, e.g., substitutions, to the amino acid sequence of SEQ ID NO: 11; optionally, provided that position 449 of SEQ ID NO: 11 is not K, e.g., is R.

[0115] 89. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-88, wherein the insert comprises the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648).

[0116] 90. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-88, wherein the insert comprises the amino acid sequence of GGT LAVVSL (SEQ ID NO: 3654).

[0117] 91. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-88, wherein the insert comprises the amino acid sequence of IVMNSLK (SEQ ID NO: 3651).

[0118] 92. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-88, wherein the insert comprises an amino acid sequence chosen from RDSPKGW (SEQ ID NO: 3649), YSTDVRM (SEQ ID NO: 3650), RESPRGL (SEQ ID NO: 3652), SFNDTRA (SEQ ID NO: 3653), YGLPKGP (SEQ ID NO: 3655) or STGTLRL (SEQ ID NO: 3656).

[0119] 93. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-92, wherein the insert is present in loop VIII of the parental amino acid sequence.

[0120] 94. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-90 or 93, wherein the insert is present immediately subsequent to position 586 in the parental amino acid sequence.

[0121] 95. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-89 or 93-94, wherein the insert comprises the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648) and is inserted immediately subsequent to position 586 of the parental amino acid sequence.

[0122] 96. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-88, 90, or 93-94, wherein the insert comprises the amino acid sequence of GGT LAVVSL (SEQ ID NO: 3654) and is inserted immediately subsequent to position 586 of the parental amino acid sequence.

[0123] 97. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-90, 93-96, which comprises an amino acid other than "A" at position 587 and/or an amino acid other than "Q" at position 588 of the parental sequence.

[0124] 98. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-90 or 93-97, further comprising a deletion of amino acid "A" at position 587 and/or a deletion of amino acid "Q" at position 588 of the parental amino acid sequence.

[0125] 99. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-89, 93-95, or 97-98, comprising:

- (i) an insert comprising the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), which is inserted immediately subsequent to position 586 of the parental amino acid sequence; and
- (ii) a deletion of the amino acids "AQ" at positions 587 and 588 of the parental amino acid sequence.

[0126] 100. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-88, 90, 93-94, or 96-98, comprising:

- (i) an insert comprising the amino acid sequence of GGT LAVVSL (SEQ ID NO: 3654), which is inserted immediately subsequent to position 586 of the parental amino acid sequence; and
- (ii) a deletion of the amino acids "AQ" at positions 587 and 588 of the parental amino acid sequence.

[0127] 101. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-88, 91, or 93, wherein the insert is inserted immediately subsequent to position 588 in the parental amino acid sequence.

102. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-88, 91, 93, or 101, wherein the insert comprises the amino acid sequence of IVMNLSLK (SEQ ID NO: 3651) and is inserted immediately subsequent to position 588 of the parental amino acid sequence.

[0128] 103. The AAV capsid polypeptide, e.g., the AAV capsid variant, of embodiment 83-88, or 92-93, wherein the insert is inserted immediately subsequent to position 589 in the parental amino acid sequence.

[0129] 104. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 83-88, 92-93, or 103, wherein the insert comprises an amino acid sequence chosen from RDSPK GW (SEQ ID NO: 3649), YSTDVRM (SEQ ID NO: 3650), RESPRGL (SEQ ID NO: 3652), SFNDTRA (SEQ ID NO: 3653), YGLPKGP (SEQ ID NO: 3655) or STGTLRL (SEQ ID NO: 3656) and is inserted immediately subsequent to position 589 of the parental amino acid sequence.

[0130] 105. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which does not comprise an insert sequence present immediately subsequent to position 586, 588, or 589 numbered relative to SEQ ID NO: 138, having at least 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, of any of SEQ ID NOs: 1-1724, e.g., as described in Table 6.

[0131] 106. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which does not comprise the amino acid sequence of TLAVPFK (SEQ ID NO: 1262) present immediately subsequent to position 588, numbered according to SEQ ID NO: 138.

[0132] 107. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which has an increased tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138.

[0133] 108. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-12, 15-44, 46-74, 82-89, 91-95, 97-99, 101-107, which transduces a brain region, e.g., selected from dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus and putamen, optionally wherein the level of transduction is at least 5, 10, 50, 100, 200, 500, 1,000, 2,000, 5,000, or 10,000-fold greater as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay, a qRT-PCR, or a RT-ddPCR assay, e.g., as described in Example 5.

[0134] 109. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which is enriched at least about 5, 6, 7, 8, 9, or 10-fold, in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4.

[0135] 110. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-14, 20-22, 24-34, 39-40, 42-44, 47-62, 64-70, 79-80, 82-89, 92-95, 97-99, or 103-109, which is enriched at least about 20, 30, 40, or 50-fold in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4.

[0136] 111. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-10, 20-22, 26-32, 39-40, 42-44, 47-62, 64-68, 82-89, 92-95, 97-99, or 103-110, which is enriched at least about 100, 200, 300, or 400-fold in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4.

[0137] 112. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-10, 20-21, 26-30, 39-40, 43-44, 48-62, 64-66, 82-89, 93-95, 97-99, or 105-111, which delivers an increased level of viral genomes to a brain region, optionally wherein the level of viral genomes is increased by at least 5, 10, 20, 30, 40 or 50-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5).

[0138] 113. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-12, 15-44, 46-74, 82-89, 91-95, 97-99, 101-112, which delivers an increased level of a payload to a brain region, optionally wherein the level of the payload is increased by at least 5, 10, 50, 100, 200, 500, 1,000, 2,000, 5,000, or 10,000-fold, as compared to a reference sequence of SEQ ID

NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5).

[0139] 114. The AAV capsid polypeptide, e.g., the AAV capsid variant, of embodiment 113, wherein the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

[0140] 115. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-12, 15-44, 46-74, 82-89, 91-95, 97-99, 101-114, which delivers an increased level of a payload to a spinal cord region, optionally wherein the level of the payload is increased by at least 10, 20, 50, 100, 200, 300, 400, 500, 600, 700, 800 or 900-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR assay (e.g., as described in Example 5).

[0141] 116. The AAV capsid polypeptide, e.g., the AAV capsid variant, of embodiment 115, wherein the spinal cord region comprises a cervical, thoracic, and/or lumbar region.

[0142] 117. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 15-20, 23, 26-28, 35-36, 39, 41, 46, 48-61, 63-64, 71-72, 83-88, 91, 93, 101-102, 105-109, or 113-116, which shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG).

[0143] 118. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-10, 20-21, 26-30, 39-40, 43-44, 48-62, 64-66, 82-89, 93-95, 97-99, or 105-116, wherein the capsid variant:

(i) is enriched at least about 300, or 400-fold in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4;

(ii) transduces a brain region, e.g., selected from dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus and putamen, wherein the level of transduction is at least 500, 1,000, 2,000, 5,000, or 10,000-fold greater as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay, a qRT-PCR, or a RT-ddPCR assay, e.g., as described in Example 5;

(iii) delivers an increased level of a payload to a brain region, optionally wherein the level of the payload is increased by at least 500, 1,000, 2,000, 5,000, or 10,000-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5), optionally wherein the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus;

(iv) delivers an increased level of a payload to a spinal cord region, optionally wherein the level of the payload is increased by at least 50, 100, 200, 300, 400, 500, 600, 700, 800 or 900-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-

PCR assay (e.g., as described in Example 5), optionally wherein the spinal cord region comprises a cervical, thoracic, and/or lumbar region; and/or

(v) delivers an increased level of viral genomes to a brain region, optionally wherein the level of viral genomes is increased by at least 5, 10, 20, 30, 40 or 50-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5), optionally wherein the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

[0144] 119. An AAV capsid polypeptide, e.g., an AAV capsid variant comprising: (a) the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648); (b) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648); or (c) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648); and wherein the capsid variant:

(i) is enriched at least about 300 or 400-fold in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4;

(ii) transduces a brain region, e.g., selected from dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus and putamen, wherein the level of transduction is at least 500, 1,000, 2,000, 5,000, or 10,000-fold greater as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay, a qRT-PCR, or a RT-ddPCR assay, e.g., as described in Example 5;

(iii) delivers an increased level of a payload to a brain region, optionally wherein the level of the payload is increased by at least 500, 1,000, 2,000, 5,000, or 10,000-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5), optionally wherein the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus;

(iv) delivers an increased level of a payload to a spinal cord region, optionally wherein the level of the payload is increased by at least 50, 100, 200, 300, 400, 500, 600, 700, 800 or 900-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR assay (e.g., as described in Example 5), optionally wherein the spinal cord region comprises a cervical, thoracic, and/or lumbar region; and/or

(v) delivers an increased level of viral genomes to a brain region, optionally wherein the level of viral genomes is increased by at least 5, 10, 20, 30, 40 or 50-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5), optionally wherein the brain region comprises a frontal

cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

[0145] 120. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 15-20, 23, 26-28, 35-36, 39, 41, 46, 48-61, 63-64, 71-72, 83-88, 91, 93, 101-102, 105-109, or 113-117, wherein the AAV capsid variant has an increased tropism for a muscle cell or tissue, e.g., a heart tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138.

[0146] 121. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-3, 15-20, 23, 26-28, 35-36, 39, 41, 46, 48-61, 63-64, 71-72, 83-88, 91, 93, 101-102, 105-109, 113-117, or 120, which delivers an increased level of a payload to a muscle region, optionally wherein the level of the payload is increased by at least 10, 15, 20, 30, or 40-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an IHC assay or a RT-ddPCR assay (e.g., as described in Example 5).

[0147] 122. The AAV capsid polypeptide, e.g., the AAV capsid variant, of embodiment 120 or 121, wherein the muscle region comprises a heart muscle, quadriceps muscle, and/or a diaphragm muscle region.

[0148] 123. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 120-122, wherein the muscle region comprises a heart muscle region, e.g., a heart atrium muscle region or a heart ventricle muscle region.

[0149] 124. The AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of the preceding embodiments, which is isolated, e.g., recombinant.

[0150] 125. A polynucleotide encoding the polypeptide, e.g., the AAV capsid variant of any one of embodiments 1-124.

[0151] 126. The polynucleotide of embodiment 125, which comprises:

(i) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of any of SEQ ID NOs: 3660-3671; or

(ii) the nucleotide sequence of any one of SEQ ID NOs: 3660-3671, or nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0152] 127. The polynucleotide of embodiment 125 or 126, which comprises the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0153] 128. The polynucleotide of any one of embodiments 125-127, which comprises a nucleotide sequence that is codon optimized.

[0154] 129. A peptide, e.g., a targeting peptide, comprising:

- (a) the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659;
- (b) an amino acid sequence comprising no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or
- (c) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659.

[0155] 130. A peptide, e.g., a targeting peptide, comprising the amino acid sequence of any one of embodiments 1-106.

[0156] 131. A peptide, e.g., a targeting peptide, comprising:

- (i) the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648);
- (ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648); or
- (iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648).

[0157] 132. A peptide, e.g., a targeting peptide, encoded by:

- (i) the nucleotide sequence of SEQ ID NO: 3660 or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or
- (ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3660.

[0158] 133. A peptide, e.g., a targeting peptide, wherein the nucleotide sequence encoding the peptide comprises:

- (i) the nucleotide sequence of SEQ ID NO: 3660 or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or
- (ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3660.

[0159] 134. A peptide, e.g., a targeting peptide, comprising:

- (i) the amino acid sequence of IVMNSLK (SEQ ID NO: 3651);
- (ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of IVMNSLK (SEQ ID NO: 3651); or
- (iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of IVMNSLK (SEQ ID NO: 3651).

[0160] 135. A peptide, e.g., a targeting peptide, encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3663, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3663.

[0161] 136. A peptide, e.g., a targeting peptide, wherein the nucleotide sequence encoding the peptide comprises:

(i) the nucleotide sequence of SEQ ID NO: 3663, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3663.

[0162] 137. A peptide, e.g., a targeting peptide, comprising:

(i) the amino acid sequence of RDSPKGW (SEQ ID NO: 3649);

(ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of RDSPKGW (SEQ ID NO: 3649); or

(iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of RDSPKGW (SEQ ID NO: 3649).

[0163] 138. A peptide, e.g., a targeting peptide, encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3661, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3661.

[0164] 139. A peptide, e.g., a targeting peptide, wherein the nucleotide sequence encoding the peptide comprises:

(i) the nucleotide sequence of SEQ ID NO: 3661, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3661.

[0165] 140. A peptide, e.g., a targeting peptide, comprising:

(i) the amino acid sequence of YSTDVRM (SEQ ID NO: 3650);

(ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of YSTDVRM (SEQ ID NO: 3650); or

(iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of YSTDVRM (SEQ ID NO: 3650).

[0166] 141. A peptide, e.g., a targeting peptide, encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3662, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3662.

[0167] 142. A peptide, e.g., a targeting peptide, wherein the nucleotide sequence encoding the peptide comprises:

(i) the nucleotide sequence of SEQ ID NO: 3662, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3662.

[0168] 143. A peptide, e.g., a targeting peptide, comprising:

(i) the amino acid sequence of RESPRGL (SEQ ID NO: 3652);

(ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of RESPRGL (SEQ ID NO: 3652); or

(iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of RESPRGL (SEQ ID NO: 3652).

[0169] 144. A peptide, e.g., a targeting peptide, encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3664, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3664.

[0170] 145. A peptide, e.g., a targeting peptide, wherein the nucleotide sequence encoding the peptide comprises:

(i) the nucleotide sequence of SEQ ID NO: 3664, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3664.

[0171] 146. An AAV capsid polypeptide, e.g., an AAV capsid variant, comprising the peptide, e.g., targeting peptide, of any one of embodiments 129-145.

[0172] 147. A polynucleotide encoding the peptide, e.g., targeting peptide, of any one of embodiments 129-145.

[0173] 148. A polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant comprising:

(a) the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659;

(b) an amino acid sequence comprising no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or

(c) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659;

optionally wherein the amino acid sequence of (a), (b), and/or (c) is present immediately subsequent to position 586, 588, or 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0174] 149. A polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, wherein the AAV capsid variant comprises:

(i) the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648);

(ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648); or

(iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648);

optionally wherein the amino acid sequence of (i), (ii), and/or (iii) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0175] 150. The polynucleotide of embodiment 149, which comprises:

(i) the nucleotide sequence of SEQ ID NO: 3660 or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3660.

[0176] 151. A polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, wherein the AAV capsid variant comprises:

(i) the amino acid sequence of IVMNSLK (SEQ ID NO: 3651);

(ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of IVMNSLK (SEQ ID NO: 3651); or

(iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of IVMNSLK (SEQ ID NO: 3651);

optionally wherein the amino acid sequence of (i), (ii), and/or (iii) is present immediately subsequent to position 588, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0177] 152. The polynucleotide of embodiment 151, which comprises:

(i) the nucleotide sequence of SEQ ID NO: 3663, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3663.

[0178] 153. A polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, wherein the AAV capsid variant comprises:

(i) the amino acid sequence of RDSPKGW (SEQ ID NO: 3649);

(ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of RDSPKGW (SEQ ID NO: 3649); or

(iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of RDSPKGW (SEQ ID NO: 3649);

optionally wherein the amino acid sequence of (i), (ii), and/or (iii) is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0179] 154. The polynucleotide of embodiment 153, which comprises:

(i) the nucleotide sequence of SEQ ID NO: 3661, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3661.

[0180] 155. A polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, wherein the AAV capsid variant comprises:

(i) the amino acid sequence of YSTDVRM (SEQ ID NO: 3650);

(ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of YSTDVRM (SEQ ID NO: 3650); or

(iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of YSTDVRM (SEQ ID NO: 3650);

optionally wherein the amino acid sequence of (i), (ii), and/or (iii) is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0181] 156. The polynucleotide of embodiment 155, which comprises:

(i) the nucleotide sequence of SEQ ID NO: 3662, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3662.

[0182] 157. A polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, wherein the AAV capsid variant comprises:

(i) the amino acid sequence of RESPRGL (SEQ ID NO: 3652);

(ii) an amino acid sequence comprising at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of RESPRGL (SEQ ID NO: 3652); or

(iii) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of RESPRGL (SEQ ID NO: 3652);

optionally wherein the amino acid sequence of (i), (ii), and/or (iii) is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0183] 158. The polynucleotide of embodiment 157, which comprises:

(i) the nucleotide sequence of SEQ ID NO: 3664, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3664.

[0184] 159. The polynucleotide of any one of embodiments 147-158, wherein the AAV capsid variant comprises:

(i) the amino acid sequence of any one of SEQ ID NOs: 3636-3647, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto; or

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of any one of SEQ ID NOs: 3636-3647.

[0185] 160. The polynucleotide of any one of embodiments 147-159, comprising the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0186] 161. The polynucleotide, peptide, or AAV capsid polypeptide, e.g., AAV capsid variant, of any one of embodiments 125-160, which is isolated, e.g., recombinant.

[0187] 162. An AAV particle comprising the AAV capsid polypeptide, e.g., the AAV capsid variant, of any one of embodiments 1-124 or 146.

[0188] 163. The AAV particle of embodiment 162, which comprises a nucleotide sequence encoding a payload.

[0189] 164. The AAV particle of embodiment 163, wherein the encoded payload comprises a therapeutic protein or functional variant thereof; an antibody or antibody fragment; an enzyme; a component of a gene editing system; an RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA); or a combination thereof.

[0190] 165. The AAV particle of embodiment 164, wherein the therapeutic protein or functional variant thereof, e.g., a recombinant protein, is associated with (e.g., aberrantly expressed in) a neurological or neurodegenerative disorder, a muscular or neuromuscular disorder, or a neuro-oncological disorder.

[0191] 166. The AAV particle of embodiment 164 or 165, the therapeutic protein or functional variant thereof is chosen from apolipoprotein E (APOE) (e.g., ApoE2, ApoE3 and/or ApoE4); human survival of motor neuron (SMN) 1 or SMN2; glucocerebrosidase (GBA1); aromatic L-amino acid decarboxylase (AADC); aspartoacylase (ASPA); tripeptidyl peptidase I (CLN2); beta-galactosidase (GLB1); N-sulphoglucosamine sulphohydrolase (SGSH); N-acetyl-alpha-glucosaminidase (NAGLU); iduronate 2-sulfatase (IDS); intracellular cholesterol transporter (NPC1); gigaxonin (GAN); or a combination thereof.

[0192] 167. The AAV particle of embodiment 164, wherein the antibody or antibody binding fragment binds to:

(i) a CNS related target, e.g. an antigen associated with a neurological or neurodegenerative disorder, e.g., β -amyloid, APOE, tau, SOD1, TDP-43, huntingtin (HTT), and/or synuclein;

(ii) a muscular or neuromuscular related target, e.g., an antigen associated with a muscular or neuromuscular disorder; or

(iii) a neuro-oncology related target, e.g., an antigen associated with a neuro-oncological disorder, e.g., HER2, or EGFR (e.g., EGFRvIII).

- [0193] 168. The AAV particle of embodiment 164, wherein the enzyme comprises a meganuclease, a zinc finger nuclease, a TALEN, a recombinase, integrase, a base editor, a Cas9, or a fragment thereof.
- [0194] 169. The AAV particle of embodiment 164, wherein the component of a gene editing system comprises one or more components of a CRISPR-Cas system.
- [0195] 170. The AAV particle of embodiment 164 or 169, wherein the one or more components of the CRISPR-Cas system comprises a Cas9, e.g., a Cas9 ortholog or a Cpf1, and a single guide RNA (sgRNA), optionally wherein:
- (i) the sgRNA is located upstream (5') of the cas9 enzyme; or
 - (ii) the sgRNA is located downstream (3') of the cas9 enzyme.
- [0196] 171. The AAV particle of embodiment 164, wherein the RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA), modulates, e.g., inhibits, expression of, a CNS related gene, mRNA, and/or protein.
- [0197] 172. The AAV particle of embodiment 171, wherein the CNS related gene is chosen from SOD1, MAPT, APOE, HTT, C9ORF72, TDP-43, APP, BACE, SNCA, ATXN1, ATXN3, ATXN7, SCN1A-SCN5A, SCN8A-SCN11A, or a combination thereof.
- [0198] 173. The AAV particle of any one of embodiments 162-172, which comprises a viral genome comprising a promoter operably linked to the nucleic acid sequence encoding the payload.
- [0199] 174. The AAV particle of embodiment 173, wherein the promoter is chosen from human elongation factor 1 α -subunit (EF1 α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β -actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC), neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF- β), intercellular adhesion molecule 2 (ICAM-2), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β -globin minigene n β 2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), a cardiovascular promoter (e.g., α MHC, cTnT, and CMV-MLC2k), a liver promoter (e.g., hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512) or a fragment, e.g., a truncation, or a functional variant thereof.
- [0200] 175. The AAV particle of any one of embodiments 173 or 174, wherein the viral genome further comprises a polyA signal sequence.
- [0201] 176. The AAV particle of any one of embodiments 173-175, wherein the viral genome further comprises an inverted terminal repeat (ITR) sequence.

[0202] 177. The AAV particle of any one of embodiments 173-176, wherein the viral genome comprises an ITR sequence positioned 5' relative to the encoded payload.

[0203] 178. The AAV particle of any one of embodiments 173-177, wherein the viral genome comprises an ITR sequence positioned 3' relative to the encoded payload.

[0204] 179. The AAV particle of any one of embodiments 173-178, wherein the viral genome comprises an ITR sequence positioned 5' relative to the encoded payload and an ITR sequence positioned 3' relative to the encoded payload.

[0205] 180. The AAV particle of any one of embodiments 173-179, wherein the viral genome further comprises an enhancer, a Kozak sequence, an intron region, and/or an exon region.

[0206] 181. The AAV particle of any one of embodiments 173-180, wherein the viral genome further comprises a miR binding site, e.g., a miR binding site that modulates, e.g., reduces, expression of the payload encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed.

[0207] 182. The AAV particle of any one of embodiments 173-181, wherein the viral genome comprises at least 1-5 copies of a miR binding site, e.g., at least 1, 2, 3, 4, or 5 copies.

[0208] 183. The AAV particle of any one of embodiments 173-182, wherein the viral genome comprises at least 3 copies of a miR binding site, optionally wherein all three copies comprise the same miR binding site, or at least one, two, or all of the copies comprise a different miR binding site.

[0209] 184. The AAV particle of any one of embodiments 173-182, wherein the viral genome comprises at least 4 copies of a miR binding site, optionally wherein all four copies comprise the same miR binding site, or at least one, two, three, or all of the copies comprise a different miR binding site.

[0210] 185. The AAV particle of any one of embodiments 181-184, wherein the miR binding site comprises a miR122 binding site, a miR183 binding site, a miR-142-3p, or a combination thereof, optionally wherein:

(i) the miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 3672, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 3672;

(ii) the miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 3675, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 3675; and/or

(iii) the miR-142-3p binding site comprises the nucleotide sequence of SEQ ID NO: 3674, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 3674.

[0211] 186. The AAV particle of any one of embodiments 173-185, wherein the viral genome is single stranded.

[0212] 187. The AAV particle of any one of embodiments 173-186, wherein the viral genome further comprises a nucleotide sequence encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein.

[0213] 188. The AAV particle of embodiment 187, wherein the Rep78 protein, the Rep68 protein, the Rep52 protein, and/or the Rep40 protein are encoded by at least one Rep gene.

[0214] 189. The AAV particle of any one of embodiments 173-188, wherein the viral genome further comprises a nucleic acid sequence encoding the AAV capsid variant of any one of embodiments 1-124 or 146.

[0215] 190. The AAV particle of any one of embodiments, 162-189, which is isolated, e.g., recombinant.

[0216] 191. A polypeptide comprising a parental amino acid sequence of any of SEQ ID NO: 1-1724, having inserted therein one or more targeting peptide inserts, said targeting peptide inserts comprising individually a contiguous amino acid sequence region of 2-9 amino acids selected from any of the targeting peptides of SEQ ID NO: 1725-3622.

[0217] 192. The polypeptide of embodiment 191, wherein the polypeptide has a first targeting peptide insert, said first targeting peptide insert having a contiguous amino acid region of at least 5 amino acids selected from any of the targeting peptides of SEQ ID NO: 1725-3622.

[0218] 193. An AAV capsid comprising VP1, VP2 and VP3 proteins, wherein each of said VP1, VP2 and VP3 proteins comprises a polypeptide of any of those of embodiment 191 or 192.

[0219] 194. The polypeptide of embodiment 191, wherein the parental amino acid sequence is SEQ ID NO: 138.

[0220] 195. The polypeptide of embodiment 194, wherein the parental amino acid sequence has the substitution, K449R.

[0221] 196. The polypeptide of embodiment 194 or 195, wherein said first targeting peptide insert comprises the amino acid sequence PLNGAVHLY (SEQ ID NO: 3648) which is inserted immediately after amino acid 586 of the parental amino acid sequence.

[0222] 197. The polypeptide of embodiment 196, further comprising a deletion of the amino acids "AQ" at positions 587-588 of the parental amino acid sequence.

- [0223] 198. The polypeptide of embodiment 194 or 195, wherein said first targeting peptide insert comprises the amino acid sequence GGTLAVVSL (SEQ ID NO: 3654) which is inserted immediately after amino acid 586 of the parental amino acid sequence.
- [0224] 199. The polypeptide of embodiment 198, further comprising a deletion of the amino acids "AQ" at positions 587-588 of the parental amino acid sequence.
- [0225] 200. The polypeptide of embodiment 194 or 195, wherein said first targeting peptide insert comprises a 7 amino acid sequence selected from RDSPKGW (SEQ ID NO: 3649), YSTDVRM (SEQ ID NO: 3650), RESPRGL (SEQ ID NO: 3652), SFNDTRA (SEQ ID NO: 3653), YGLPKGK (SEQ ID NO: 3655) or STGTLRL (SEQ ID NO: 3656) which is inserted immediately after amino acid 589 of the parental amino acid sequence.
- [0226] 201. The polypeptide of embodiment 194 or 195, wherein said first targeting peptide insert comprises a 7 amino acid sequence IVMNSLK (SEQ ID NO: 3651) which is inserted immediately after amino acid 588 of the parental amino acid sequence.
- [0227] 202. The polypeptide of embodiment 191, wherein the parental amino acid sequence is SEQ ID NO: 5.
- [0228] 203. The polypeptide of embodiment 202, wherein the parental amino acid sequence has the substitution, K449R.
- [0229] 204. An AAV capsid comprising VP1, VP2 and VP3 proteins, wherein each of said VP1, VP2 and VP3 proteins comprises a polypeptide of any of those of embodiments 194-203.
- [0230] 205. A polynucleotide encoding the polypeptides or capsid proteins of any of embodiments 191-204.
- [0231] 206. The polynucleotide of embodiment 205, which is DNA and the DNA sequence is codon optimized.
- [0232] 207. An AAV particle comprising a capsid of any of embodiments 193 or 205 and a vector genome encoding a therapeutic payload.
- [0233] 208. The AAV particle of embodiment 207, wherein the therapeutic payload is a gene of interest.
- [0234] 209. The AAV particle of embodiment 208, wherein the therapeutic payload encodes a therapeutic RNA.
- [0235] 210. An AAV VP1 capsid selected from the group consisting of any of SEQ ID NO: 3636-3647.
- [0236] 211. A polynucleotide encoding any of the AAV VP1 capsid proteins of embodiment 210.
- [0237] 212. A vector comprising a polynucleotide encoding the AAV capsid variant of any one of embodiments 1-124 or 146, the polynucleotide of any one of embodiments 126-128, 147-161, 205-206, or 211, a polynucleotide encoding the peptide, e.g., targeting peptide, of any one of embodiments

129-145 or 161, or a polynucleotide encoding the polypeptide of any one of embodiments 191-192 or 194-203.

[0238] 213. A cell, e.g., a host cell, comprising the AAV capsid variant of any one of embodiments 1-124 or 146, the polynucleotide of any one of embodiments 126-128, 147-161, 205-206, or 211, the peptide of any one of embodiments 129-145 or 161, the polypeptide of any one of embodiments 191-192 or 194-203, the AAV particle of any one of embodiments 162-190 or 207-209, or the vector of embodiment 212.

[0239] 214. The cell of embodiment 213, wherein the cell is a mammalian cell or an insect cell.

[0240] 215. The cell of embodiment 213 or 214, wherein the cell is a cell of a brain region or a spinal cord region, optionally a cell of the frontal cortex, sensory cortex, motor cortex, caudate, dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus, putamen, cervical spinal cord region, thoracic spinal cord region, and/or lumbar spinal cord region.

[0241] 216. The cell of embodiment 213 or 214, wherein the cell is a neuron, a sensory neuron, a motor neuron, an astrocyte, or a muscle cell (e.g., a cell of the heart, diaphragm, or quadriceps).

[0242] 217. A method of making an AAV particle, comprising

(i) providing a host cell comprising a viral genome; and

(ii) incubating the host cell under conditions suitable to enclose the viral genome in the AAV capsid variant of any one of embodiments 1-124 or 146 or an AAV capsid variant encoded by the polynucleotide of any one of embodiments 125-128 or 147-161;

thereby making the AAV particle.

[0243] 218. The method of embodiment 217, further comprising, prior to step (i), introducing a first nucleic acid molecule comprising the viral genome into the host cell.

[0244] 219. The method of embodiment 217 or 218, wherein the host cell comprises a second nucleic acid encoding the capsid variant.

[0245] 220. The method of any one of embodiments 217-219, wherein the second nucleic acid molecule is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule.

[0246] 221. A pharmaceutical composition comprising the AAV particle of any one of embodiments 162-190, an AAV particle comprising the capsid variant of any one of embodiments 1-124 or 146, an AAV particle comprising the peptide of any one of embodiments 129-145 or 161, or an AAV particle comprising the polypeptide of any one of embodiments 191-192 or 194-203, and a pharmaceutically acceptable excipient.

[0247] 222. A method of delivering a payload to a cell or tissue (e.g., a CNS cell, a CNS tissue, a muscle cell, or a muscle tissue), comprising administering an effective amount of the pharmaceutical composition of embodiment 221, the AAV particle of any one of embodiments 162-190, an AAV

particle comprising the capsid variant of any one of embodiments 1-124 or 146, an AAV particle comprising the peptide of any one of embodiments 129-145 or 161, or an AAV particle comprising the polypeptide of any one of embodiments 191-192 or 194-203.

[0248] 223. The method of embodiment 222, wherein the cell is a cell of a brain region or a spinal cord region, optionally a cell of the frontal cortex, sensory cortex, motor cortex, caudate, dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus, putamen, cervical spinal cord region, thoracic spinal cord region, and/or lumbar spinal cord region.

[0249] 224. The method of embodiment 222 or 223, wherein the cell is a neuron, a sensory neuron, a motor neuron, an astrocyte, or a muscle cell (e.g., a cell of the heart, diaphragm, or quadriceps).

[0250] 225. The method of any one of embodiments 222-224, wherein the cell or tissue is within a subject.

[0251] 226. The method of embodiment 225, wherein the subject has, has been diagnosed with having, or is at risk of having a neurological, e.g., a neurodegenerative disorder.

[0252] 227. The method of embodiment 225, wherein the subject has, has been diagnosed with having, or is at risk of having a muscular disorder or a neuromuscular disorder.

[0253] 228. The method of embodiment 225, wherein the subject has, has been diagnosed with having, or is at risk of having a neuro-oncological disorder.

[0254] 229. A method of treating a subject having or diagnosed with having a neurological disorder, e.g., a neurodegenerative disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 221, the AAV particle of any one of embodiments 162-190, an AAV particle comprising the capsid variant of any one of embodiments 1-124 or 146, an AAV particle comprising the peptide of any one of embodiments 129-145 or 161, or an AAV particle comprising the polypeptide of any one of embodiments 191-192 or 194-203.

[0255] 230. A method of treating a subject having or diagnosed with having a muscular disorder or a neuromuscular disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 221, the AAV particle of any one of embodiments 162-190, an AAV particle comprising the capsid variant of any one of embodiments 1-124 or 146, an AAV particle comprising the peptide of any one of embodiments 129-145 or 161, or an AAV particle comprising the polypeptide of any one of embodiments 191-192 or 194-203.

[0256] 231. A method of treating a subject having or diagnosed with having a neuro-oncological disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 221, the AAV particle of any one of embodiments 162-190, an AAV particle comprising the capsid variant of any one of embodiments 1-124 or 146, an AAV particle

comprising the peptide of any one of embodiments 129-145 or 161, or an AAV particle comprising the polypeptide of any one of embodiments 191-192 or 194-203.

[0257] 232. The method of any one of embodiments 229-231, where treating comprises prevention of progression of the disease or disorder in the subject.

[0258] 233. The method of embodiment 225-232, wherein the subject is a human.

[0259] 234. The method of any one of embodiments 225-233, wherein the AAV particle is administered to the subject intramuscularly, intravenously, intracerebrally, intrathecally, intracerebroventricularly, via intraparenchymal administration, or via intra-cisterna magna injection (ICM).

[0260] 235. The method of any one of embodiments 225-233, wherein the AAV particle is administered to the subject via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.

[0261] 236. The method of any one of embodiments 225-235, wherein the AAV particle is administered to the subject intravenously.

[0262] 237. The method of any one of embodiments 222-236, wherein administration of the AAV particle results in a decreased presence, level, and/or activity of a gene, mRNA, protein, or combination thereof.

[0263] 238. The method of any one of embodiments 222-148, wherein administration of the AAV particle results in an increased presence, level, and/or activity of a gene, mRNA, protein, or a combination thereof.

[0264] 239. The pharmaceutical composition of embodiment 221, the AAV particle of any one of embodiments 162-190, an AAV particle comprising the capsid variant of any one of embodiments 1-124 or 146, an AAV particle comprising the polypeptide of any one of embodiments 129-145 or 161, or an AAV particle comprising the polypeptide of any one of embodiments 191-192 or 194-203, for use in a method of delivering a payload to a cell or tissue.

[0265] 240. The pharmaceutical composition of embodiment 221, the AAV particle of any one of embodiments 162-190, an AAV particle comprising the capsid variant of any one of embodiments 1-124 or 196, an AAV particle comprising the polypeptide of any one of embodiments 129-145 or 161, or an AAV particle comprising the polypeptide of any one of embodiments 191-192 or 194-203, for use in a method of treating a neurological disorder, neurodegenerative, disorder, muscular disorder, neuromuscular disorder, or a neuro-oncological disorder.

[0266] 241. The pharmaceutical composition of embodiment 221, the AAV particle of any one of embodiments 162-190, an AAV particle comprising the capsid variant of any one of embodiments 1-124 or 146, an AAV particle comprising the peptide of any one of embodiments 129-145 or 161, or an

AAV particle comprising the polypeptide of any one of embodiments 191-192 or 194-203, for use in the manufacture of a medicament.

[0267] 242. Use of the pharmaceutical composition of embodiment 221, the AAV particle of any one of embodiments 162-190, an AAV particle comprising the capsid variant of any one of embodiments 1-124 or 146, an AAV particle comprising the peptide of any one of embodiments 129-145 or 161, or an AAV particle comprising the polypeptide of any one of embodiments 191-192 or 194-203 in the manufacture of a medicament for treating a neurological disorder, a neurodegenerative disorder, a muscular disorder, a neuromuscular disorder, or a neuro-oncological disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

[0268] The foregoing and other objects, features, and advantages will be apparent from the following description of particular embodiments of the disclosure, as illustrated in the accompanying drawings. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the disclosure.

[0269] FIG. 1A and FIG. 1B provide diagrams of identification and design of non-human primate (NHP) TRACER AAV capsid libraries.

[0270] FIG. 2 provides a diagram of orthogonal evolution of TRACER AAV capsid libraries.

[0271] FIG. 3 provides a diagram of high-throughput screening by next-generation sequencing in non-human primate.

[0272] FIG. 4 provides a diagram of an exemplary TRACER AAV library design (SEQ ID NO: 3696-3699).

[0273] FIG. 5 provides a diagram of an alternative TRACER backbone construct.

[0274] FIG. 6A, FIG. 6B, and FIG. 6C show mRNA quantification of AAV particle transduction in NHP tissues using qRT-PCR.

[0275] FIG. 7 shows mRNA quantification of AAV particle transduction in NHP tissues using ddPCR.

[0276] FIG. 8 shows mRNA quantification of AAV particle transduction in the spinal cord and dorsal root ganglia of NHP.

[0277] FIG. 9A, FIG. 9B, FIG. 9C, and FIG. 9D show viral genome quantification in NHP tissues.

[0278] FIG. 10A and FIG. 10B show payload-HA quantification in peripheral tissues following AAV particle transduction as fold over TBP transcript (FIG. 10A) and as fold over AAV9 (FIG. 10B).

[0279] FIG. 11A and FIG. 11B show brain transgene mRNA expression (RT-ddPCR) as fold over TBP (housekeeping gene).

[0280] FIG. 12A and FIG. 12B show brain viral DNA biodistribution (ddPCR) as vector genomes per cell.

[0281] FIG. 13A and FIG. 13B show brain transgene mRNA expression (RT-ddPCR) as fold over AAV9.

[0282] FIG. 14A and FIG. 14B show brain viral DNA biodistribution (ddPCR) as fold over AAV9.

[0283] FIG. 15A and FIG. 15B show spinal cord (FIG. 15A) and DRG (FIG. 15B) transgene mRNA expression as fold over TATA box binding protein.

[0284] FIG. 16A and FIG. 16B show spinal cord (FIG. 16A) and DRG (FIG. 16B) viral genome biodistribution as vector genomes per cell.

[0285] FIG. 17A and FIG. 17B show spinal cord (FIG. 17A) and DRG (FIG. 17B) mRNA expression as fold over AAV9.

[0286] FIG. 18A and FIG. 18B show spinal cord (FIG. 18A) and DRG (FIG. 18B) viral genome biodistribution as fold over AAV9.

[0287] FIG. 19A, FIG. 19B, FIG. 19C, FIG. 19D, and FIG. 19E show images of the brain transduction profile for TTD-001 and AAV9 as determined by immunohistochemical analyses of the dentate nucleus (FIG. 19A), cerebellar cortex (FIG. 19B), cortex (FIG. 19C), brain stem, hippocampus, thalamus and putamen (FIG. 19D) and dorsal root ganglion (FIG. 19E).

[0288] FIG. 20A and FIG. 20B show immunohistochemistry images of the DRG de-targeting characteristic of capsid variant TTD-004, compared to AAV9.

[0289] FIG. 21A and FIG. 21B show viral genome biodistribution in peripheral tissues quantified as vector genomes per cell.

[0290] FIG. 22A, FIG. 22B, and FIG. 22C show immunohistochemistry images of the heart of a female NHP at day 14 post-intravenous administration of AAV particles comprising a TTD-001 capsid variant, a TTD-004 capsid variant, or a wild-type AAV9 control capsid polypeptide. FIG. 22A provides a series of global images of the heart muscle, FIG. 22B provides a series of images of the left ventricle of the heart, and FIG. 22C provides a series of images of the right ventricle of the heart. For each series of images in FIGs. 22A-22C, the top left panel shows staining following administration of AAV particles comprising a TTD-001 capsid variant, the top right panel shows staining following administration of AAV particles comprising a TTD-004 capsid variant, and the bottom panel shows staining following administration of AAV particles comprising a wild-type AAV9 control capsid variant.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0291] The details of one or more embodiments of the disclosure 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 disclosure, the preferred materials and methods are now described. Other features, objects and advantages of the disclosure 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 disclosure belongs. In the case of conflict, the present description will control. Certain terms are defined in the Definition section and throughout.

[0292] Described herein, *inter alia*, are compositions comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, e.g., an AAV capsid variant described herein, and methods of making and using the same. Generally, the AAV capsid variant has enhanced tropism for a cell or tissue, e.g., for the delivery of a payload to said cell or tissue, for example a CNS tissue, a CNS cell, a muscle cell, or a muscle tissue.

[0293] As demonstrated in the Examples herein below, certain AAV capsid variants described herein show multiple advantages over wild-type AAV9, including (i) increased penetrance through the blood brain barrier following intravenous administration, (ii) wider distribution throughout the multiple brain regions, e.g., frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus, and/or (iii) elevated payload expression in multiple brain regions. Without wishing to be bound by theory, it is believed that these advantages may be due, in part, to the dissemination of the AAV capsid variants through the brain vasculature. In some embodiments, the AAV capsids described herein enhance the delivery of a payload to multiple regions of the brain including for example, the frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

[0294] According to the present disclosure, AAV particles with enhanced tropism for a target tissue (e.g., CNS) are provided, as well as associated processes for their targeting, preparation, formulation and use. Peptides, e.g., targeting peptides, and nucleic acid sequences encoding the peptides, e.g., targeting peptides, are also provided. These peptides, e.g., targeting peptides, may be inserted into an AAV capsid protein sequence to alter tropism to a particular cell-type, tissue, organ or organism, *in vivo*, *ex vivo* or *in vitro*.

[0295] Several approaches have been used previously to produce AAV capsids with enhanced tropism for a cell or tissue, e.g., a CNS cell or tissue. One approach used co-infection of cultured cells (Grimm et al., 2008, the contents of which are herein incorporated by reference in its entirety) or *in situ* animal tissue (Lisowski et al., 2014, the contents of which are herein incorporated by reference in its entirety) with adenovirus, in order to trigger exponential replication of infectious AAV DNA. Another approach involved the use of cell-specific CRE transgenic mice (Deverman et al., 2016, the contents of which are herein incorporated by reference in its entirety) allowing viral DNA recombination specifically in astrocytes, followed by recovery of CRE-recombined capsid variants. Both approaches have had limited success.

[0296] The transgenic CRE system used by Deverman et al. (2016) has limited tractability in other animal species and AAV variants selected by directed evolution in mouse tissue do not show similar properties in large animals. Previously described transduction-specific approaches are not amenable to large animal studies because: 1) many tissues of interest (e.g. CNS) are not readily accessible to adenovirus co-infection, 2) the specific adenovirus tropism itself would bias the library distribution, and 3) large animals are typically not amenable to transgenesis or genetic engineering to express CRE recombinase in defined cell types.

[0297] To address these limitations, a broadly-applicable functional AAV capsid library screening platform for cell type-specific biopanning in non-transgenic animals has been developed and is described in the appended Examples. In the TRACER (Tropism Redirection of AAV by Cell type-specific Expression of RNA) platform system, the capsid gene is placed under the control of a cell type-specific promoter to drive capsid mRNA expression in the absence of helper virus co-infection. Without wishing to be bound by theory, it is believed that this RNA-driven screen increases the selective pressure in favor of capsid variants which transduce a specific cell type. The TRACER platform allows for generation of AAV capsid libraries whereby specific recovery and subcloning of capsid mRNA expressed in transduced cells is achieved with no need for transgenic animals or helper virus co-infection. Without wishing to be bound by theory, it is believed that since mRNA transcription is a hallmark of full transduction, the methods disclosed herein allow identification of fully infectious AAV capsid mutants, and in addition to its higher stringency, this method allows identification of capsids with high tropism for particular cell types using libraries designed to express CAP mRNA under the control of any cell-specific promoter such as, but not limited to, synapsin-1 promoter (neurons), GFAP promoter (astrocytes), TBG promoter (liver), CAMK promoter (skeletal muscle), MYH6 promoter (cardiomyocytes). Described herein are novel AAV capsid variants generated using the TRACER method which demonstrate enhanced tropism in for example a CNS cell, a CNS tissue, a muscle cell, or a muscle tissue.

[0298] The AAV particles and payloads of the disclosure may be delivered to one or more target cells, tissues, organs, or organisms. In some embodiments, the AAV particles of the disclosure demonstrate enhanced tropism for a target cell type, tissue or organ. As a non-limiting example, the AAV particle may have enhanced tropism for cells and tissues of the central or peripheral nervous systems (CNS and PNS, respectively), or cells and tissues of a muscle. The AAV particles of the disclosure may, in addition, or alternatively, have decreased tropism for an undesired target cell-type, tissue or organ.

[0299] In some embodiments, an AAV comprises a small non-enveloped icosahedral capsid virus of the Parvoviridae family and is characterized by a single stranded DNA viral genome. Parvoviridae family viruses consist of two subfamilies: Parvovirinae, which infect vertebrates, and Densovirinae, which infect invertebrates. The Parvoviridae family comprises the Dependovirus genus which

includes AAV, capable of replication in vertebrate hosts including, but not limited to, human, primate, bovine, canine, equine, and ovine species.

[0300] 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.

[0301] In some embodiments, AAV are used as a biological tool due to a relatively simple structure, their ability to infect a wide range of cells (including quiescent and dividing cells) without integration into the host genome and without replicating, and their relatively benign immunogenic profile. The genome of the virus may be manipulated to contain a minimum of components for the assembly of a functional recombinant virus, or viral particle, which is loaded with or engineered to target a particular tissue and express or deliver a desired payload.

[0302] In some embodiments, the AAV, is a naturally occurring (e.g., wild-type) AAV or a recombinant AAV. In some embodiments, the wild-type AAV vector genome is a linear, single-stranded DNA (ssDNA) molecule approximately 5,000 nucleotides (nt) in length. In some embodiments, inverted terminal repeats (ITRs) cap the viral genome at both the 5' and the 3' end, providing origins of replication for the viral genome. In some embodiments, an AAV viral genome typically comprises two ITR sequences. These ITRs have a characteristic T-shaped hairpin structure defined by a self-complementary region (145nt in wild-type AAV) at 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.

[0303] In some embodiments, the wild-type AAV viral genome further comprises nucleotide sequences for two open reading frames, one for the four non-structural Rep proteins (Rep78, Rep68, Rep52, Rep40, encoded by Rep genes) and one for the three capsid, or structural, proteins (VP1, VP2, VP3, encoded by capsid genes or Cap genes). The Rep proteins are used for replication and packaging, while the capsid proteins are assembled to create the protein shell of the AAV, or AAV capsid polypeptide, e.g., an AAV capsid variant. Alternative splicing and alternate initiation codons and promoters result in the generation of four different Rep proteins from a single open reading frame and the generation of three capsid proteins from a single open reading frame. Though it varies by AAV serotype, as a non-limiting example, for AAV9/hu.14 (SEQ ID NO: 123 of US 7,906,111, the contents of which are herein incorporated by reference in their entirety) VP1 refers to amino acids 1-736, VP2 refers to amino acids 138-736, and VP3 refers to amino acids 203-736. In some embodiments, for any one of the amino acid sequences of SEQ ID NOs: 3636-3647, VP1 comprises amino acids 1-743, VP2 comprises amino acids 138-743, and VP3 comprises amino acids 203-743. In other words, VP1 is the full-length capsid sequence, while VP2 and VP3 are shorter components of the whole. As a result, changes in the sequence in the VP3 region, are also changes to VP1 and VP2,

however, the percent difference as compared to the parent sequence will be greatest for VP3 since it is the shortest sequence of the three. Though described here in relation to the amino acid sequence, the nucleic acid sequence encoding these proteins can be similarly described. Together, the three capsid proteins assemble to create the AAV capsid protein. While not wishing to be bound by theory, the AAV capsid protein typically comprises a molar ratio of 1:1:10 of VP1:VP2:VP3.

[0304] AAV vectors of the present disclosure may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. In addition to single stranded AAV viral genomes (e.g., ssAAVs), the present disclosure also provides for self-complementary AAV (scAAVs) viral genomes. scAAV vector genomes contain DNA strands which anneal together to form double stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the transduced cell. In some embodiments, the AAV particle of the present disclosure is an scAAV. In some embodiments, the AAV particle of the present disclosure is an ssAAV.

[0305] 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; WO2005005610; and WO2005072364, the content of each of which is incorporated herein by reference in its entirety).

[0306] As described herein, the AAV particles of the disclosure comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, and a viral genome, have enhanced tropism for a cell-type or a tissue, e.g., a CNS cell-type, region, or tissue, or a muscle cell-type or tissue. In some embodiments, the AAV particles of the disclosure comprising a capsid with an inserted peptide, e.g., a targeting peptide, and a viral genome, may have enhanced tropism for a cell-type, region, or tissue of the human CNS or a muscle.

Peptides, e.g., Targeting peptides

[0307] Disclosed herein are peptides, e.g., targeting peptides, and associated AAV particles comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, with a peptide, e.g., targeting peptide insert, for enhanced or improved transduction of a target tissue (e.g., cells of the CNS or PNS). In some, embodiments, the peptide, e.g., targeting peptide, is an isolated, e.g., recombinant, peptide, e.g., targeting peptide. In some embodiments, the nucleic acid encoding the peptide, e.g., targeting peptide, is an isolated, e.g., recombinant nucleic acid.

[0308] In some embodiments, the peptide, e.g., targeting peptide, may direct an AAV particle to a cell, region, or tissue of the CNS. The cell of the CNS may be, but is not limited to, neurons (e.g., excitatory, inhibitory, motor, sensory, autonomic, sympathetic, parasympathetic, Purkinje, Betz, etc.), glial cells (e.g., microglia, astrocytes, oligodendrocytes) and/or supporting cells of the brain such as immune cells (e.g., T cells). The tissue of the CNS may be, but is not limited to, the cortex (e.g.,

frontal, parietal, occipital, temporal), thalamus, hypothalamus, striatum, putamen, caudate nucleus, hippocampus, entorhinal cortex, basal ganglia, or deep cerebellar nuclei.

[0309] In some embodiments, the peptide, e.g., targeting peptide, may direct an AAV particle to a cell, region, or tissue of the PNS. The cell or tissue of the PNS may be, but is not limited to, a dorsal root ganglion (DRG).

[0310] In some embodiments, the peptide, e.g., targeting peptide, may direct an AAV particle to the CNS (e.g., the cortex) after intravenous administration. In some embodiments, the peptide, e.g., targeting peptide, may direct an AAV particle to the CNS (e.g., the cortex) following focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.

[0311] In some embodiments, the peptide, e.g., targeting peptide, may direct an AAV particle to the PNS (e.g., DRG) after intravenous administration. In some embodiments, the peptide, e.g., targeting peptide, may direct an AAV particle to the PNS (e.g., DRG) following focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.

[0312] In some embodiments, the peptide, e.g., targeting peptide, may direct an AAV particle to a cell, region, or tissue of a muscle. In some embodiments, the muscle is a heart muscle. In some embodiments, the peptide, e.g., targeting peptide, may direct an AAV particle to a muscle cell, region, or tissue after intravenous administration.

[0313] A peptide, e.g., a targeting peptide, may vary in length. In some embodiments, the peptide, e.g., targeting peptide, is about 3 to about 20 amino acids in length. As non-limiting examples, the targeting peptide may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 3-5, 3-8, 3-10, 3-12, 3-15, 3-18, 3-20, 5-10, 5-15, 5-20, 10-12, 10-15, 10-20, 12-20, or 15-20 amino acids in length. In some embodiments, a peptide comprises about 6 to 12 amino acids in length, e.g., about 9 amino acids in length. In some embodiments, a peptide comprises about 5 to 10 amino acids in length, e.g., about 7 amino acids in length.

[0314] A peptide, e.g., a targeting peptide, may be contiguous (or continuous) or noncontiguous (or not continuous), or split, or divided across two or more amino acid sequences by intervening amino acid sequences that may vary in length. The contiguous peptide, e.g., targeting peptide, may vary in length. As non-limiting examples, the contiguous peptide, e.g., targeting peptide, may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 3-5, 3-8, 3-10, 3-12, 3-15, 3-18, 3-20, 5-10, 5-15, 5-20, 10-12, 10-15, 10-20, 12-20, or 15-20 amino acids in length. The noncontiguous, or split, peptide, e.g., targeting peptide, may vary in length. As non-limiting examples, the noncontiguous, or split, peptide, e.g., targeting peptide, may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 3-5, 3-8, 3-10, 3-12, 3-15, 3-18, 3-20, 5-10, 5-15, 5-20, 10-12, 10-15, 10-20, 12-20, or 15-20 amino acids in length. The intervening amino acid sequence may vary in length. As non-limiting examples,

the intervening peptide, e.g., targeting peptide, may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 3-5, 3-8, 3-10, 3-12, 3-15, 3-18, 3-20, 5-10, 5-15, 5-20, 10-12, 10-15, 10-20, 12-20, or 15-20 amino acids in length.

[0315] In some embodiments, a peptide, e.g., a targeting peptide, of the present disclosure may be identified and/or designed by any sliding window algorithm known in the art.

[0316] In some embodiments, a peptide, e.g., a targeting peptide, and associated AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be identified from libraries of AAV capsid polypeptides, e.g., AAV capsid variants. In some embodiments, the peptide, e.g., targeting peptide, may be a 5-10 amino acid sequence, e.g., a 6-10 amino acid sequence, a 6-9 amino acid sequence, a 7-10 amino acid sequence, a 7-9 amino acid sequence, an 8-10 amino acid sequence, a 7 amino acid sequence, an 8 amino acid sequence, or a 9 amino acid sequence. In some embodiments, the peptide, e.g., targeting peptide, may be a 5 amino acid sequence (5-mer). In some embodiments, the peptide, e.g., targeting peptide, may be a 6 amino acid sequence (6-mer). In some embodiments, the peptide, e.g., targeting peptide, may be a 7 amino acid sequence (7-mer). In some embodiments, the peptide, e.g., targeting peptide, may be a 9 amino acid sequence (9-mer). In some embodiments, the peptides, e.g., targeting peptides, may also differ in their method of creation or design, with non-limiting examples including, random peptide selection, site saturation mutagenesis, and/or optimization of a particular region of the peptide (e.g., flanking regions or central core).

[0317] In some embodiments, a peptide library, e.g., a targeting peptide library, comprises targeting peptides of 7 amino acids (7-mer) in length randomly generated by PCR.

[0318] In some embodiments, a peptide, e.g., a targeting peptide, library comprises peptides, e.g., targeting peptides, with 3 mutated amino acids. In some embodiments, these 3 mutated amino acids are consecutive, or contiguous, amino acids. In another embodiment, these 3 mutated amino acids are not consecutive, or noncontiguous, or split, amino acids. In some embodiments, the peptide, e.g., targeting peptide, is a 5-mer. In some embodiments, the peptide, e.g., targeting peptide, is a 6-mer. In some embodiments, the parent peptide, e.g., targeting peptide, is a 7-mer. In another embodiment, the parent peptide is a 9-mer.

[0319] In some embodiments, a peptide, e.g., a targeting peptide, library comprises 7-mer peptides, e.g., targeting peptides, wherein the amino acids of the peptide, e.g., targeting peptide, and/or the flanking sequences are evolved through site saturation mutagenesis of 3 consecutive amino acids. In some embodiments, NNK (N = any base; K = G or T) codons are used to generate the site saturated mutation sequences.

[0320] AAV particles comprising capsid proteins with a peptide, e.g., a targeting peptide, insert (e.g., an AAV capsid variant) are generated and viral genomes encoding a reporter (e.g., GFP) encapsulated within. These AAV particles (or AAV capsid library) comprising AAV capsid variants

are then administered to a transgenic rodent (e.g. mouse) by intravenous delivery to the tail vein. Administration of these capsid libraries to cre-expressing mice results in expression of the reporter payload in the target tissue, due to the expression of Cre.

[0321] In some embodiments, AAV capsid mRNA expression may be modulated, e.g., under the control of, or driven by, a cell-type specific promoter. Such capsids, which may comprise peptide, e.g., targeting peptide, inserts and viral genomes encoding a reporter encapsulated within, may be administered, e.g., by intravenous delivery to the tail vein, to a non-transgenic rodent (e.g. mouse), such as but not limited to a C57BL/6 mouse, a BALB/C mouse and a rat. Administration of such capsid libraries to a non-transgenic rodent may result in the expression of the reporter payload in the target tissue, due to the cell-type specific promoter.

[0322] In some embodiments, AAV capsid mRNA expression may be under the control of, or driven by, a cell-type specific promoter. Such capsids, which may comprise a peptides, e.g., targeting peptide inserts, and viral genomes encoding a reporter encapsulated within, may be administered, e.g., by intravenous delivery to the saphenous vein, to a non-human primate, such as but not limited to a cynomolgus macaque and a rhesus macaque. Administration of such capsid libraries to a non-human primate may result in the expression of the reporter payload in the target tissue, due to the cell-type specific promoter

[0323] In some embodiments, AAV particles comprising capsid proteins with peptide, e.g., targeting peptide, inserts may hereinafter also be referred to as peptide display capsid libraries.

[0324] AAV particles and/or viral genomes may be recovered from the target tissue for identification of peptides, e.g., targeting peptides, and associated AAV particles that are enriched, indicating enhanced transduction of target tissue. Standard methods in the art, such as, but not limited to next generation sequencing (NGS), viral genome quantification, biochemical assays, immunohistochemistry and/or imaging of target tissue samples may be used to determine enrichment.

[0325] A target tissue may be any cell, tissue or organ of a subject. As non-limiting examples, samples may be collected from brain, spinal cord, dorsal root ganglia and associated roots, liver, heart, gastrocnemius muscle, soleus muscle, pancreas, kidney, spleen, lung, adrenal glands, stomach, sciatic nerve, saphenous nerve, thyroid gland, eyes (with or without optic nerve), pituitary gland, skeletal muscle (rectus femoris), colon, duodenum, ileum, jejunum, skin of the leg, superior cervical ganglia, urinary bladder, ovaries, uterus, prostate gland, testes, and/or any sites identified as having a lesion, or being of interest.

[0326] In some embodiments a peptide, e.g., a targeting peptide, may comprise a sequence as set forth in Table 1. In some embodiments a peptide, e.g., a targeting peptide, may comprise a sequence as set forth in Table 2. In some embodiments, the peptide, e.g., targeting peptide, comprises an amino acid sequence of any one of peptide 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, e.g., as described in Table 2. In some embodiments, the peptide, e.g., targeting peptide, is isolated, e.g., recombinant.

Table 1. Exemplary Peptide Sequences, e.g., Targeting Peptides

Peptide Sequence	SEQ ID NO:	Peptide Sequence	SEQ ID NO:	Peptide Sequence	SEQ ID NO:	Peptide Sequence	SEQ ID NO:
PLNGAVHLYA	1725	AQANPVSIMS	2199	AQFRSAITSA	2673	AQAPTSASRA	3147
AQARDSPKGW	1726	AQASMQAVKD	2200	AQANMTKQSL	2674	AQAPTSCLAT	3148
LTNGAVRDRP	1727	AQAVGGHSVA	2201	AQNAGSTSRA	2675	AQAPYTPSSF	3149
VQAFTHDSRG	1728	AQAVAASTRL	2202	VLGSAVTGRA	2676	AQAQGGAYREM	3150
AQAYSTDVRM	1729	GGTHAVSSFA	2203	AQPMLQSSSA	2677	AQAQKSPQFR	3151
AQAYSTDVRI	1730	AQAADSSGFR	2204	AQLGTPSLSA	2678	AQAQLGTSSP	3152
AQAFTAAERM	1731	AQQSHVPQTA	2205	AQATAHTGVP	2679	AQAQPNYASV	3153
AQTHLQIGVA	1732	AQARVGNTNV	2206	AQAVGRDNRL	2680	AQAQRGLHAV	3154
AQSNVLSLA	1733	AQTVSYSDLA	2207	AQATSASVWA	2681	AQAQSQSWSS	3155
AQAYSTDERM	1734	AQAEHGLARS	2208	AQAGSEASLR	2682	AQAQTRPPLK	3156
AQAYSTDVRL	1735	AQASNYPVAA	2209	AQANQNRTAF	2683	AQAQTSRAMD	3157
AQATVSTLRM	1736	VLLSAVGMAA	2210	AQASAQVKRS	2684	AQAQVSQMSL	3158
AQAYSTDERK	1737	AQALSGQNRG	2211	AQATSGVHHP	2685	AQARA AHMAQ	3159
AQAYSTDMRM	1738	AQAWGQETRQ	2212	AQTHMQIGVA	2686	AQARA AVPSK	3160
VVNGAVLHVA	1739	AQGYSTDVRM	2213	AQSHIFTPA	2687	AQARA QGHSY	3161
AQAYSTDVTM	1740	AQAGSVMSRE	2214	AQLFHTGSPA	2688	AQARASYNM	3162
AQAHLQIGVA	1741	AQAGSLSARG	2215	LASRAVVGTA	2689	AQARATLGST	3163
FLDPAVSSKA	1742	AQATALAPKS	2216	AQALLRVGVG	2690	AQARDASGVA	3164
AQAYVSTLRM	1743	AQAIRQNGSS	2217	AQITLPSGTA	2691	AQARDRMMIN	3165
AQAQTGPPLK	1744	AQLQDNQLA	2218	AQAEKSLGRQ	2692	AQARDRMMYN	3166
EQASRLPTPG	1745	AKAYSTDVRM	2219	AQTSNTTTRA	2693	AQAREQNVSS	3167
AQASVSTMRM	1746	AQSVDRILLA	2220	AQAHTQASYM	2694	AQARFPSVYA	3168
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TQAYSTDVRM	1748	AQTNLQPRGA	2222	AQATPSSTAM	2696	AQARGDMFAW	3170
AQALPSNERL	1749	PNTIAVGQRA	2223	AQSTVNRTYA	2697	AQARGDSGVS	3171
AQAYSTDVRT	1750	AQAHATLSLS	2224	AQAGHGPSTR	2698	AQARGLA EVE	3172
AQSSLPEMVA	1751	NHLRAVGSPA	2225	AQLSLVPLQA	2699	AQARGNNLYT	3173
AQAGEQSTRL	1752	AQETDRNLRA	2226	AQLHSPIPSA	2700	AQARGSPMSR	3174
AQASNDVGRA	1753	AQARAETSGS	2227	AQSLARDGLA	2701	AQARGTQTAE	3175
AQATFTASEY	1754	AQHRELD SYA	2228	AQAPPSPAM	2702	AQARGTTTAE	3176
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AQARTIDQCC	1756	AQVGQTSSWA	2230	AQAGQARSLA	2704	AQARITTDMS	3178
AQEYNSNPKA	1757	AQANSAALLM	2231	AQPVGRVPPA	2705	AQARLPMLVG	3179
AQVVDNSTHA	1758	AQAIHRTAT	2232	AQAREQRGPV	2706	AQARMPVVFV	3180
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AQALTQDERW	1762	AQQGHTVNNA	2236	AQALHAGHHP	2710	AQARQSSFTI	3184
AQAQLSTLRP	1763	AQASLPISTR	2237	AQSKRDDPSA	2711	AQARSGVASL	3185

AQVVMGISVA	1764	AQHIDSMRPT	2238	AQTSRELMA	2712	AQARSLEPGI	3186
AQAYTTDVRM	1765	AQAQDTENMR	2239	AQALPASGAR	2713	AQARSPVVEK	3187
AQHIDSMRPP	1766	RTGAAVTGAA	2240	AQSNALLSLA	2714	AQARSSDRGS	3188
AQASTGTLRL	1767	AQASSVRGMG	2241	AQASPVVGVS	2715	AQARTIDQSC	3189
AQHRALDYVA	1768	AQPGIESTIA	2242	AQARGDSYMA	2716	AQARTPLGYQ	3190
AQARESPLGL	1769	AQHVDLDSKA	2243	AQAGASSLTV	2717	AQARTTSFVA	3191
AQALLAGTRV	1770	AQATTVPALG	2244	AQALRPVNGT	2718	AQARVDVQLP	3192
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AQASLSSTRP	1772	AQAGYISSAS	2246	AQFPPLSRSA	2720	AQASAKPLIE	3194
AQAMGSRSDQ	1773	AQTLILGDPA	2247	AQVARGTVQA	2721	AQASARMPSS	3195
AQAAQGTYRG	1774	AQAASGLTMM	2248	AQTSTQSPPG	2722	AQASAVRMAR	3196
SQENAVFSKA	1775	AQALERPPSG	2249	AQARDGMNVR	2723	AQASDPPRSS	3197
AQALSLSTRP	1776	TTYDAVHSKA	2250	AQAVSRNVVV	2724	AQASDRVSRG	3198
AQAAAGTLRD	1777	AQAMLDsang	2251	AQHTATRSVA	2725	AQASGIAAGA	3199
AQASRLPTPG	1778	AQAMHQTDFK	2252	AQAVREDGHA	2726	AQASGYTSVS	3200
AQAGSLSERG	1779	KSTVAVQSVa	2253	TNSSAVAASA	2727	AQASHSTLGT	3201
AQSKGDDGFTA	1780	AQATAGTLIG	2254	AQATFQLAST	2728	AQASLKILSL	3202
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AQAYSTDARM	1783	AQSFSSDNL	2257	AQATSSLHVL	2731	AQASLQIMSL	3205
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AQAGVSTALH	1787	AQAHTVSPHL	2261	AQTHLQIRVA	2735	AQASRESPTTR	3209
AQSYSTDVRM	1788	GILGAVLPRA	2262	AQAPPSKAM	2736	AQASRIHSCC	3210
AQPLMSHTDA	1789	AQHNSSSLLA	2263	AQIVSKAMPA	2737	AQASRNLSAG	3211
AQAAALASRP	1790	AQAPQVAGTM	2264	AQASVRNNPS	2738	AQASRTSPPL	3212
AQAAITSTIS	1791	AQHQDSRPMA	2265	AQAESVAAL	2739	AQASSKSACQ	3213
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GGTLAVVSLA	1798	AQAGSSSVTW	2272	AQAQASSYGS	2746	AQASYQTSLM	3220
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AQAFAMPKGL	1800	AQANSAGVLA	2274	AQSLSRASTA	2748	AQATCQCAST	3222
AQALVSTSRP	1801	AQLLGDAVKA	2275	AQASTFVQTI	2749	AQATFLQAST	3223
AQASFQCAST	1802	SSGNAVSSLA	2276	AQASSKVVA	2750	AQATFQQTST	3224
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AQASTQSPPG	1804	AQYHTRGFAA	2278	AQAYSTGVRM	2752	AQATGSDSRR	3226
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AQAIQDRTVV	1809	TQYRAVEGQA	2283	AQRVNQVSTA	2757	AQATRQAHPs	3231
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SVHGAVGILA	1932	ISLNAVSGKA	2406	AQTHLQIWVA	2880	AQMSRTRLPA	3354
AQPYVVSGAA	1933	AQGVHGHYVA	2407	AQTNLKPRGA	2881	AQMTYSQPKA	3355
AQWTHNITAA	1934	AQAYSKDVRM	2408	AQTNLQIGVA	2882	AQNGKILVPA	3356
PTNAAVRTNA	1935	VPSIAVSSHA	2409	ILAPAVSSKA	2883	AQNRSLPHQA	3357

AHAYSTDVRM	1936	AQSSRHDDLA	2410	AQAHKVLDFG	2884	AQNSANTTCA	3358
PLAAAVGMKA	1937	AQANGSGSRG	2411	AQAYSTDVSM	2885	AQPGIPFHGA	3359
AQARDNSVML	1938	AQVGIADRRRA	2412	AQAYSTDVWM	2886	AQPGQSFPAA	3360
AQAQFPRNGG	1939	AQARGMESML	2413	AQAGMPRGPS	2887	AQPGYHLTSA	3361
GALNAVNGVA	1940	AQAGVSTAGH	2414	AQHLPALKMA	2888	AQPLRMGNLA	3362
AQASHQOGVP	1941	AQVSTRNLIA	2415	AQAIGLNESA	2889	AQPSGITALA	3363
SYQSAVVPQA	1942	AQAVPRLTAG	2416	AQTQLQIGVA	2890	AQPTRLVGGA	3364
AQSIMGTIRA	1943	AQRHMELEA	2417	AQAYSPDVRM	2891	AQPVNRDRLA	3365
AQAYVSQAQG	1944	SQSRVWWEA	2418	AQANSTDERM	2892	AQQEKSSTPA	3366
AQATGNQAHF	1945	QSHTAVSSLA	2419	HATVAVQGAA	2893	AQQLVALPFA	3367
AQVTVGTPIA	1946	AKASVSTLRM	2420	AQACSTDVRM	2894	AQQPSRAAWA	3368
AQAQSTFRG	1947	AQASGSSQWA	2421	AQIKSLTSVA	2895	AQQPSYISTA	3369
SVHMAVTVSA	1948	AQPNAQYMKA	2422	EQAYSTDVRM	2896	AQQSANTMAA	3370
AQAQSTLNLG	1949	AQAMGTGSSL	2423	AQANSTDVRM	2897	AQQSFPRTA	3371
AQDQTGPPLK	1950	AQAFSTSQLT	2424	AQAMPRTPGV	2898	AQQSPVAVRA	3372
HLAHAVSTAA	1951	AQAKDQSQRL	2425	GEGTAVTATA	2899	AQQTTSWSEA	3373
AQALARDSSF	1952	AQVGGNGSRA	2426	PTNAAVRTKA	2900	AQQTIVRTDA	3374
AQLLSGTLKA	1953	AQANGASRAV	2427	AQTHLQIGEA	2901	AQQVQFRFEA	3375
AQASLLPTPG	1954	QVNKAVLDFA	2428	AQADSTDVRM	2902	AQRALNKSDA	3376
AQPMAGQSTA	1955	AQETLSSTRA	2429	VTFAAVTDKA	2903	AQRDLAHTQA	3377
AQARSLEPDI	1956	GVYGAHVHSSA	2430	AQAYYTDVRK	2904	AQRDLHSQA	3378
AQFVTGNQDA	1957	AQTITIENVA	2431	EQTHLQIGVA	2905	AQRDRDARSA	3379
AQATFKTSVP	1958	AQALMKIADG	2432	AQAYSTDVRV	2906	AQREFTPMDA	3380
LNARAVEGPA	1959	AQANVSLQAA	2433	AQQFQTQNA	2907	AQRGFPASTA	3381
AQALPNSGRP	1960	AQSTTSHLRA	2434	AQITVSHSTA	2908	AQRGYDLSPA	3382
AQALNGSPEA	1961	AQLSNLVSVA	2435	AQLGRMQYAA	2909	AQRGYDLSTA	3383
AQATSLHPLP	1962	AQANSTPTRQ	2436	AVRVADSSSA	2910	AQRGYENKA	3384
AQAVQPPLKN	1963	AQQRGDRAAA	2437	AQIQTDLSRA	2911	AQRHLELKEA	3385
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AQHVDLASKA	1965	AQQLTYGSSA	2439	AQAYSTDVRK	2913	AQRLHSSATA	3387
AQASFATMRP	1966	AQPAEKQYSA	2440	TQAHAGTIYS	2914	AQRLRQQEDA	3388
AQAMPLNARS	1967	AQAMPRSRGD	2441	AQARSLEPVN	2915	AQRLSGQSSA	3389
AQALVGQMRG	1968	AQGLSGRALA	2442	AQAYVSQGMS	2916	AQRNSYLSDA	3390
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AQGHGDLHRA	1971	AQTGVTSQA	2445	AQAGLSDPRM	2919	AQRQGDQQA	3393
AQAADRSPVH	1972	AQALVTSSEK	2446	PTNAADRTNA	2920	AQRSASGIQA	3394
GALNAVTVGA	1973	AQASPHSSMA	2447	AQAPQVEGTM	2921	AQRSGSPQPA	3395
AQAERMASLG	1974	AQALTQDEM	2448	AQAFTPAERM	2922	AQRSIMKGQA	3396
AQAPPTTTRL	1975	AQAFSTQQRL	2449	AQGPLYGLRA	2923	AQRSIMQGKA	3397
AQAAVGGTLA	1976	AQAGSQVTQA	2450	AQTNLQQRGA	2924	AQRSLASVTA	3398
AQSLGTGMHA	1977	AQOSTLALKA	2451	AQPRFNLTQA	2925	AQRSYPSTSA	3399
AQSLGSPALA	1978	AQALNGSHAA	2452	AQAYSMDVRM	2926	AQRTSDLLQA	3400

AQASVSVTRP	1979	AQATEGHLRS	2453	AQLGGQSQVA	2927	AQRTSSMSEA	3401
AQATMSHTMA	1980	AQPMANMLMA	2454	AQGSKDGLYA	2928	AQRYLGNSLA	3402
AQAVQSLTVG	1981	PSTSAVSQKA	2455	ALAYSTDVRM	2929	AQRYTNQVPA	3403
AQSQTGTYRA	1982	AQAPPSSTEM	2456	AKSKTTLTLA	2930	AQRYVNNNSAA	3404
AQSLASVYAA	1983	AQRERVDLAA	2457	EQAFTAAERM	2931	AQSFSSSEQLA	3405
STKLAVHEQA	1984	AQASVTLPRT	2458	AQDSVSTLRM	2932	AQSGIRDARA	3406
AQSHLFPTPA	1985	AQAYPSSSKA	2459	AQVYSTDVLM	2933	AQSGKSIAGA	3407
AQGTWSSSEA	1986	AQAHSGSAIP	2460	AQGNMLVKDA	2934	AQSGNHFGKA	3408
AQTPQGLTKA	1987	AQSPSQSLKA	2461	AQARSLEQVI	2935	AQSGRVVTLA	3409
AQVSLGTQYA	1988	AQATPPATSP	2462	AQAFSTSQFT	2936	AQSIQYLDYA	3410
AQDSRLPTPG	1989	CLGAAVNQCA	2463	LTYGAVRDRA	2937	AQSIQYSHTA	3411
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AQATMSEQL	1991	AQAQKANNVG	2465	AQAAITSTIT	2939	AQSKSAITWA	3413
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AQINFLSGVA	1994	TVYTAVGVSA	2468	VQAYSTDVRM	2942	AQSLGTGLQA	3416
PQHLAVSSEA	1995	LGRGAVLDMA	2469	SVHGAVGIMA	2943	AQSLQHLDDA	3417
AQALGNFPAV	1996	AQANVRSDQM	2470	AQTSQLYQNA	2944	AQSMDWPPSA	3418
AQANASTVRV	1997	AQARDSQKGW	2471	AQARSMEPVI	2945	AQSMNPSPMA	3419
AQRIVDLTTA	1998	AQTPGSRSA	2472	SQAYSTDVRM	2946	AQSMSARGLA	3420
VRQVAVEGVA	1999	AQALPSNARQ	2473	AQRLQNDNLA	2947	AQSNLSYARA	3421
AQAPASSQKL	2000	AQASATSVVH	2474	AQEVNDSTLA	2948	AQSNSYLDSDA	3422
AQQIDSMRPA	2001	AQINLGTMR	2475	VSTEAVSSAA	2949	AQSQAQVQSA	3423
AQAHGTSSLF	2002	AQVYNNTSAA	2476	AQASPLPTPG	2950	AQSQFLGLRA	3424
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AQLHLAETRA	2004	AQLRTDYTRA	2478	AQAQTGTPLK	2952	AQSQSGTAWA	3426
AQALTHDERW	2005	AQAYSTDVKM	2479	AQSKTITFLA	2953	AQSRGQDKAA	3427
NTVRVIMEA	2006	AQTSQLYQPA	2480	AQTTFFQAST	2954	AQSRMLPTSA	3428
AQAYVAGSRP	2007	AQALTQEERW	2481	AQLSTSGLLA	2955	AQSRVLSHQA	3429
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AQAQEQVFS	2009	VTGSAVAGIA	2483	AQTVSVHDRA	2957	AQSTLTVLPA	3431
AQACVSTAVH	2010	AQAFSTDVRM	2484	AQSKTTLTLP	2958	AQSVQYSTSA	3432
AQAFTHDSRG	2011	AQAHGPTSGV	2485	AQATFQQASS	2959	AQSWVGPAVA	3433
AQASHQGTVG	2012	AQAGVGLPIA	2486	AQAKGSRSDQ	2960	AQSYASSYAA	3434
AQAVLVTEQG	2013	AQVNSGQARA	2487	AQAANTSTIS	2961	AQTKSFSSAA	3435
AQAVVSTAVH	2014	AQAQTGPPMK	2488	SVNTAVASLA	2962	AQTLARPRIA	3436
AQATSRETKG	2015	AQARLAPVAC	2489	AQAPPSSTAM	2963	AQTLPFISSA	3437
YQQPAVSSRA	2016	LSIGAVASMA	2490	LTNGSVRDRA	2964	AQTMGGQYSA	3438
AQANMGLSLS	2017	AQAQDLGVMR	2491	AQRQGPDPMA	2965	AQTMMSGMVA	3439
AQWTSSMSEA	2018	PTGLAVTSPA	2492	AQARSLEPLI	2966	AQTMVSARPA	3440
AQASISIMST	2019	AQSASTSWSA	2493	AQAGRMSQSG	2967	AQTNLNFNLA	3441
AQASVAPLTC	2020	AQNGSNVRNA	2494	AQTLMSHTDA	2968	AQTPAFINLA	3442
AQLVTVEKQA	2021	AQASISSSAT	2495	AQAPGMGAPL	2969	AQTPRQLASA	3443

AQAATAGEKL	2022	AQNSHAHLAA	2496	GAGPAVTATA	2970	AQTQGS SGWA	3444
AQALSHGPGG	2023	AQAVGVKQFF	2497	AQAQPGPPLK	2971	AQTQSIDPSA	3445
AQSNAHIEIA	2024	AQAHLSPTHA	2498	AQLIDSMRPA	2972	AQTQVPSGAA	3446
AQARSSSTGI	2025	AQPAYGSSYA	2499	AQAQTGPPQK	2973	AQTRGDSVGA	3447
AQAVGGDVTR	2026	AQAHQARSGS	2500	AQARVAVKLP	2974	AQTSQMYQTA	3448
AQAPRTVYQG	2027	AQAHTSPTQR	2501	AQARTNNSSG	2975	AQTSVMEQRA	3449
AQALHNLGPA	2028	AQAATPSSSR	2502	AQARSLAPVI	2976	AQTVETHMRA	3450
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AQANGSIVLN	2033	AQHGSSEFTA	2507	AQSNSVLSLA	2981	AQVLRASQA	3455
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AQAVKQGLYE	2035	AQASSSSLRP	2509	AKATMSQTMA	2983	AQVPRYMRPA	3457
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VNGRAVSMMA	2038	AQAGSHSSVS	2512	AQHRALDSNA	2986	AQVREFRLTA	3460
SLVGAVAQMA	2039	VRAHAVTGLA	2513	QTNAAVRTNA	2987	AQVSRHVTSA	3461
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AQAGMGINLP	2043	AQAAITSTNS	2517	SVNTDVASLA	2991	AQVVYSEGRA	3465
AQANAHSITL	2044	AQARDAVQLP	2518	AQAHPSSTAM	2992	AQWKGSDTLA	3466
AQARFTTTEM	2045	AQAKELVSTS	2519	AQYISDTYRA	2993	AQWPFQMSAA	3467
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AQIHPANSRA	2060	AQAGQARSMG	2534	AQAPSHLPV	3008	CPAAAVLAAA	3482
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AQARLPHTSS	2142	VVKGAVLHVA	2616	AQAHNSDRAR	3090	RLLPAVSNDRA	3564
AQRNGSEVVA	2143	AQDTVSVPLK	2617	AQAHARGEVGQ	3091	RLSEAVSMTA	3565
AQATDRVDRP	2144	AQKGAPSLQA	2618	AQAHRHISGP	3092	RLSKAVAAGA	3566
AQASLSRERT	2145	AQASYDVGRA	2619	AQAHSRMSQ	3093	RNDVAVVHTA	3567
AQAYSTHVRM	2146	AQGPLSGMRA	2620	AQAHSVNTAS	3094	RNSYAVSEAA	3568
AQHLSAGPTA	2147	AQALGTSVPA	2621	AQAHTSTVLC	3095	RPSNAVSVHA	3569
LNGGAVSLRA	2148	AQVKNKGASTA	2622	AQAIALHRPS	3096	RTGKAVDTVA	3570
AQAYGVSSVT	2149	AQLTRTSPVA	2623	AQAICLSPDR	3097	RTPDAVHMLA	3571
AQFGSAVQLA	2150	AQADAALRFS	2624	AQAIEGRYPR	3098	SANLAVTLA	3572

AQAPPTSTRL	2151	AQVQLVVSPA	2625	AQAIPSPYSV	3099	SAVRAVTWDA	3573
AQVSTNWPKA	2152	AQAYSSDVRM	2626	AQAIRGAVQA	3100	SEIGAVYGSA	3574
AQTSTDLRA	2153	AQARSGLSLP	2627	AQAKSSPLSV	3101	SGESAVVSVA	3575
AQAHSTDVRM	2154	AQNGHKFTAA	2628	AQAKSSSPTL	3102	SGLKAVGNPA	3576
AQATLTGHVS	2155	AQGLSSATKA	2629	AQAKTASSPF	3103	SGLLAVSPPA	3577
AQATTQGALT	2156	AQGTWSTVKA	2630	AQALATLPAM	3104	SGSLAVGSMA	3578
AQAAKASDRT	2157	AQASGVGGRI	2631	AQALEHTSPR	3105	SGTRAVSPSA	3579
AQGNHGGRA	2158	AQTSYPAQKA	2632	AQALGGFRSE	3106	SGYTAVASGA	3580
AQALSTSLLL	2159	AQNAVPTHSA	2633	AQALGHQGGQ	3107	SLNAAVHSGA	3581
AQASLGSTYL	2160	AQSYPEITRA	2634	AQALIPMVRG	3108	SLNTAVASLA	3582
AQAFSTVGAV	2161	AQTGLSTSSA	2635	AQALQASRPP	3109	SLSYAVDMRA	3583
AQLNGLVTTA	2162	AQYDTHNFAA	2636	AQALQPFSEH	3110	SLVGALAQMA	3584
AQASVRTLRM	2163	AQAVLSSVIQ	2637	AQALQQPQSR	3111	SLVGAVSQMA	3585
AQATMSRPWQ	2164	AQDSAVALMA	2638	AQALRASAPR	3112	SMRQAVSQYA	3586
AQSSLPAMVA	2165	AQATGKGALP	2639	AQALVGSRGQ	3113	SQAHMVASVT	3587
RETVAVGQYA	2166	AQNSRSGHDA	2640	AQALYQHHSI	3114	SQNNAVVSYA	3588
AQAFGSEGRS	2167	AQAFQKEPSV	2641	AQALYRQSET	3115	SRSKAVSWEA	3589
SSGTAVEHRA	2168	AQAGSTSGKM	2642	AQAMASSLLA	3116	SRYSAVPREA	3590
FGTNAVIPRA	2169	AQRDQAHSA	2643	AQAMGPVGKC	3117	SSPAVTRSA	3591
AQAGQARS LG	2170	AQAASALSGR	2644	AQAMGRESYN	3118	STESAVSDRA	3592
AQSFSSDNMA	2171	AQARHSSLLP	2645	AQAMGSNERY	3119	SVIGAVYGYA	3593
AQMNGLTGKA	2172	AQGPSTSYLA	2646	AQAMGTADRA	3120	SVNKAVASLA	3594
AQQNGKQHLA	2173	FLAPAVSSKA	2647	AQAMITTVHS	3121	SVNTAVASMA	3595
AQHIDSIRPA	2174	AQAGPQCSSC	2648	AQAMPRLRDA	3122	SVSKAVSLGA	3596
AQAADRLSTL	2175	AQALTQHERW	2649	AQAMRSLSAA	3123	TARYAVAQQA	3597
AQFGLKDIRA	2176	AQAIRSSERV	2650	AQAMSRLGTA	3124	TFRSAVELRA	3598
AQAHQGGATL	2177	AQAVHSSSVY	2651	AQAMSRTVMP	3125	TFYSAVKLGA	3599
AQATYNPKP	2178	AQSSRTALAA	2652	AQANCLSPDR	3126	TPIQAVRESA	3600
AQAMSNMLRN	2179	AQITFSHTRA	2653	AQANFPFGGP	3127	TQHIDSMRPA	3601
VPISAVMSTA	2180	AQALTLGGGL	2654	AQANGRDVRT	3128	TQSKTTLTLA	3602
AQHSLGNTVA	2181	AQAGKTLVL	2655	AQANKDEGMG	3129	TQYGAVECQA	3603
AQATSALSRL	2182	AQASRSNLDN	2656	AQANLQQSSG	3130	TQYGAVEGRA	3604
AQADRQTFPV	2183	AQGLSTHTA	2657	AQANLQRSSA	3131	TTALAVGDNA	3605
AQAVNSMSIG	2184	AQQSVAYNVA	2658	AQANQVRSPL	3132	TVLSAVSGGA	3606
AQALAVSKN	2185	AQHTRLSSA	2659	AQANSSLSR	3133	VAVHAVGSVA	3607
AQQQLQERFA	2186	AQAGGTPNKL	2660	AQAPGQGSQT	3134	VDTRAVGHQA	3608
AQFNGASAHA	2187	AQAFQSLTLA	2661	AQAPHRGLYT	3135	VGGAAVGTITA	3609
AQLGGQSPVA	2188	AQAVALS HQE	2662	AQAPHSSTAM	3136	VKERAVSQSA	3610
AQANGAYTDN	2189	AQMLASGIPA	2663	AQAPKVL DWG	3137	VMNGAVRLLA	3611
AQNLSSSEPA	2190	AQNRALDSYA	2664	AQAPMSRLAQ	3138	VPGSAVIAAA	3612
AQSAIVLTITA	2191	AQASGSTTRN	2665	AQAPMTSGVQ	3139	VSTYAVSMQA	3613
ITRSAPVDVA	2192	AQARGDGYVA	2666	AQAPNNGVQK	3140	VTGKAVTGVA	3614
GALKAVTGVA	2193	DARVAVL DFA	2667	AQAPQTRPGR	3141	VTRGAVEAHA	3615

AQAVGQDYLR	2194	AQAVASQVSR	2668	AQAPREHPSR	3142	VVESAVVGLA	3616
AQVTLNTPLA	2195	AQARGPSPAT	2669	AQAPRTPDLR	3143	VVNVAVLHVA	3617
AQALTQDDRW	2196	AQHRALDSYD	2670	AQAPSSDRVH	3144	VVSSAVGRTA	3618
AQAYSTNVRM	2197	AQLIDSTSRA	2671	AQAPSSQEAR	3145	YLVGAVAQMA	3619
AQAVAAPASL	2198	AQAQTLRSGS	2672	AQAPSSSYM	3146	YNRTAVSSEA	3620
						YRSTAVEGYA	3621
						AQASFNDTRA	3622

Table 2. Exemplary Peptide, e.g., Targeting Peptide Sequences

Peptide	SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:	Nucleotide Sequence
1	3648	PLNGAVHLY	3660	ccgcttaatgggiccgcctccatcttat
2	3649	RDSPKGW	3661	cgtgattctccgaagggtggca
3	3650	YSTDVRM	3662	tattctacggatgtgaggatgca
4	3651	IVMNSLK	3663	atgtttatgaattcgttgaaggc
5	3652	RESPRGL	3664	cgggagagtcctcgtggcgctgca
6	3653	SFNDTRA	3665	agttttatgatactagggtctca
7	3654	GGTLAVVSL	3666	ggtgggtacgttggccgtcgtgtcgtt
8	3655	YGLPKGP	3667	tatgggtgcccgaagggtcct
9	3656	STGTLRL	3668	tcgacigggacgcttcggctt
10	3657	YSTDERM	3669	tattcgacggatgagaggatg
11	3658	YSTDERK	3670	tattcgacggatgagaggag
12	3659	YVSSVKM	3671	tatgttctgctgttaagatg

[0327] In some embodiments, the peptide, e.g., targeting peptide, comprises at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622. In some embodiments, the peptide comprises at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 3648-3659.

[0328] In some embodiments, the 3 consecutive amino acids comprise PLN. In some embodiments, the 4 consecutive amino acids comprise PLNG (SEQ ID NO: 3678). In some embodiments, the 5 consecutive amino acids comprise PLNGA (SEQ ID NO: 3679). In some embodiments, the 6 consecutive amino acids comprise PLNGAV (SEQ ID NO: 3680). In some embodiments, the 7 consecutive amino acids comprise PLNGAVH (SEQ ID NO: 3681). In some embodiments, the 8 consecutive amino acids comprise PLNGAVHL (SEQ ID NO: 3682). In some embodiments, the 9 consecutive amino acids comprise PLNGAVHLY (SEQ ID NO: 3648).

[0329] In some embodiments, the four consecutive amino acids comprise NGAV (SEQ ID NO: 3683). In some embodiments, the four consecutive amino acids comprise GAVH (SEQ ID NO: 3684). In some embodiments, the five consecutive amino acids comprise NGAVH (SEQ ID NO: 3685). In some embodiments, the five consecutive amino acids comprise GAVHL (SEQ ID NO: 3686). In some embodiments, the five consecutive amino acids comprise AVHLY (SEQ ID NO: 3687). In some embodiments, the six consecutive amino acids comprise NGAVHL (SEQ ID NO:

3688). In some embodiments, the seven consecutive amino acids comprise NGAVHLY (SEQ ID NO: 3689).

[0330] In some embodiments, the 3 consecutive amino acids comprise YST. In some embodiments, the 4 consecutive amino acids comprise YSTD (SEQ ID NO: 3690). In some embodiments, the 5 consecutive amino acids comprise YSTDE (SEQ ID NO: 3691). In some embodiments, the 5 consecutive amino acids comprise YSTDV (SEQ ID NO: 3700). In some embodiments, the 6 consecutive amino acids comprise YSTDER (SEQ ID NO: 3692). In some embodiments, the 6 consecutive amino acids comprise YSTDVR (SEQ ID NO: 3701). In some embodiments, the 7 consecutive amino acids comprise YSTDERM (SEQ ID NO: 3657). In some embodiments, the 7 consecutive amino acids comprise YSTDERK (SEQ ID NO: 3658). In some embodiments, the 7 consecutive amino acids comprise YSTDVRM (SEQ ID NO: 3650).

[0331] In some embodiments, the 3 consecutive amino acids comprise IVM. In some embodiments, the 4 consecutive amino acids comprise IVMN (SEQ ID NO: 3693). In some embodiments, the 5 consecutive amino acids comprise IVMNS (SEQ ID NO: 3694). In some embodiments, the 6 consecutive amino acids comprise IVMNSL (SEQ ID NO: 3695). In some embodiments, the 7 consecutive amino acids comprise IVMNSLK (SEQ ID NO: 3651).

[0332] In some embodiments, the peptide, e.g., targeting peptide, comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622. In some embodiments, the peptide, e.g., targeting peptide, comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 3648-3659.

[0333] In some embodiments, the peptide, e.g., targeting peptide comprises the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), optionally wherein position 7 is H.

[0334] In some embodiments, the peptide, e.g., targeting peptide comprises the amino acid sequence of RDSPKGW (SEQ ID NO: 3649), or an amino acid sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of RDSPKGW (SEQ ID NO: 3649).

[0335] In some embodiments, the peptide, e.g., targeting peptide comprises the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), or an amino acid sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of IVMNSLK (SEQ ID NO: 3651).

[0336] In some embodiments, the peptide, e.g., targeting peptide comprises the amino acid sequence of YSTDVRM (SEQ ID NO: 3650), or an amino acid sequence having at least one, two, or

three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of YSTDVRM (SEQ ID NO: 3650).

[0337] In some embodiments, the peptide, e.g., targeting peptide comprises the amino acid sequence of RESPRGL (SEQ ID NO: 3652), or a sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of RESPRGL (SEQ ID NO: 3652).

[0338] In some embodiments, the peptide, e.g., targeting peptide comprises the amino acid sequence of any of SEQ ID NO: 1725-3622. In some embodiments, the peptide comprises the amino acid sequence of any of SEQ ID NO: 3648-3659.

[0339] In some embodiments, the peptide, e.g., targeting peptide, may comprise an amino acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of the sequences shown in Table 1 or Table 2.

[0340] In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3648. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3649. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3650. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3651. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3652. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3653. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3654. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3655. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3656. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3657. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3658. In some embodiments, the peptide, e.g., targeting peptide, comprises the amino acid sequence of SEQ ID NO: 3659.

[0341] In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1725. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1726. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1729. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1760. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1769. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 3622. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1798. In some

embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1785. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1767. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1734. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1737. In some embodiments, the peptide, e.g., targeting peptide, may comprise SEQ ID NO: 1819.

[0342] In some embodiments, a peptide, e.g., targeting peptide, may comprise 4 or more contiguous amino acids of any of the peptides, e.g., targeting peptides, disclosed herein. In some embodiments the peptide, e.g., targeting peptide, may comprise 4 contiguous amino acids of any of the sequences as set forth in Table 1 or Table 2. In some embodiments the peptide, e.g., targeting peptide, may comprise 5 contiguous amino acids of any of the sequences as set forth in Table 1 or 2. In some embodiments the peptide, e.g., targeting peptide, may comprise 6 contiguous amino acids of any of the sequences as set forth in Table 1 or 2.

[0343] In some embodiments, the peptide, e.g., targeting peptide, comprises an amino acid sequence encoded by a nucleotide sequence described herein, e.g., a nucleotide sequence of Table 2. In some embodiments, the peptide comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of any of SEQ ID NOs: 3660-3671. In some embodiments, the peptide comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 3660-3671, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0344] In some embodiments, the peptide, e.g., targeting peptide comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3660. In some embodiments, the peptide comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 3660, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0345] In some embodiments, the peptide, e.g., targeting peptide, comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3663. In some embodiments, the peptide comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 3663, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0346] In some embodiments, the nucleotide sequence encoding a peptide, e.g., targeting peptide, described herein e.g., peptide 1-12, comprises a nucleotide sequence described herein, e.g., as described in Table 2. In some embodiments, the nucleic acid sequence encoding a peptide described herein comprises the nucleotide sequence of any of SEQ ID NOs: 3660-3671, or a nucleotide

sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleic acid sequence encoding a peptide described herein comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of any of SEQ ID NOs: 3660-3671. In some embodiments, the nucleotide sequence encoding a peptide, e.g., targeting peptide, described herein is isolated, e.g., recombinant.

[0347] In some embodiments the nucleotide sequence encoding a peptide, e.g., targeting peptide, described herein comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3660. In some embodiments the nucleic acid sequence encoding a peptide described herein comprises a nucleotide sequence comprising the nucleotide sequence of SEQ ID NO: 3660, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0348] In some embodiments, the nucleic acid encoding a peptide described herein comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of SEQ ID NO: 3663. In some embodiments the nucleic acid encoding a peptide described herein comprises a nucleotide sequence comprising the nucleotide sequence of SEQ ID NO: 3663, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0349] In some embodiments, an AAV particle of the disclosure comprises an AAV capsid, e.g., and AAV capsid variant, with a peptide, e.g., targeting peptide, insert (e.g., an AAV capsid variant), wherein the peptide, e.g., targeting peptide, has an amino acid sequence as set forth in any of Table 1 or Table 2.

[0350] In some embodiments, an AAV particle of the disclosure comprises an AAV capsid polypeptide, e.g., an AAV capsid variant, with a peptide, e.g., targeting peptide, insert (e.g., an AAV capsid variant), wherein the peptide has an amino acid having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence in any of Table 1 or Table 2.

[0351] In some embodiments, the AAV particle of the disclosure comprises an AAV capsid polypeptide, e.g., an AAV capsid variant, with a peptide, e.g., targeting peptide, insert (e.g., an AAV capsid variant), wherein the peptide, e.g., targeting peptide, has an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, or 9 contiguous amino acids of any of the sequences as set forth in any of Table 1 or 2.

[0352] In some embodiments, the AAV particle of the disclosure comprises an AAV capsid, e.g., an AAV capsid variant, with a peptide, e.g., a targeting peptide, insert (e.g., an AAV capsid variant), wherein the peptide, e.g., targeting peptide, has an amino acid sequence substantially identical thereto

(e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the sequences as set forth in any of Table 1 or 2.

[0353] In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 1 to the amino acid at position 2 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 1 to the amino acid at position 3 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 2 to the amino acid at position 3 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 1 to the amino acid at position 4 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide may include the amino acid at position 2 to the amino acid at position 4 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide may include the amino acid at position 3 to the amino acid at position 4 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 1 to the amino acid at position 5 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 2 to the amino acid at position 5 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 3 to the amino acid at position 5 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 4 to the amino acid at position 5 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 1 to the amino acid at position 6 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 2 to the amino acid at position 6 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 3 to the amino acid at position 6 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 4 to the amino acid at position 6 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 5 to the amino acid at position 6 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 1 to the amino acid at position 7 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 2 to the amino acid at position 7 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 3 to the amino acid at position 7 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 4 to the amino acid at position 7 of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the peptide, e.g., targeting peptide, may

[illegible]

targeting peptide, may include the amino acid at position 5 to the amino acid at position 10 of SEQ ID NO: 1725-3622. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 6 to the amino acid at position 10 of SEQ ID NO: 1725-3622. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 7 to the amino acid at position 10 of SEQ ID NO: 1725-3622. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 8 to the amino acid at position 10 of SEQ ID NO: 1725-3622. In some embodiments, the peptide, e.g., targeting peptide, may include the amino acid at position 9 to the amino acid at position 10 of SEQ ID NO: 1725-3622.

[0354] The present disclosure also provides a nucleic acid or polynucleotide encoding any of the above described peptides, e.g., targeting peptides, and AAV capsid polypeptides, e.g., AAV capsid variants, AAV particles, vectors, and cells comprising the same.

[0355] In some embodiments, an insertion of a peptide, e.g., targeting peptide, into a parent AAV capsid, e.g., a parental sequence, results in a combination insertion/replacement as compared to the parent amino acid sequence. In some embodiments, all the amino acids of a peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence. In some embodiments, one amino acid of the peptide, e.g., targeting peptide, replaces one amino acid in the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence. In some embodiments, two amino acids of the peptide, e.g., targeting peptide, replace two amino acids in the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence. In some embodiments, three amino acids of the peptide, e.g., targeting peptide, replace three amino acids in the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence. In some embodiments, four amino acids of the peptide, e.g., targeting peptide, replace four amino acids in the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence. In some embodiments, five amino acids of the peptide, e.g., targeting peptide, replace five amino acids in the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence. In some embodiments, six amino acids of the peptide, e.g., targeting peptide, replace six amino acids in the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence. In some embodiments, seven amino acids of the peptide, e.g., targeting peptide, replace seven amino acids in the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence. In some embodiments, eight amino acids of the peptide, e.g., targeting peptide, replace eight amino acids in the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence. In some embodiments, nine amino acids of the peptide, e.g., targeting peptide, replace nine amino acids in the parent AAV capsid

while the remaining amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid sequence.

[0356] In some embodiments, one amino acid of the peptide, e.g., targeting peptide, is inserted into the parent AAV capsid, e.g., parental sequence, while the remaining amino acids of the peptide, e.g., targeting peptide, replace corresponding amino acids in the parent AAV capsid sequence. In some embodiments, two amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, replace corresponding amino acids in the parent AAV capsid sequence. In some embodiments, three amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, replace corresponding amino acids in the parent AAV capsid sequence. In some embodiments, four amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, replace corresponding amino acids in the parent AAV capsid sequence. In some embodiments, five amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, replace corresponding amino acids in the parent AAV capsid sequence. In some embodiments, six amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, replace corresponding amino acids in the parent AAV capsid sequence. In some embodiments, seven amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, replace corresponding amino acids in the parent AAV capsid sequence. In some embodiments, eight amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, replace corresponding amino acids in the parent AAV capsid sequence. In some embodiments, nine amino acids of the peptide, e.g., targeting peptide, are inserted into the parent AAV capsid while the remaining amino acids of the peptide, e.g., targeting peptide, replace corresponding amino acids in the parent AAV capsid sequence.

[0357] In some embodiments, certain amino acids of the peptide, e.g., targeting peptide, may be anchored and/or retained as in the original parent AAV capsid sequence, e.g., parental sequence. In certain embodiments, these anchored amino acids are centrally located in the peptide, e.g., targeting peptide, resulting in a split insertion-anchor-insertion design. Similarly, as a non-limiting example, the insertion of a peptide, e.g., targeting peptide, may result in a split insertion-replacement-insertion design. As a non-limiting example, the insertion of a peptide, e.g., targeting peptide, into a parent AAV capsid sequence may result in a split replacement-insertion-replacement design. As a non-limiting example, a split design peptide, e.g., targeting peptide, may be as shown in FIG. 4 (e.g., TNHQSXXXAVVXXAQAQT (SEQ ID NO: 3699)).

[0358] In some embodiments, an insertion of a peptide, e.g., targeting peptide, into the parent AAV capsid sequence, e.g., parental sequence, may result in the replacement or mutation of at least one amino acid of the parent AAV capsid. In certain embodiments, the first amino acid (N-terminal) of the peptide, e.g., targeting peptide, replaces an amino acid in the parent AAV capsid sequence. In certain embodiments, the first two amino acids (N-terminal) of the peptide, e.g., targeting peptide, replace two amino acids in the parent AAV capsid sequence. In certain embodiments, the first three amino acids (N-terminal) of the peptide, e.g., targeting peptide, replace three amino acids in the parent AAV capsid sequence. In certain embodiments, the first four amino acids (N-terminal) of the peptide, e.g., targeting peptide, replace four amino acids in the parent AAV capsid sequence. In certain embodiments, the first five amino acids (N-terminal) of the peptide, e.g., targeting peptide, replace five amino acids in the parent AAV capsid sequence. In certain embodiments, the first six amino acids (N-terminal) of the peptide, e.g., targeting peptide, replace six amino acids in the parent AAV capsid sequence. In certain embodiments, the first seven amino acids (N-terminal) of the peptide, e.g., targeting peptide, replace seven amino acids in the parent AAV capsid sequence. In certain embodiments, the first eight amino acids (N-terminal) of the peptide, e.g., targeting peptide, replace eight amino acids in the parent AAV capsid sequence. In certain embodiments, the first nine amino acids (N-terminal) of the peptide, e.g., targeting peptide, replace nine amino acids in the parent AAV capsid sequence. In certain embodiments, the first ten amino acids (N-terminal) of the peptide, e.g., targeting peptide, replace ten amino acids in the parent AAV capsid sequence.

[0359] In certain embodiments, the last amino acid (C-terminal) of the peptide, e.g., targeting peptide, replaces an amino acid in the parent AAV capsid sequence. In certain embodiments, the last two amino acids (C-terminal) of the peptide, e.g., targeting peptide, replace two amino acids in the parent AAV capsid sequence. In certain embodiments, the last three amino acids (C-terminal) of the peptide, e.g., targeting peptide, replace three amino acids in the parent AAV capsid sequence. In certain embodiments, the last four amino acids (C-terminal) of the peptide, e.g., targeting peptide, replace four amino acids in the parent AAV capsid sequence. In certain embodiments, the last five amino acids (C-terminal) of the peptide, e.g., targeting peptide, replace five amino acids in the parent AAV capsid sequence. In certain embodiments, the last six amino acids (C-terminal) of the peptide, e.g., targeting peptide, replace six amino acids in the parent AAV capsid sequence. In certain embodiments, the last seven amino acids (C-terminal) of the peptide, e.g., targeting peptide, replace seven amino acids in the parent AAV capsid sequence. In certain embodiments, the last eight amino acids (C-terminal) of the peptide, e.g., targeting peptide, replace eight amino acids in the parent AAV capsid sequence. In certain embodiments, the last nine amino acids (C-terminal) of the peptide, e.g., targeting peptide, replace nine amino acids in the parent AAV capsid sequence. In certain embodiments, the last ten amino acids (C-terminal) of the peptide, e.g., targeting peptide, replace ten amino acids in the parent AAV capsid sequence.

[0360] In certain embodiments, the first (N-terminal) and last (C-terminal) amino acids of the peptide, e.g., targeting peptide, may replace amino acids in the parent AAV capsid sequence, e.g., parental sequence. In certain embodiments, the first two (N-terminal) and last two (C-terminal) amino acids of the peptide, e.g., targeting peptide, may replace amino acids in the parent AAV capsid sequence. In certain embodiments, the first three (N-terminal) and last three (N-terminal) amino acids of the peptide, e.g., targeting peptide, may replace amino acids in the parent AAV capsid sequence. In certain embodiments, the replacements are asymmetrical in terms of N-terminal and C-terminal replacements and may be any combination of the any of the above.

[0361] In certain embodiments, one amino acid of the peptide, e.g., targeting peptide, replaces an amino acid in the parent AAV capsid sequence, e.g., parental sequence. In certain embodiments, two amino acids of the peptide, e.g., targeting peptide, replace two amino acids in the parent AAV capsid sequence. In certain embodiments, three amino acids of the peptide, e.g., targeting peptide, replace three amino acids in the parent AAV capsid sequence. In certain embodiments, four amino acids of the peptide, e.g., targeting peptide, replace four amino acids in the parent AAV capsid sequence. In certain embodiments, five amino acids of the peptide, e.g., targeting peptide, replace five amino acids in the parent AAV capsid sequence. In certain embodiments, six amino acids of the peptide, e.g., targeting peptide, replace six amino acids in the parent AAV capsid sequence. In certain embodiments, seven amino acids of the peptide, e.g., targeting peptide, replace seven amino acids in the parent AAV capsid sequence. In certain embodiments, eight amino acids of the peptide, e.g., targeting peptide, replace eight amino acids in the parent AAV capsid sequence. In certain embodiments, nine amino acids of the peptide, e.g., targeting peptide, replace nine amino acids in the parent AAV capsid sequence. In certain embodiments, ten amino acids of the peptide, e.g., targeting peptide, replace ten amino acids in the parent AAV capsid sequence. In certain embodiments, all amino acids of the peptide, e.g., targeting peptide, replace the same number of amino acids in the parent AAV capsid sequence.

[0362] In some embodiments, the AAV particle of the disclosure may comprise a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, wherein said polynucleotide further comprising a nucleic acid insert, e.g., a targeting nucleic acid insert, wherein the nucleic acid insert has a nucleotide sequence substantially comprising any of those as described in Hanlon et al., 2019 (Hanlon et al., Mol Ther Methods Clin Dev. 2019 Oct 23;15:320-332, the contents of which are herein incorporated by reference in its entirety). As a non-limiting the nucleic acid insert, e.g., targeting nucleic acid insert, has a nucleotide sequence substantially comprising AAV-S. As a non-limiting example, the targeting nucleic acid insert has a nucleotide sequence substantially comprising AAV-F.

[0363] The AAV particle of the disclosure comprising a nucleic acid insert, e.g., a targeting nucleic acid insert, may have a polynucleotide sequence encoding a capsid polypeptide with 50%,

51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more, identity to the parent capsid sequence.

[0364] The AAV particle of the disclosure comprising a peptide, e.g., a targeting peptide, insert, may have an amino acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more, identity to the parent capsid sequence.

AAV Capsid Polypeptide, e.g., AAV Capsid Variant

[0365] In some embodiments, a peptide, e.g., targeting peptide, is inserted, included or otherwise incorporated into a polypeptide. In some embodiments, such a polypeptide may be referred to as the “parental polypeptide” or “starting polypeptide” or “parental amino acid sequence” and such an insert may be referred to as “targeting peptide insert”, “peptide insert” or “amino acid sequence insert”. In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant described herein may comprise a peptide, e.g., targeting peptide, insert and a polypeptide, e.g., a larger polypeptide described herein. In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant has an amino acid sequence that is longer than the parent AAV capsid. In other embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant has an amino acid sequence that is the same length as the parent AAV capsid. In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant has an amino acid sequence that is shorter than the parent AAV capsid.

[0366] Where a peptide, e.g., targeting peptide, including sequences of 5-50 contiguous amino acids, is inserted into a parental polypeptide, the insertion may be between two amino acids in the parental polypeptide. Insertion may also be a split insertion whereby one contiguous portion of a peptide insert is inserted between a first set of two amino acids in the parental polypeptide and a second portion of the peptide is inserted between a second set of two amino acids in the parental polypeptide, e.g., a different site. Between this first site and second site, any number of amino acids of the parental polypeptide may be retained. In some embodiments, 1, 2, 3, 4, 5, 6, 7, 8, or 9 amino acids in the parental polypeptide may be retained between the first and second peptide insert.

[0367] In some embodiments, a peptide, e.g., targeting peptide, inserts may, in whole or in part, replace one or more amino acids in the parental polypeptide. For example, a peptide insert of 4 amino acids may be inserted immediately after position 586 in the parental polypeptide wherein the last two amino acids of the peptide insert replace the amino acids at positions 587 and 588 of the parental polypeptide. Consequently, the newly formed polypeptide will have increased in length by only two amino acids, e.g., 2 inserted and 2 substituted. In some embodiments, a combinatorial

insert/substitutional (i/s) variant may comprise one or more amino acid inserts and one or more amino acid substitutions, e.g., each from 1 to 15 amino acids in length and from 1 to 15 in number.

[0368] A peptide, e.g., targeting peptide, may be stand-alone peptides or may be inserted into or conjugated to a parent sequence. In some embodiments, the peptides, e.g., targeting peptides, are inserted into the capsid protein of an AAV particle.

[0369] One or more peptides, e.g., targeting peptides, may be inserted into a parent AAV capsid sequence to generate the AAV particles of the disclosure.

[0370] A peptide, e.g., targeting peptide, may be inserted into a parent AAV capsid sequence in any location that results in fully functional AAV particles, e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant described herein. The peptide, e.g., targeting peptide may be inserted in VP1, VP2 and/or VP3. Numbering of the amino acid residues may differ across AAV serotypes. As used herein, amino acid positions of the parent AAV capsid sequence are described using AAV9 (SEQ ID NO: 138) as reference.

[0371] In some embodiments, the peptide, e.g., targeting peptide, is inserted in a hypervariable region of the AAV capsid sequence. Non-limiting examples of such hypervariable regions include Loop I, Loop II, Loop IV, Loop VI, and Loop VIII of the parent AAV capsid. While not wishing to be bound by theory, it is believed in some embodiments that these surface exposed loops, which may hereinafter also be referred to as surface loops, are typically unstructured and poorly conserved, making them suitable regions for insertion of peptides, e.g., targeting peptides.

[0372] In some embodiments, a peptide, e.g., targeting peptide, is inserted into Loop I. In another embodiment, the peptide, e.g., targeting peptide, is used to replace a portion, or all of Loop I. As a non-limiting example, addition of the peptide, e.g., targeting peptide, to the parent AAV capsid sequence may result in the replacement or mutation of at least one amino acid of the parent AAV capsid.

[0373] In some embodiments, a peptide, e.g., targeting peptide, is inserted into Loop II. In another embodiment, the targeting peptide is used to replace a portion, or all of Loop II. As a non-limiting example, addition of the targeting peptide to the parent AAV capsid sequence may result in the replacement or mutation of at least one amino acid of the parent AAV capsid.

[0374] In some embodiments, the peptide, e.g., targeting peptide, is inserted into Loop IV. In another embodiment, the peptide, e.g., targeting peptide, is used to replace a portion, or all of Loop IV. As a non-limiting example, addition of the peptide, e.g., targeting peptide, to the parent AAV capsid sequence may result in the replacement or mutation of at least one amino acid of the parent AAV capsid.

[0375] In some embodiments, the peptide, e.g., targeting peptide, is inserted into Loop VI. In another embodiment, the peptide, e.g., targeting peptide, is used to replace a portion, or all of Loop VI. As a non-limiting example, addition of the peptide, e.g., targeting peptide, to the parent AAV

capsid sequence may result in the replacement or mutation of at least one amino acid of the parent AAV capsid.

[0376] In some embodiments, the peptide, e.g., targeting peptide, is inserted into Loop VIII. In another embodiment, the peptide, e.g., targeting peptide, is used to replace a portion, or all of Loop VIII. As a non-limiting example, addition of the peptide, e.g., targeting peptide, to the parent AAV capsid sequence may result in the replacement or mutation of at least one amino acid of the parent AAV capsid.

[0377] In some embodiments, more than one peptide, e.g., targeting peptide, is inserted into a parent AAV capsid sequence. As a non-limiting example, peptide, e.g., targeting peptide, may be inserted at both Loop IV and Loop VIII in the same parent AAV capsid sequence.

[0378] A peptide, e.g., targeting peptide, may be inserted at any amino acid position of the parent AAV capsid sequence, such as, but not limited to, between amino acids at positions 586-592, 588-589, 586-589, 452-458, 262-269, 464-473, 491-495, 546-557 and/or 659-668.

[0379] In some embodiments, the peptide, e.g., targeting peptide, is inserted into a parent AAV capsid sequence between amino acids at positions 588 and 589 (Loop VIII). In some embodiments, the parent AAV capsid is AAV9 (SEQ ID NO: 138). In some embodiments, the parent AAV capsid is K449R AAV9 (SEQ ID NO: 11).

[0380] In some embodiments, the peptide, e.g., targeting peptide, is inserted into a parent AAV capsid sequence between amino acids at positions 454, 455, 457, 458, 459, 460, and/or 461 (Loop IV).

[0381] In some embodiments, the peptide, e.g., targeting peptide, is inserted into a parent AAV capsid sequence between amino acids at positions 586, 587, 588, 589, and/or 590 (Loop VIII).

[0382] In some embodiments, the peptide, e.g., targeting peptide, is inserted into a parent AAV capsid sequence Loop IV. As a non-limiting example, the parent AAV capsid may be AAV5. As a non-limiting example, the parent AAV capsid may be AAV9. As a non-limiting example, the parent AAV capsid may be AAV9hu.14 (SEQ ID NO: 137 or 138). As a non-limiting example, the parent AAV capsid may be AAV9 K449R (SEQ ID NO: 11). As a non-limiting example, the parent AAV capsid may be PHP.B (SEQ ID NO: 5 or 6). As a non-limiting example, the parent AAV capsid may be PHP.N (SEQ ID NO: 4). As a non-limiting example, the parent AAV capsid may be VOY101 (SEQ ID NO: 1 or 2). As a non-limiting example, the parent AAV capsid may be VOY201 (SEQ ID NO: 3 or 1724).

[0383] In some embodiments, the peptide, e.g., targeting peptide, are inserted into a parent AAV capsid sequence Loop VIII. As a non-limiting example, the parent AAV capsid may be AAV5. As a non-limiting example, the parent AAV capsid may be AAV9. As a non-limiting example, the parent AAV capsid may be AAV9hu.14 (SEQ ID NO: 137 or 138). As a non-limiting example, the parent AAV capsid may be AAV9 K449R (SEQ ID NO: 11). As a non-limiting example, the parent AAV

capsid may be PHP.B (SEQ ID NO: 5 or 6). As a non-limiting example, the parent AAV capsid may be PHP.N (SEQ ID NO: 4). As a non-limiting example, the parent AAV capsid may be VOY101 (SEQ ID NO: 1 or 2). As a non-limiting example, the parent AAV capsid may be VOY201 (SEQ ID NO: 3 or 1724).

[0384] In some embodiments, the peptide, e.g., a targeting peptide, is present in loop VIII of an AAV capsid polypeptide, e.g., an AAV capsid variant. In some embodiments, the peptide of an AAV capsid variant described herein, is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the peptide of an AAV capsid variant described herein, is present immediately subsequent to position 588, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the peptide of an AAV capsid variant described herein, is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0385] In some embodiments, the peptide, e.g., targeting peptide, of an AAV capsid polypeptide, e.g., an AAV capsid variant described herein comprises the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), wherein the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0386] In some embodiments, the peptide, e.g., targeting peptide, of an AAV capsid polypeptide, e.g., an AAV capsid variant described herein comprises the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654), wherein the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0387] In some embodiments, the peptide, e.g., targeting peptide, of an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), wherein the amino acid sequence of IVMNSLK (SEQ ID NO: 3651) is present immediately subsequent to position 588, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0388] In some embodiments, the peptide, e.g., targeting peptide, of an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises the amino acid sequence of any of SEQ ID NOs: 3649, 3650, 3652, 3653, or 3655-3659, wherein the amino acid sequence of any of the aforesaid sequences is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0389] The peptide, e.g., targeting peptide, described herein may increase the transduction of an AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a target tissue as compared to the parent AAV particle lacking a peptide, e.g.,

targeting peptide insert. In some embodiments, the peptide, e.g., targeting peptide increases the transduction of an AAV particle to a target tissue by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 200%, 300%, 400%, 500%, or more as compared to a parent AAV particle lacking a peptide, e.g., targeting peptide, insert.

[0390] In some embodiments, the peptide, e.g., targeting peptide, increases the transduction of an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a cell, region, or tissue of the CNS (e.g., a brain cell, brain tissue, brain region, spinal cord cell, spinal cord region, or spinal cord tissue) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 200%, 300%, 400%, 500%, or more as compared to a parent AAV particle lacking a peptide, e.g., targeting peptide, insert. In some embodiments, the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus. In some embodiments, the spinal cord region comprises a cervical, thoracic, and/or lumbar region.

[0391] In some embodiments, the peptide, e.g., targeting peptide, increases the transduction of an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a cell or tissue of the PNS by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 200%, 300%, 400%, 500%, or more as compared to a parent AAV particle lacking a peptide, e.g., targeting peptide, insert.

[0392] In some embodiments, the peptide, e.g., targeting peptide, increases the transduction of an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a cell or tissue of the DRG by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 200%, 300%, 400%, 500%, or more as compared to a parent AAV particle lacking a peptide, e.g., targeting peptide, insert.

[0393] In some embodiments, the peptide, e.g., targeting peptide, increases the transduction of an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a cell, region, or tissue of a muscle by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 200%, 300%, 400%, 500%, or more as compared to a parent AAV particle lacking a targeting peptide insert. In some embodiments, a muscle region may comprise a heart muscle, quadriceps muscle, and/or a diaphragm muscle region. In some embodiments, the muscle region comprises a heart muscle region, e.g., a heart atrium muscle region or a heart ventricle muscle region.

[0394] In some embodiments, an AAV particle described herein comprises an AAV capsid polypeptide, e.g., an AAV capsid polypeptide, e.g., an AAV capsid variant. In some embodiments, the

AAV capsid variant comprises a peptide, e.g., targeting peptide, sequence as described in Table 1 or 2.

[0395] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622. In some embodiments, the AAV capsid variant comprises at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 3648-3659. In some embodiments, the amino acid sequence is present in loop VIII. In some embodiments, the amino acid sequence is present immediately subsequent to position 586, 588, or 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0396] In some embodiments, the 3 consecutive amino acids comprise PLN. In some embodiments, the 4 consecutive amino acids comprise PLNG (SEQ ID NO: 3678). In some embodiments, the 5 consecutive amino acids comprise PLNGA (SEQ ID NO: 3679). In some embodiments, the 6 consecutive amino acids comprise PLNGAV (SEQ ID NO: 3680). In some embodiments, the 7 consecutive amino acids comprise PLNGAVH (SEQ ID NO: 3681). In some embodiments, the 8 consecutive amino acids comprise PLNGAVHL (SEQ ID NO: 3682). In some embodiments, the 9 consecutive amino acids comprise PLNGAVHLY (SEQ ID NO: 3648).

[0397] In some embodiments, the 3 consecutive amino acids comprise YST. In some embodiments, the 4 consecutive amino acids comprise YSTD (SEQ ID NO: 3690). In some embodiments, the 5 consecutive amino acids comprise YSTDV (SEQ ID NO: 3691). In some embodiments, the 5 consecutive amino acids comprise YSTDV (SEQ ID NO: 3700). In some embodiments, the 6 consecutive amino acids comprise YSTDV (SEQ ID NO: 3692). In some embodiments, the 6 consecutive amino acids comprise YSTDV (SEQ ID NO: 3701). In some embodiments, the 7 consecutive amino acids comprise YSTDV (SEQ ID NO: 3657). In some embodiments, the 7 consecutive amino acids comprise YSTDV (SEQ ID NO: 3658). In some embodiments, the 7 consecutive amino acids comprise YSTDV (SEQ ID NO: 3650).

[0398] In some embodiments, the 3 consecutive amino acids comprise IVM. In some embodiments, the 4 consecutive amino acids comprise IVMN (SEQ ID NO: 3693). In some embodiments, the 5 consecutive amino acids comprise IVMNS (SEQ ID NO: 3694). In some embodiments, the 6 consecutive amino acids comprise IVMNSL (SEQ ID NO: 3695). In some embodiments, the 7 consecutive amino acids comprise IVMNSLK (SEQ ID NO: 3651).

[0399] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 3648-3659. In some embodiments, the amino acid

sequence is present in loop VIII. In some embodiments, the amino acid sequence is present immediately subsequent to position 586, 588, or 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0400] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), optionally wherein position 7 is H.

[0401] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of RDSPKGW (SEQ ID NO: 3649), or an amino acid sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of RDSPKGW (SEQ ID NO: 3649).

[0402] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), or an amino acid sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of IVMNSLK (SEQ ID NO: 3651).

[0403] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of YSTDVRM (SEQ ID NO: 3650), or an amino acid sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of YSTDVRM (SEQ ID NO: 3650).

[0404] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of RESPRGL (SEQ ID NO: 3652), or a sequence having at least one, two, or three modifications but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of RESPRGL (SEQ ID NO: 3652).

[0405] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of any of SEQ ID NO: 1725-3622. In some embodiments, the AAV capsid variant comprises the amino acid sequence of any of SEQ ID NO: 3648-3659. In some embodiments, the amino acid sequence is present in loop VIII of an AAV capsid variant described herein. In some embodiments, the amino acid sequence is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 588, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0406] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises an amino acid sequence encoded by the nucleotide

sequence of any one of SEQ ID NOs: 3660-3671, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the AAV capsid, e.g., an AAV capsid variant described herein, comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of any of SEQ ID NOs: 3660-3671.

[0407] In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide, e.g., the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises the nucleotide sequence of any one of SEQ ID NOs: 3660-3671, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, nucleic acid sequence encoding the AAV capsid variant, e.g., an AAV capsid variant described herein, comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of any of SEQ ID NOs: 3660-3671.

[0408] In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide, e.g., the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises the nucleotide sequence of SEQ ID NO: 3660, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleic acid sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of SEQ ID NO: 3660.

[0409] In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide, e.g., the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises the nucleotide sequence of SEQ ID NO: 3663, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleic acid sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of SEQ ID NO: 3663.

[0410] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid residue other than "A" at position 587 and/or an amino acid residue other than "Q" at position 588, numbered according to SEQ ID NO: 138.

[0411] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648) wherein the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0412] In some embodiments, the polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654), wherein the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0413] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), wherein the amino acid sequence of IVMNSLK (SEQ ID NO: 3651) is present immediately subsequent to position 588, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0414] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of any of SEQ ID NOs: 3649, 3650, 3652, 3653, or 3655-3659, wherein the amino acid sequence of any of the aforesaid sequences is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0415] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, further comprises a substitution at position K449, e.g., a K449R substitution, numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a modification, e.g., an insertion, substitution, and/or deletion in loop I, II, IV, and/or VI.

[0416] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, further comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid variant further comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0417] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, of the present disclosure comprises a parental amino acid sequence having an insert, e.g., a peptide, e.g., a targeting peptide, wherein the insert comprises the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the insert comprises at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659. In some embodiments, the insert comprises an amino acid sequence comprising at least one, two, or three modifications, but no more than four modifications, e.g., substitutions, relative to the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659.

[0418] In some embodiments, the parental sequence of an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises an amino acid sequence comprising at least one, two, or three modifications but no more than 30, 20 or 10 modifications, e.g., substitutions, to the amino acid

sequence of SEQ ID NO: 138. In some embodiments, the parental sequence comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the parental sequence further comprises a substitution at position K449, e.g., a K449R substitution. In some embodiments, the parental sequence comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the polynucleotide encoding the parental sequence described herein comprises the nucleotide sequence of SEQ ID NO: 137, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0419] In some embodiments, the parental sequence of an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises an amino acid sequence comprising at least one, two, or three modifications but no more than 30, 20 or 10 modifications, e.g., substitutions, to the amino acid sequence of SEQ ID NO: 11, e.g., provided that position 449 of SEQ ID NO: 11 is not K, e.g., is R. In some embodiments, the parental sequence of an AAV capsid variant described herein comprises the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto, e.g., provided that position 449 of SEQ ID NO: 11 is not K, e.g., is R.

[0420] In some embodiments, the insert of an AAV capsid variant is inserted into loop VIII of the parental amino acid sequence described herein. In some embodiments, the insert is inserted immediately subsequent to position 586, 588, or 589 in the parental amino acid sequence described herein.

[0421] In some embodiments, the AAV capsid variant further comprises an amino acid other than "A" at position 587 and/or an amino acid other than "Q" at position 588 of the parental sequence described herein. In some embodiments, the AAV capsid variant further comprises a deletion at position 587 and/or a deletion at position 588 of the parental amino acid sequence described herein. In some embodiments, the AAV capsid variant comprises a deletion of the amino acids "AQ" at positions 587-588 of the parental amino acid sequence described herein.

[0422] In some embodiment, the insert of an AAV capsid variant described herein comprises the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648). In some embodiments, the insert sequence of PLNGAVHLY (SEQ ID NO: 3648) is inserted immediately subsequent to position 586 of the parental amino acid sequence. In some embodiments, the AAV capsid variant further comprises a deletion of the amino acids "AQ" at positions 587-588 of the parental amino acid sequence. In some embodiments, the AAV capsid variant comprises an insert comprising the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), which is inserted immediately subsequent to

position 586 of the parental amino acid sequence and a deletion of the amino acids "AQ" at positions 587-588 of the parental amino acid sequence.

[0423] In some embodiments, the insert of an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654). In some embodiments, the insert sequence of GGTLAVVSL (SEQ ID NO: 3654) is inserted immediately subsequent to position 586 of the parental amino acid sequence. In some embodiments, the AAV capsid variant further comprises a deletion of the amino acids "AQ" at positions 587-588 of the parental amino acid sequence. In some embodiments, the AAV capsid variant comprises an insert comprising the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654), which is inserted immediately subsequent to position 586 of the parental amino acid sequence and a deletion of the amino acids "AQ" at positions 587-588 of the parental amino acid sequence.

[0424] In some embodiments, the insert of an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises the amino acid sequence of IVMNSLK (SEQ ID NO: 3651). In some embodiments, the insert sequence of IVMNSLK (SEQ ID NO: 3651) is inserted immediately subsequent to position 588 of the parental amino acid sequence. In some embodiments, the AAV capsid variant comprises an insert comprising the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), which is inserted immediately subsequent to position 589 of the parental amino acid sequence.

[0425] In some embodiments, the insert of an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises the amino acid sequence of RDSPKGW (SEQ ID NO: 3649), YSTDVRM (SEQ ID NO: 3650), RESPRGL (SEQ ID NO: 3652), SFNDTRA (SEQ ID NO: 3653), YGLPKGP (SEQ ID NO: 3655) or STGTLRL (SEQ ID NO: 3656). In some embodiments, the insert sequence of RDSPKGW (SEQ ID NO: 3649), YSTDVRM (SEQ ID NO: 3650), RESPRGL (SEQ ID NO: 3652), SFNDTRA (SEQ ID NO: 3653), YGLPKGP (SEQ ID NO: 3655) or STGTLRL (SEQ ID NO: 3656) is inserted immediately subsequent to position 589 of the parental amino acid sequence. In some embodiments, the AAV capsid variant comprises an insert comprising the amino acid sequence of RDSPKGW (SEQ ID NO: 3649), YSTDVRM (SEQ ID NO: 3650), RESPRGL (SEQ ID NO: 3652), SFNDTRA (SEQ ID NO: 3653), YGLPKGP (SEQ ID NO: 3655) or STGTLRL (SEQ ID NO: 3656), which is inserted immediately subsequent to position 589 of the parental amino acid sequence.

[0426] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, of the present disclosure comprises an amino acid sequence as described herein, e.g. an amino acid sequence of an AAV capsid variant chosen from TTD-001, TTD-002, TTD-003, TTD-004, TTD-005, TTD-006, TTD-007, TTD-008, TTD-009, TTD-010, TTD-011, or TTD-012, e.g., as described in Tables 3 and 4.

[0427] In some embodiments, an AAV capsid polypeptide, e.g. the AAV capsid variant, comprises a VP1, VP2, and/or VP3 protein comprising an amino acid sequence described herein, e.g. an amino acid sequence of an AAV capsid variant chosen from TTD-001, TTD-002, TTD-003, TTD-

004, TTD-005, TTD-006, TTD-007, TTD-008, TTD-009, TTD-010, TTD-011, or TTD-012, e.g., as described in Tables 3 and 4.

[0428] In some embodiments, an AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence encoded by a nucleotide sequence as described herein, e.g. a nucleotide sequence of an AAV capsid variant chosen from TTD-001, TTD-002, TTD-003, TTD-004, TTD-005, TTD-006, TTD-007, TTD-008, TTD-009, TTD-010, TTD-011, or TTD-012, e.g., as described in Tables 3 and 5.

[0429] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, of the present disclosure comprises a nucleotide sequence described herein, e.g. a nucleotide sequence of an AAV capsid variant chosen from TTD-001, TTD-002, TTD-003, TTD-004, TTD-005, TTD-006, TTD-007, TTD-008, TTD-009, TTD-010, TTD-011, or TTD-012, e.g., as described in Tables 3 and 5.

[0430] In some embodiments, insertion of a nucleic acid sequence, targeting nucleic acid sequence, or a peptide, e.g., targeting peptide, into a parent AAV sequence generates the non-limiting exemplary full length capsid sequences, e.g., an AAV capsid polypeptide, e.g., an AAV capsid variant, as described in Tables 3, 4 and 5.

Table 3. Exemplary full length capsid sequences (VP1 with insert)

Serotype	VP1 DNA SEQ ID NO:	VP1 PRT SEQ ID NO:	Peptide PRT SEQ ID NO:	Peptide DNA SEQ ID NO:
TTD-001	3623	3636	1725 or 3648	3660
TTD-002	3624 or 3625	3637	1726 or 3649	3661
TTD-003	3626	3638	1729 or 3650	3662
TTD-004	3627	3639	1760 or 3651	3663
TTD-005	3628	3640	1769 or 3652	3664
TTD-006	3629	3641	3622 or 3653	3665
TTD-007	3630	3642	1798 or 3654	3666
TTD-008	3631	3643	1785 or 3655	3667
TTD-009	3632	3644	1767 or 3656	3668
TTD-010	3633	3645	1734 or 3657	3669
TTD-011	3634	3646	1737 or 3658	3670
TTD-012	3635	3647	1819 or 3659	3671

Table 4. Exemplary full length capsid amino acid sequences

Name and Annotation	SEQ ID NO:	Amino Acid Sequence
TTD-001 9mer peptide underlined, starts at position 587 (immediately)	3636	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP G YKYLGPNGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGGNLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVPDPQPIGEPFAAPS GVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDRTITSTR

subsequent to position 586); 743 aa		TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDNRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQ VFTDSYQLPYVLGSAHEGCLPPFPADVFEMI PQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRLMNPFLID QYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRV TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYQVATNHQSP <u>PL</u> <u>NGAVHLY</u> AQAQTGWVQNGGILPGMVWQDRDVYLQGPWAKIPHTDGNFH PSPLMGGFGMKHPPQILIKNTVPADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENS KRWNPEIQYTSNYKSNNVFAVNTGEGVYSEPRPIG TRYLTRNL
TTD-002 7mer peptide underlined, starts at position 590 (immediately subsequent to position 589); 743 aa	3637	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLPGPNGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLYNHADA EFQERLKEDTSFGGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVDPQPIGEPAPAPS GVGSLTMASSGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDRTITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDNRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQ VFTDSYQLPYVLGSAHEGCLPPFPADVFEMI PQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRLMNPFLID QYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRV TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYQVATNHQSAQ <u>ARDSPKGW</u> AQAQTGWVQNGGILPGMVWQDRDVYLQGPWAKIPHTDGNFH PSPLMGGFGMKHPPQILIKNTVPADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENS KRWNPEIQYTSNYKSNNVFAVNTGEGVYSEPRPIG TRYLTRNL
TTD-003 7mer peptide underlined, starts at position 590 (immediately subsequent to position 589); 743 aa	3638	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLPGPNGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLYNHADA EFQERLKEDTSFGGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVDPQPIGEPAPAPS GVGSLTMASSGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDRTITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDNRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQ VFTDSYQLPYVLGSAHEGCLPPFPADVFEMI PQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRLMNPFLID QYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRV TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYQVATNHQSAQ <u>AYSTDVRM</u> AQAQTGWVQNGGILPGMVWQDRDVYLQGPWAKIPHTDGNFH PSPLMGGFGMKHPPQILIKNTVPADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENS KRWNPEIQYTSNYKSNNVFAVNTGEGVYSEPRPIG TRYLTRNL
TTD-004 7mer peptide underlined, starts at position 589 (immediately subsequent to position 588); 743 aa	3639	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLPGPNGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLYNHADA EFQERLKEDTSFGGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVDPQPIGEPAPAPS GVGSLTMASSGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDRTITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDNRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQ VFTDSYQLPYVLGSAHEGCLPPFPADVFEMI PQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRLMNPFLID QYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRV TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG

		SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPFVATESYQGVATNHQSAQ <u>IVMNSLKAQAQTGWVQNQGILPGMVWQDRDVYLQGP</u> IWAKIPHTDGNFH PSPLMGFGMKHPPQILIKNTVPADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENSkrwnPEIQYTSNYYKSNNVEFAVNTEGVYSEPRPIG TRYLTRNL
TTD-005 7mer peptide underlined, starts at position 590 (immediately subsequent to position 589); 743 aa	3640	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLGPNGLDKGEFVNAAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFSGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTDGDESVPDPQPIGEPAPAPS GVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSSQWLGDVRVITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYDFNRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLSTVQ VFTDSYQLPYVLGSAHEGCLPPFPADVEMI PQYGYLTLDGSSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRMLNPLID QYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVS TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPFVATESYQGVATNHQSAQ <u>ARES</u> <u>PRGLQAQTGWVQNQGILPGMVWQDRDVYLQGP</u> IWAKIPHTDGNFH PSPLMGFGMKHPPQILIKNTVPADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENSkrwnPEIQYTSNYYKSNNVEFAVNTEGVYSEPRPIG TRYLTRNL
TTD-006 7mer peptide underlined, starts at position 590 (immediately subsequent to 589); 743 aa	3641	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLGPNGLDKGEFVNAAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFSGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTDGDESVPDPQPIGEPAPAPS GVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSSQWLGDVRVITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYDFNRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLSTVQ VFTDSYQLPYVLGSAHEGCLPPFPADVEMI PQYGYLTLDGSSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRMLNPLID QYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVS TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPFVATESYQGVATNHQSAQ <u>ASFND</u> <u>TRAQAQTGWVQNQGILPGMVWQDRDVYLQGP</u> IWAKIPHTDGNFH PSPLMGFGMKHPPQILIKNTVPADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENSkrwnPEIQYTSNYYKSNNVEFAVNTEGVYSEPRPIG TRYLTRNL
TTD-007 9mer peptide underlined, starts at position 587 (immediately subsequent to position 586); 743 aa	3642	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLGPNGLDKGEFVNAAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFSGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTDGDESVPDPQPIGEPAPAPS GVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSSQWLGDVRVITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYDFNRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLSTVQ VFTDSYQLPYVLGSAHEGCLPPFPADVEMI PQYGYLTLDGSSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRMLNPLID QYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVS TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPFVATESYQGVATNHQSAQ <u>TLAVVSLAQAQTGWVQNQGILPGMVWQDRDVYLQGP</u> IWAKIPHTDGNFH PSPLMGFGMKHPPQILIKNTVPADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENSkrwnPEIQYTSNYYKSNNVEFAVNTEGVYSEPRPIG TRYLTRNL

TTD-008 7mer peptide underlined, starts at position 590 (immediately subsequent to 589); 743 aa	3643	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLGPNGLDKGEFVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVDPQPIGEPAAAPS GVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDVRVITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDNRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIANNLSTVQ VFTDSQYQLPYVLGSAHEGCLPPFPADVEMI PQYGYLTLDGSGQAVGRS SFYCLEYFSPQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRLMNLID QYLYYLSKTINGSGQNQQTLKFSSVAGPSNMAVQGRNYIPGPSYRQQRVS TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYQGVATNHQSAQ <u>AYGLPKGP</u> QAQTGWVQNQGILPGMVWQDRDVYLQGP IAWAKI PHTDGNFH PSPLMGGFGMKHPPPPQILIKNTFPVADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENS KRWNPEIQYTSNYKSNNVFAVNTGEGVYSEPRPIG TRYLTRNL
TTD-009 7mer peptide underlined, starts at position 590 (immediately subsequent to 589); 743 aa	3644	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLGPNGLDKGEFVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVDPQPIGEPAAAPS GVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDVRVITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDNRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIANNLSTVQ VFTDSQYQLPYVLGSAHEGCLPPFPADVEMI PQYGYLTLDGSGQAVGRS SFYCLEYFSPQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRLMNLID QYLYYLSKTINGSGQNQQTLKFSSVAGPSNMAVQGRNYIPGPSYRQQRVS TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYQGVATNHQSAQ <u>ASTGTLRL</u> QAQTGWVQNQGILPGMVWQDRDVYLQGP IAWAKI PHTDGNFH PSPLMGGFGMKHPPPPQILIKNTFPVADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENS KRWNPEIQYTSNYKSNNVFAVNTGEGVYSEPRPIG TRYLTRNL
TTD-010 7mer peptide underlined, starts at position 590 (immediately subsequent to 589); 743 aa	3645	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLGPNGLDKGEFVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVDPQPIGEPAAAPS GVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDVRVITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDNRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIANNLSTVQ VFTDSQYQLPYVLGSAHEGCLPPFPADVEMI PQYGYLTLDGSGQAVGRS SFYCLEYFSPQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRLMNLID QYLYYLSKTINGSGQNQQTLKFSSVAGPSNMAVQGRNYIPGPSYRQQRVS TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYQGVATNHQSAQ <u>AYSTDERM</u> QAQTGWVQNQGILPGMVWQDRDVYLQGP IAWAKI PHTDGNFH PSPLMGGFGMKHPPPPQILIKNTFPVADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENS KRWNPEIQYTSNYKSNNVFAVNTGEGVYSEPRPIG TRYLTRNL
TTD-011 7mer peptide underlined, starts at position 590 (immediately subsequent to 589); 743 aa	3646	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLGPNGLDKGEFVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGGNLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVDPQPIGEPAAAPS GVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDVRVITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDNRFHCHFS

		PRDWQRLINNNWGFPRPKRLNFKLFNIQVKEVTDNNGVKTIANNLSTVQ VFTDSDYQLPYVLGSAHEGCLPPFPADVEMI PQYGYLT LNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRMLNPLID QYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVS TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPFVATESYGGQVATNHQSAQ <u>AYSTDERK</u> QAQTGWVQNGGILPGMVWQDRDVYLQGP I WAKI PHTDGNFH PSPLMGGFGMKHPPFQILIKNT PVPADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENS KRWNPEIQYTSNYYKSNNVEFAVNTG VYSEPRPIG TRYLTRNL
TTD-012 7mer peptide underlined, starts at position 590 (immediately subsequent to 589); 743 aa	3647	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLP YKYLPGPNGLDKGEFVNAADAAALEHDKAYDQQLKAGDNPYLYKHADA EFQERLKEDTSFGGNLGRAVFPQAKKRLEPLGLVEEAAKTAPGKKRPVE QSPQEPDSSAGIGKSGAQPAKKRLNFGQTDTESVDPQPIGEPAPAPS GVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSSQLWGLDRVITSTR TWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDENRFHCHFS PRDWQRLINNNWGFPRPKRLNFKLFNIQVKEVTDNNGVKTIANNLSTVQ VFTDSDYQLPYVLGSAHEGCLPPFPADVEMI PQYGYLT LNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVFFHSSYAHSSQSLDRMLNPLID QYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVS TTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSG SLIFGKQGTGRDNVDADKVMITNEEEIKTTNPFVATESYGGQVATNHQSAQ <u>AYVSSVKM</u> QAQTGWVQNGGILPGMVWQDRDVYLQGP I WAKI PHTDGNFH PSPLMGGFGMKHPPFQILIKNT PVPADPPTAFNKDKLNSFITQYSTGQV SVEIEWELQKENS KRWNPEIQYTSNYYKSNNVEFAVNTG VYSEPRPIG TRYLTRNL

Table 5. Exemplary full length capsid nucleic acid sequences

Name and Annotation	SEQ ID NO:	NT Sequence
TTD-001 9mer peptide underlined	3623	atggctgccgatgggttatcttccagattggctcgaggacaaccttagtgaaggaaattcgcg agtgggtgggctttgaaacctggagccctcaacccaaggcaaatcaacaacatcaagacaa cgctcgaggctcttggtcttccgggttacaaaataccttggaccggcaacggactcgacaag ggggagccgggtcaacgcagcagacgcggcgccctcgagcagcagacaaggcctacgaccagc agctcaaggccggagacaacccgtacctcaagtacaaccacgcgcgacgcgaggttccagga gcggtcctaaaagaagatacgtcttttgggggcaacctcgggcgagcagctcttccaggccaaa aagaggcttcttgaacctcttggtctggttgagggaagcggctaagacggctcctggaaaga agaggcctgtagagcagctctcctcagggaaccggactcctccgcgggtattggcaaatcggg tgcacagcccgctaaaaagagactcaatcttgggtcagactggcgacacagagtcagtccca gacctcaaccaatcgggagaacctcccgacgccccctcaggtgtgggatctcttacaatgg cttcaggtgggtggcgacacagtgccagacaataacgaagggtgcgagtgagggtgggtagttc ctcgggaaattggcattgcgattcccaatggctgggggacagagtcacaccaccagcacc cgaacctgggcccctgcccacctacaacaatacctctacaagcaaatctccaacagcacat ctggaggatcttcaaatgacaacgcctacttgggtcagacacccccctgggggtattttga cttcaacagattccactgccacttctcaccacgtgactggcagcgactcatcaacaacaac tggggattccggcctaagcgactcaacttcaagctcttcaacattcaggtcaaaagggtta cggacaacaatggagtcagaccatcgccaataaccttaccagcaggtccaggtcttcac ggactcagactatcagctcccgtagctgctcggtcggtcagcaggggctgctcccgccg tccccagcggaagtttctatgattcctcagtagcgggtatctgacgcttaattgatggaaagcc aggcctgggtcggtctgctcttttactgctggaatatctccgctcgcaaatgctaagaac gggtaacaaactccagttcagctacaggtttgagaacgtacctttccatagcagctacgct cacagccaaagcctggaccgactaatgaatccactcatcgaccaatacttgtactatctct caaagactattaacgggtctggacagaaatcaacaaacgctaaaattcagtggtggccggacc cagcaacatggctgtccagggaagaaactacatacctggaccagctaccgacaacaacgt gtctcaaccactgtgactcaaaacaacaacagcgaatttgcttggcctggagcttctctt

		gggctctcaatggacgtaataagcttgatgaatcctggacctgctatggccagccacaaaga aggagaggacggtttctttcctttgtctggatctttatttttggcaaacagggaactgga agagacaacgtggatgcggaacaaagtcatgataaccaacgaagaagaattaaaactacta acccggtagcaacggagtcctatggacaagtggccacaaaccaccagagt<u>ccgcttaatgg</u> <u>tgccgtccatcttttat</u>gctcaggcgagaccggctgggttcaaaaccaaggaatacttcg ggtaggttttggcaggacagagatgtgtacctgcaaggaccatttggggccaaaattctc acacggacggcaactttcaccttctcogctgatgggaggggttggaaatgaagcaccggcc tcctcagatcctcatcaaaaacacacctgtacctgcGatctccaaaggccttcaacaag gacaagctgaactctttcatcaccagttattctactggccaagtacagctggagatcgagt gggagctgcagaaggaaaaacagcaagcgGtggaaaccggagatccagtacacttccaacta ttacaagtctaataatgttgaaatttgcgtgtaataactgaagggttatatagtgaacccgc ccattggcaccagatacctgactcgtaactctgtaa
TTD-002 7mer peptide underlined	3624	atggctgcccgatgggttatcttcagattggctcgaggacaaccttagtgaaggaaattcgg agtgggtgggtctttgaaacctggagccctcaacccaaggcaaatcaacaacatcaagacaa cgctcgaggtcttgtgcttcgggttcaaaataccttggaccgggcaacggactcgacaag ggggagccgggtcaacgcagcagacgcgggcgccctcgagcacgacaaggccctacgaccagc agctcaaggccgggagacaacccgtacctcaagtacaaccaacggcagcggcaggttccagga goggtcaaaagaagatacgtcttttgggggcaacctcggggcagcagctcttcaggccaaa aagaggtctcttgaacctcttgggtctgggtgaggaagcggctaagacggctcctggaaaga agaggcctgtagagcagtcctcctcaggaaccggactcctccggggtattggcaaatcggg tgcacagcccgtcaaaaagagactcaatttcgggtcagactggcgacacagagtcagtcacca gacctcaaccaatcgggaacctcccgacgccccctcaggtgtgggtctcttacaattgg cttcaggtggtggcgaccagtgggcagacaataacgaagggtccgatggagtgggtagtctc ctcgggaaattggcatttgcgattcccaatggctgggggacagagtcacaccaccagcacc cgaaacctgggcccgtcccaacctacaacaatcacctctacaagcaaatctcccaagcacat ctggaggatcttcaaatgacaaacgctacttcgggtacagcacccccctgggctcttga cttcaacagattccactgccacttctcaccacgtgactggcagcgaactcatcaacaacaac tggggattccggcctaaagcgactcaacttcaagctcttcaacattcagggtcaagaggtta cggacaacaatggagtcgaagaccatcgccaataacacctaccagcacgggtccaggtcttcac ggactcagactatcagctcccgtaacgtgctcgggtcgggtcagcagggctcctcccgccg ttccacagcggacgttttcatgattcctcagtaacgggtatctgacgcttaagtatggaagcc aggcgtgggtcgttctgtccttttactgcctggaatatttcccgctcgcaaatgctaagaac gggttaacaacttccagttcagctacaggtttgagaacgtacctttccatagcagctacgct cacagccaaagcctggacgactaatgaatccactcactcgaccaatcttgtactatctct caaaagactattaaagggttctggacagaatcaacaacgctaaaaattcaggtggccggacc cagcaacatggctgtccagggaagaaaactacatacctggaccagctaccgacaacaacgt gtctcaaccactgtgactcaaaacaacaacagcgaatttgcctggcctggagcttctctt gggtctcattggacgtaataagcttgatgaatcctggacctgctatggccagccacaaaga aggagaggacggtttcttcttctgtctggatctttattttggcaaacagggaactgga agagacaacgtggatgcggaacaaagtcatgataaccaacgaagaagaattaaaactacta acccggtagcaacggagtcctatggacaagtggccacaaaccaccagagtgcacagggt<u>cg</u> <u>tgattctccgaagggttggc</u>agggcgagaccggctgggttcaaaaccaaggaatacttcg ggtaggttttggcaggacagagatgtgtacctgcaaggaccatttggggccaaaattctc acacggacggcaactttcaccttctcogctgatgggaggggttggaaatgaagcaccggcc tcctcagatcctcatcaaaaacacacctgtacctgcGatctccaaaggccttcaacaag gacaagctgaactctttcatcaccagttattctactggccaagtacagctggagatcgagt gggagctgcagaaggaaaaacagcaagcgGtggaaaccggagatccagtacacttccaacta ttacaagtctaataatgttgaaatttgcgtgtaataactgaagggttatatagtgaacccgc ccattggcaccagatacctgactcgtaactctgtaa
	3625	atggctgcccgatgggttatcttcagattggctcgaggacaaccttagtgaaggaaattcgg agtgggtgggtctttgaaacctggagccctcaacccaaggcaaatcaacaacatcaagacaa cgctcgaggtcttgtgcttcgggttcaaaataccttggaccgggcaacggactcgacaag ggggagccgggtcaacgcagcagacgcgggcgccctcgagcacgacaaggccctacgaccagc agctcaaggccgggagacaacccgtacctcaagtacaaccaacggcagcggcaggttccagga goggtcaaaagaagatacgtcttttgggggcaacctcggggcagcagctcttcaggccaaa aagaggtctcttgaacctcttgggtctgggtgaggaagcggctaagacggctcctggaaaga agaggcctgtagagcagtcctcctcaggaaccggactcctccggggtattggcaaatcggg tgcacagcccgtcaaaaagagactcaatttcgggtcagactggcgacacagagtcagtcacca gacctcaaccaatcgggaacctcccgacgccccctcaggtgtgggtctcttacaactgg cttcaggtggtggcgaccagtgggcagacaataacgaagggtccgatggagtgggtagtctc

		ctcgggaaattggcattgcatcccaatggctgggggacagagtcacaccaccagcaacc cgaacctgggcccctgccacctacaacaatcacctctacaagcaaatctccacagcacat ctggaggatcttcaaatagacaacgcctactctgggtacagcaccctgggggtattttga cttcaacagattccaactgccacttctcaccacgtgactggcagcgactcatcaacaacaac tggggattccggcctaagcgactcaacttcaagctcttcaacattcaggtcaagaggtta cggacaacaatggagtcgaagccatcgccaataacctaccagcagcgtccaggtcttcac ggactcagactatcagctcccgtagctgctcgggtcgggtcagcagggctgctcccgccg ttccagcggacgttttcatgattcctcagtagcgggtatctgacgcttaatgatggaagcc aggcgtgggtcgttcgtctcttactgctggaatatttcccgctcgcaaatgctaagaac gggtacaacttccagttcagctacgagtttgagaacgtacctttccatagcagctacgct cacagccaaagcctggacccgactaatgaatccactcatcgaccaatacttgactatctct caaagactattaaaggcttctggacagaatcaacaaacgctaaaattcagtggtggccggacc cagcaacatggctgtccagggaagaaactacatacctggaccagctaccgacaacaacgt gtctcaaccactgtgactcaaaaacaacaacagcgaatttgcttggcctggagctctctct gggtctcattggacgtaatagtcttgatgaatcctggacctgctatggccagccacaaga aggagaggaccgtttcttctcttctgctggatctttaatttttggcaacaaggaactgga agagacaacgtggatcgggacaagtcagataaccaacgaagaagaattaaaactacta accggtagcaacggagtcctatggacaagtggccacaaccaccagagtgccaggtctcgt <u>tgattctccgaagggttggcaggcgcagaccggctgggttcaaaaccaaggaatacttccg</u> ggtaggttttggcaggacagagatgtgtacctgcaaggaccatttggggccaaaattctc acacggacggcaactttcaccttctccgctgatgggaggggttgggaatgaagcaccgcgc tctcagatcctcatcaaaaaacacactgtacctgaggatcctccaacggccttcaacaag gacaagctgaactcttcatcaccagtatctactggccaagtcagcgtggagatcgagt gggagctgcagaaggaacacagcaagcgtggaacccggagatccagtagacttccaacta ttacaagtctaataatgttgaaatttgcgttgaataactgaaggtgtatatagtgaacccgc ccattggcaccagataactcgtactcgttaactgttaa
TFD-003 7mer peptide underlined	3626	atggctgccgatggltatcttccagattggctcgaggacaaccttagtgaaggaattcgcg agtgtgggttttgaacctggagccctcaacccaaggcaaatcaacaacatcaagacaa cgctcgaggtcttctgtctcgggttacaataaccttggaccggcaacggactcgacaag ggggagccggtcaacgcagacgcggcgccctcgagcagcagcagcagcagcagcagc agctcaaggccggagacaacccgtaacctcaagtaaccaacgcgcagcagcagcagcagc gcccgtcaaaagaagatcgtcttttgggggcaacctcgggcagcagcagcagcagcagc aagaggtctcttgaacctcttgggtctggttgagggaagcggctaaagacggctcctggaaga agagcctgtagagcagctctcctcagggaacggactcctccggggatattggcaaatcggg tgcaagcccgctaaaaagagactcaatttccggtcagactggcgacacagagtcagtcoca gacctcaaccaatcggagaacctcccgagcccccctcaggtgtgggtagctcttacaatgg cttcaggtgtgtggcgacacagtgccagacaataacgaaggtgccagtgagggtggttagtct ctcgggaattggcattgcgattcccaatggctgggggacagagtcacaccaccagcacc cgaacctgggcccgtgccacctacaacaatcacctctacaagcaaatctccaacagcat ctggaggatcttcaaatgacaacgcctactctgggtacagcaccctgggggtattttga cttcaacagattccaactgccacttctcaccacgtgactggcagcgactcatcaacaacaac tggggattccggcctaagcgactcaacttcaagctcttcaacattcaggtcaagaggtta cggacaacaatggagtcgaagccatcgccaataaccttaccagcagcgtccaggtcttccac ggactcagactatcagctcccgtagctgctcgggtcgggtcagcagggctgctcccgccg ttccagcggacgttttcatgattcctcagtagcgggtatctgacgcttaatgatggaagcc aggcgtgggtcgttcgtctcttactgctggaatatttcccgctcgcaaatgctaagaac gggtacaacttccagttcagctacgagtttgagaacgtacctttccatagcagctacgct cacagccaaagcctggacccgactaatgaatccactcatcgaccaatacttgactatctct caaagactattaaaggcttctggacagaatcaacaaacgctaaaattcagtggtggccggacc cagcaacatggctgtccagggaagaaactacatacctggaccagctaccgacaacaacgt gtctcaaccactgtgactcaaaaacaacaacagcgaatttgcttggcctggagctctctct gggtctcattggacgtaatagtcttgatgaatcctggacctgctatggccagccacaaga aggagaggaccgtttcttctcttctgctggatctttaatttttggcaacaaggaactgga agagacaacgtggatcgggacaagtcagataaccaacgaagaagaattaaaactacta accggtagcaacggagtcctatggacaagtggccacaaccaccagagtgccaggtctta <u>ttctacggatgtgaggatgcaaggcgcagaccggctgggttcaaaaccaaggaatacttccg</u> ggtaggttttggcaggacagagatgtgtacctgcaaggaccatttggggccaaaattctc acacggacggcaactttcaccttctccgctgatgggaggggttgggaatgaagcaccgcgc tctcagatcctcatcaaaaaacacactgtacctgcgagatcctccaacggccttcaacaag gacaagctgaactcttcatcaccagtatctactggccaagtcagcgtggagatcgagt

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TTD-011 7mer peptide underlined	3634	atggctgcccagtggttatcttccagattggctcgaggacaacotttagtgaaggaattccgg agtgggtgggtcttgaacccctggagccctcaacccaaggcaaatcaacaacatcaagacaa cgctcgagggtctgtgcttccgggttacaataccttggacccgggcaacggactcgacaag ggggagccggtcaacgcagcagacggcgccctcgagcagcagacagcagcagcagcagc agctcaaggccgggagacaaacccgtacotcaagtacaaccaacgcgcagcgcaggttccagga gocgctcaaaagaagatacgtcttttggggcaacccctggggcagcagcttctccaggccaaa aagaggtctcttgaacctcttggctctggttgaggaaagccggctaagacggctcctggaaaga agaggcctgtagagcagtcctcctcaggaaacggactcctccgcggtattggcaaatcggg tgcaacgcccgtcaaaagagactcaatttccggtcagactggcgacacagagtcagtcagcca gacctcaaccaatccggagaacctcccgacgccccctcaggtgtgggactctcttacaatgg cttcagggtggtggcgacacagtgagacataacgaaggtgcccagtgagtgagggtagttc ctcgggaaattggcattgcgattcccaatggctgggggacagagtcataccaccagcacc cgaaacotgggcccctgcccactacaacaatcacctctacaagcaaatctccaacagccat ctggaggatcttcaaatgacaaacgctacttccggtacagcaacccctgggggtattttga cttcaacagattccactgcccacttctcaccacgtgactggcagcagctcatcaacaacaac tggggattccggcctaagcgactcaacttcaagctcttcaacattcagggtcaaaagggtta cggacaacaatggagtcgaagaccatcgccaataaccttaccagcaccggtccaggtcttcac ggactcagactatcagctcccgtagctgctcgggtcgggtcacgagggtcgtcctcccgccg tccccagcggacgttttcatgattcctcagtagcgggtatctgacgcttaatgatggaagcc agggcgtgggtcgttccgtccctttactgcttgaatatctcccgctcgaaatgctaagaac gggttaacaacttccagttcagctacgagtttgagaacgtacctttccatagcagctacgct cacagccaaagcctggaccgactaatgaatccactcatcgaccaatacttgtactatctct caaaagactattaacggttctggacagaatcaacaaacgctaaaaattcagtggtggccggacc cagcaacatggctgtccagggaagaaactacatacctggaccagctaccgacaacaacgt gtctcaaccactgtgactcaaaacaacaacagcgaatttgcttggcctggagcttctctt gggtctcfaatggacgtaataagcttgatgaatcctggacctgctatggccagccacaaga aggagaggacogtttcttctcttctgtctggatctttaaatttttggcaacaaggaaactgga agagacaacgtggatgaggacaaagtcatgataaccaacgaagaagaattaaaaactacta aocggtagcaacggagtcctatggacaagtggccacaacacacaggtgcccagggtgta <u>ttcgaaggatgagaggaa</u>caggcgacagccggctgggttcaaaaccaaggaaatacttccg ggtatgggtttggcaggacagagatgtgtacctgcaaggacccatttgggccaatactctc acaggacggcaactttcaccttctccgctgatgggaggggttggaaatgaagcacccggcc tctcagatcctcatcaaaaacacacotgtacctgcGatcctccaacggccttcaacaag gacaagctgaactcttccatcacccagtattctactggccaagtacgctggagatcaggt gggagctgcagaaggaaaacagcaagcgGtggaaacccggagatccagtaacttccaacta ttacaagtctaataatgttgatttgcgtgtaataactgaagggttatatagtgaacccgc ccattggcaccagatacctgactcgttaactctgtaa

TTD-012 7mer peptide underlined	3635	atggctgccgatgggttatcttccagattggctcgaggacaaccttagtgaaggaattcgcg agtgggtgggcttttgaacctggagccctcaacccaaggcaaatcaacaacatcaagacaa cgctcgaggtcttctgtcttcgggttacaataaccttggaccgggcaacggactcgacaag ggggagccgggtcaacgcagcagacgcggcgccctcgagcagcacaaggcctacgaccagc agctcaaggccggagacaacccgtacctcaagtaacaaccacgcgcagccgagttccagga gcccgtcaaagaagatacgtcttttgggggcaacctcggggcagcagctctccaggccaaa aagaggcttcttgaacctcttgggtctggttgaggaaagcggttaagacggctcctggaaaga agaggcctgtagagcagctctcctcaggaaccggactcctccgcgggtattggcaaatcggg tgcacagcccgctaaaaagagactcaatttcgggtcagactggcgacacagagtcagtcacca gacctcaaccaatcggagaacctccgcagcccccctcagggtgtgggtctcttacaattgg cttcaggtgtggcgaccagtggtggcagacaataacgaagggtgcgatggagtgggtagtctc ctcgggaaattggcatttgcgattcccaatggctgggggacagagtcacaccaccagcacc cgaacctgggcccctgccacctacaacaatcacctctacaagcaaatctccaacagcacat ctggaggatcttcaaatgacaacgcctacttcgggtacagcccccctcgggggtatttga cttcaacagattccactgccacttctcaccacgtgactggcagcagactcatcaacaacaac tggggattccggccctaaagcactcaacttcaagctcttcaacattcagggtcaagagggtta cggacaacaatggagtcagaccatcgccaaataaccttaccagcagcgggtccaggtcttcac ggactcagactatcagctcccgtaactgctcgggtcgggtcagcagggctgcctcccgccg ttccagcgggacgttttcatgattcctcagtcaggggtatctgacgcttaatgatggaagcc aggccgtgggtcgttctgtcttcttactgctggaatatttcccgctcgaatgctaaagaac gggtacaacttccagttcagctacaggtttgagaacgtacctttccatagcagctacgt cacagccaaaagcctggaccgactaatgaatccactcactogaccaatacttctgactatctc caaagactattaacggttcttgacagaatcaacaacgcgtaaaaattcagtggtggccggacc cagcaacatggtctgtccagggaagaaaactacatacctggaccagctaccgacaacaacgt gtctcaaccactgtgactcaaaaacaacacagcgaatttgcctggcctggagctctctctt gggtctcaatggagctaatagcttgatgaatcctggacctgctatggcagccacaaaga aggagaggaccgttttcttcttcttcttcttcttcttcttcttcttcttcttcttcttctt agagacaacgtggatgcggacaaagtcatgataaccaacgaagaagaatttaaaactacta acccggtagcaacggagtcctatggacaagtggccacaaaccaccagagtgacacagggt <u>ta</u> <u>tgtttcgtctgttaagatg</u> caggcgccagaccggctgggttcaaaaccaagggaatacttcg ggatagggttggcagcagagagatgtgtacctgcaaggaccatttggggccaaaattctctc acacggacggcaacttccaccttctcgcgtgatggagggtttggaaatgaagcaccggcc tcctcagatcctcatcaaaaacacacotgtacctgcGatctctccaaaggccttcaacaag gacaagctgaactcttctcatcaaccagttattctactggccaagtacgcgtggagatcgagt gggagctgcagaagaaaacagcaagcgGtggaaaccggagatccagtcacttccaaacta ttacaagtctaataatgtttgaatttgcgtgttaatactgaagggtgtatatagtgaacccgc ccattggcaccagatacctgactcgttaactctgtaa
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[0431] In some embodiments, the polynucleotide encoding an AAV capsid polypeptide, e.g., AAV capsid variant, described herein comprises the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the polynucleotide encoding an AAV capsid variant described herein comprises the nucleotide sequence of SEQ ID NO: 3623, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the polynucleotide encoding an AAV capsid variant described herein comprises the nucleotide sequence of SEQ ID NO: 3627, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the nucleic acid sequence encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein is codon optimized.

[0432] In some embodiments, a polynucleotide encoding the AAV capsid polypeptide, e.g., the AAV capsid variant, (e.g., VP1) of an AAV particle may comprise a nucleic acid sequence with 50%,

51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of those described herein or provided by any of SEQ ID NO: 3623-3635.

[0433] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, (e.g., VP1) may comprise a nucleic acid sequence having at least 80% identity to any of SEQ ID NO: 3623-3635. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, (e.g., VP1) may comprise a nucleic acid sequence having at least 85% identity to any of SEQ ID NO: 3623-3635. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, (e.g., VP1) is encoded by a nucleic acid sequence having at least 90% identity to any of SEQ ID NO: 3623-3635. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, (e.g., VP1) may comprise a nucleic acid sequence having at least 95% identity to any of SEQ ID NO: 3623-3635. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, (e.g., VP1) may comprise a nucleic acid sequence having at least 96% identity to any of SEQ ID NO: 3623-3635. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, (e.g., VP1) may comprise a nucleic acid sequence having at least 97% identity to any of SEQ ID NO: 3623-3635. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, (e.g., VP1) may comprise a nucleic acid sequence having at least 98% identity to any of SEQ ID NO: 3623-3635. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, (e.g., VP1) may comprise a nucleic acid sequence having at least 99% identity to any of SEQ ID NO: 3623-3635. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, (e.g., VP1) may comprise a nucleic acid sequence given by any of SEQ ID NO: 3623-3635.

[0434] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 80% identity to SEQ ID NO: 3623. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 85% identity to SEQ ID NO: 3623. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 90% identity to SEQ ID NO: 3623. In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 95% identity to SEQ ID NO: 3623. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 96% identity to SEQ ID NO: 3623. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant,

may comprise a nucleic acid sequence having at least 97% identity to SEQ ID NO: 3623. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 98% identity to SEQ ID NO: 3623. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 99% identity to SEQ ID NO: 3623.

[0435] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence comprising SEQ ID NO: 3623.

[0436] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence consisting of SEQ ID NO: 3623.

[0437] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 80% identity to SEQ ID NO: 3624 or 3625. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 85% identity to SEQ ID NO: 3624 or 3625. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 90% identity to SEQ ID NO: 3624 or 3625. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 95% identity to SEQ ID NO: 3624 or 3625. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 96% identity to SEQ ID NO: 3624 or 3625. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 97% identity to SEQ ID NO: 3624 or 3625. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 98% identity to SEQ ID NO: 3624 or 3625. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 99% identity to SEQ ID NO: 3624 or 3625.

[0438] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence comprising SEQ ID NO: 3624 or 3625.

[0439] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence consisting of SEQ ID NO: 3624 or 3625.

[0440] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 80% identity to SEQ ID NO: 3626. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 85% identity to SEQ ID NO: 3626. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 90% identity to SEQ ID

NO: 3626. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 95% identity to SEQ ID NO: 3626. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 96% identity to SEQ ID NO: 3626. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 97% identity to SEQ ID NO: 3626. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 98% identity to SEQ ID NO: 3626. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 99% identity to SEQ ID NO: 3626.

[0441] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence comprising SEQ ID NO: 3626.

[0442] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence consisting of SEQ ID NO: 3626.

[0443] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 80% identity to SEQ ID NO: 3627. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 85% identity to SEQ ID NO: 3627. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 90% identity to SEQ ID NO: 3627. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 95% identity to SEQ ID NO: 3627. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 96% identity to SEQ ID NO: 3627. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 97% identity to SEQ ID NO: 3627. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 98% identity to SEQ ID NO: 3627. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 99% identity to SEQ ID NO: 3627.

[0444] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence comprising SEQ ID NO: 3627.

[0445] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence consisting of SEQ ID NO: 3627.

[0446] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 80% identity to SEQ ID NO: 3628. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 85% identity to SEQ ID NO: 3628. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 90% identity to SEQ ID NO: 3628. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 95% identity to SEQ ID NO: 3628. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 96% identity to SEQ ID NO: 3628. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 97% identity to SEQ ID NO: 3628. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 98% identity to SEQ ID NO: 3628. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may comprise a nucleic acid sequence having at least 99% identity to SEQ ID NO: 3628.

[0447] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence comprising SEQ ID NO: 3628.

[0448] In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, may have a nucleic acid sequence consisting of SEQ ID NO: 3628.

[0449] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises a VP2 protein comprising the amino acid sequence corresponding to positions 138-743, of any one of SEQ ID NOs: 3636-3647, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid comprises a VP3 protein comprising the amino acid sequence corresponding to positions 203-743, of any one of SEQ ID NOs: 3636-3647, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0450] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, e.g., an AAV capsid variant described herein, comprises the amino acid sequence of any one of SEQ ID NOs: 3636-3647, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, e.g., an AAV capsid variant described herein, comprises an amino acid sequence having at least one, two, or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any one of SEQ ID NOs: 3636-3647.

[0451] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) of an AAV particle may comprise an amino acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of those described herein or provided as any of SEQ ID NO: 3636-3647.

[0452] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) may comprise an amino acid sequence having at least 80% identity to any of SEQ ID NO: 3636-3647. In some embodiments, an AAV capsid (e.g., VP1) may comprise an amino acid sequence having at least 85% identity to any of SEQ ID NO: 3636-3647. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) may comprise an amino acid sequence having at least 90% identity to any of SEQ ID NO: 3636-3647. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) may comprise an amino acid sequence having at least 95% identity to any of SEQ ID NO: 3636-3647. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) may comprise an amino acid sequence having at least 96% identity to any of SEQ ID NO: 3636-3647. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) may comprise an amino acid sequence having at least 97% identity to any of SEQ ID NO: 3636-3647. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) may comprise an amino acid sequence having at least 98% identity to any of SEQ ID NO: 3636-3647. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) may comprise an amino acid sequence having at least 99% identity to any of SEQ ID NO: 3636-3647. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) may have an amino acid sequence comprising any of SEQ ID NO: 3636-3647. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, (e.g., VP1) may have an amino acid sequence consisting of any of SEQ ID NO: 3636-3647.

[0453] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 80% identity to SEQ ID NO: 3636. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 85% identity to SEQ ID NO: 3636. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 90% identity to SEQ ID NO: 3636. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 95% identity to SEQ ID NO: 3636. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 96% identity to SEQ ID NO: 3636. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 97% identity to SEQ ID NO: 3636. In some embodiments, an AAV capsid polypeptide, e.g., AAV

capsid variant, may comprise an amino acid sequence having at least 98% identity to SEQ ID NO: 3636. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 99% identity to SEQ ID NO: 3636.

[0454] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence comprising SEQ ID NO: 3636. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 3636.

[0455] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence consisting of SEQ ID NO: 3636.

[0456] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3636 is encoded by a nucleic acid sequence comprising SEQ ID NO: 3623. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3636 is encoded by a codon-optimized nucleic acid sequence having 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%, or 99% identity to SEQ ID NO: 3623.

[0457] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 80% identity to SEQ ID NO: 3637. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 85% identity to SEQ ID NO: 3637. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 90% identity to SEQ ID NO: 3637. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 95% identity to SEQ ID NO: 3637. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 96% identity to SEQ ID NO: 3637. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 97% identity to SEQ ID NO: 3637. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 98% identity to SEQ ID NO: 3637. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 99% identity to SEQ ID NO: 3637.

[0458] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence comprising SEQ ID NO: 3637. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 3637.

[0459] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence consisting of SEQ ID NO: 3637.

[0460] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3637 is encoded by a nucleic acid sequence comprising SEQ ID NO: 3624 or 3625. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3637 is encoded by a codon-optimized nucleic acid sequence having 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%, or 99% identity to SEQ ID NO: 3624 or 3625.

[0461] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 80% identity to SEQ ID NO: 3638. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 85% identity to SEQ ID NO: 3638. In some embodiments, an AAV capsid, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 90% identity to SEQ ID NO: 3638. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 95% identity to SEQ ID NO: 3638. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 96% identity to SEQ ID NO: 3638. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 97% identity to SEQ ID NO: 3638. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 98% identity to SEQ ID NO: 3638. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 99% identity to SEQ ID NO: 3638.

[0462] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence comprising SEQ ID NO: 3638. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 3638.

[0463] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence consisting of SEQ ID NO: 3638.

[0464] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3638 is encoded by a nucleic acid sequence comprising SEQ ID NO: 3626. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3638 is encoded by a codon-optimized nucleic acid sequence having 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%, or 99% identity to SEQ ID NO: 3626.

[0465] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 80% identity to SEQ ID NO: 3639. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 85% identity to SEQ ID NO: 3639. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 90% identity to SEQ ID NO: 3639. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 95% identity to SEQ ID NO: 3639. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 96% identity to SEQ ID NO: 3639. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 97% identity to SEQ ID NO: 3639. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 98% identity to SEQ ID NO: 3639. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 99% identity to SEQ ID NO: 3639.

[0466] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence comprising SEQ ID NO: 3639. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 3639.

[0467] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence consisting of SEQ ID NO: 3639.

[0468] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3639 is encoded by a nucleic acid sequence comprising SEQ ID NO: 3627. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3639 is encoded by a codon-optimized nucleic acid sequence having 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%, or 99% identity to SEQ ID NO: 3627.

[0469] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 80% identity to SEQ ID NO: 3640. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 85% identity to SEQ ID NO: 3640. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 90% identity to SEQ ID NO: 3640. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 95% identity to SEQ ID NO: 3640. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 96% identity to SEQ ID NO: 3640. In some embodiments, an AAV

capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 97% identity to SEQ ID NO: 3640. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 98% identity to SEQ ID NO: 3640. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may comprise an amino acid sequence having at least 99% identity to SEQ ID NO: 3640.

[0470] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence comprising SEQ ID NO: 3640. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 3640.

[0471] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, may have an amino acid sequence consisting of SEQ ID NO: 3640.

[0472] In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3640 is encoded by a nucleic acid sequence comprising SEQ ID NO: 3628. In some embodiments, an AAV capsid polypeptide, e.g., AAV capsid variant, comprising an amino acid sequence given as SEQ ID NO: 3640 is encoded by a codon-optimized nucleic acid sequence having 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%, or 99% identity to SEQ ID NO: 3628.

[0473] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein has an increased tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138.

[0474] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein transduces a brain region, e.g., selected from dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus and putamen. In some embodiments, the level of transduction of said brain region is at least 5, 10, 50, 100, 200, 500, 1,000, 2,000, 5,000, or 10,000-fold greater as compared to a reference sequence of SEQ ID NO: 138.

[0475] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein is enriched at least about 5, 6, 7, 8, 9, or 10-fold, in the brain compared to a reference sequence of SEQ ID NO: 138. In some embodiments, an AAV capsid variant described herein is enriched at least about 20, 30, 40, or 50-fold in the brain compared to a reference sequence of SEQ ID NO: 138. In some embodiments, an AAV capsid variant described herein is enriched at least about 100, 200, 300, or 400-fold in the brain compared to a reference sequence of SEQ ID NO: 138.

[0476] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein delivers an increased level of viral genomes to a brain region. In some embodiments, the level of viral genomes is increased by at least 5, 10, 20, 30, 40 or 50-fold, as compared to a reference

sequence of SEQ ID NO: 138. In some embodiments, the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

[0477] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein delivers an increased level of a payload to a brain region. In some embodiments, the level of the payload is increased by at least 5, 10, 50, 100, 200, 500, 1,000, 2,000, 5,000, or 10,000-fold, as compared to a reference sequence of SEQ ID NO: 138. In some embodiments, the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

[0478] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein delivers an increased level of a payload to a spinal cord region. In some embodiments, the level of the payload is increased by at least 10, 20, 50, 100, 200, 300, 400, 500, 600, 700, 800 or 900-fold, as compared to a reference sequence of SEQ ID NO: 138. In some embodiments, the spinal cord region comprises a cervical, thoracic, and/or lumbar region.

[0479] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG).

[0480] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein has an increased tropism for a muscle cell or tissue, e.g., a heart cell or tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant delivers an increased level of a payload to a muscle region. In some embodiments, the payload is increased by at least 10, 15, 20, 30, or 40-fold, as compared to a reference sequence of SEQ ID NO: 138. In some embodiments, the muscle region comprises a heart muscle, quadriceps muscle, and/or a diaphragm muscle region. In some embodiments, the muscle region comprises a heart muscle region, e.g., a heart atrium muscle region or a heart ventricle muscle region.

[0481] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, of the present disclosure is isolated, e.g., recombinant. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, of the present disclosure is isolated, e.g., recombinant.

[0482] In any of the DNA and RNA sequences referenced and/or described herein, the single letter symbol has the following description: A for adenine; C for cytosine; G for guanine; T for thymine; U for Uracil; W for weak bases such as adenine or thymine; S for strong nucleotides such as cytosine and guanine; M for amino nucleotides such as adenine and cytosine; K for keto nucleotides such as guanine and thymine; R for purines adenine and guanine; Y for pyrimidine cytosine and thymine; B for any base that is not A (e.g., cytosine, guanine, and thymine); D for any base that is not

C (e.g., adenine, guanine, and thymine); H for any base that is not G (e.g., adenine, cytosine, and thymine); V for any base that is not T (e.g., adenine, cytosine, and guanine); N for any nucleotide (which is not a gap); and Z is for zero.

[0483] In any of the amino acid sequences referenced and/or described herein, the single letter symbol has the following description: G (Gly) for Glycine; A (Ala) for Alanine; L (Leu) for Leucine; M (Met) for Methionine; F (Phe) for Phenylalanine; W (Trp) for Tryptophan; K (Lys) for Lysine; Q (Gln) for Glutamine; E (Glu) for Glutamic Acid; S (Ser) for Serine; P (Pro) for Proline; V (Val) for Valine; I (Ile) for Isoleucine; C (Cys) for Cysteine; Y (Tyr) for Tyrosine; H (His) for Histidine; R (Arg) for Arginine; N (Asn) for Asparagine; D (Asp) for Aspartic Acid; T (Thr) for Threonine; B (Asx) for Aspartic acid or Asparagine; J (Xle) for Leucine or Isoleucine; O (Pyl) for Pyrrolysine; U (Sec) for Selenocysteine; X (Xaa) for any amino acid; and Z (Glx) for Glutamine or Glutamic acid.

[0484] Also provided herein are polynucleotide sequences encoding any of the AAV capsid variants described above and AAV particles, vectors, and cells comprising the same.

AAV serotypes and capsids

[0485] In some embodiments, an AAV particle of the present disclosure may comprise or be derived from any natural or recombinant AAV serotype. AAV serotypes may differ in characteristics such as, but not limited to, packaging, tropism, transduction and immunogenic profiles. While not wishing to be bound by theory, it is believed in some embodiments, that the AAV capsid protein, e.g., an AAV capsid variant, can modulate, e.g., direct, AAV particle tropism to a particular tissue.

[0486] In some embodiments, an AAV particle may have a capsid protein, e.g., an AAV capsid variant, and ITR sequences derived from the same parent serotype (e.g., AAV2 capsid and AAV2 ITRs). In another embodiment, the AAV particle may be a pseudo-typed AAV particle, wherein the capsid protein and ITR sequences are derived from different parent serotypes (e.g., AAV9 capsid and AAV2 ITRs; AAV2/9).

[0487] The AAV particles of the present disclosure may comprise an AAV capsid protein, e.g., an AAV capsid variant, with a peptide, e.g., targeting peptide, inserted into the parent sequence. The parent capsid or serotype may comprise or be derived from any natural or recombinant AAV serotype. As used herein, a “parent” sequence is a nucleotide or amino acid sequence into which a targeting sequence is inserted (e.g., a nucleotide insertion into nucleic acid sequence or amino acid sequence insertion into amino acid sequence).

[0488] In certain embodiments, the parent AAV capsid nucleotide sequence, e.g., a parental nucleic acid sequence, is as set forth in SEQ ID NO: 137. In some embodiments, the parent AAV capsid nucleotide sequence comprises the nucleic acid sequence of SEQ ID NO: 137, or a nucleic acid sequence substantially identical (e.g., having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) at least thereto. In some embodiments, the parent AAV capsid amino acid sequence, e.g., the parental sequence, is encoded by the nucleic acid sequence of SEQ ID

NO: 137, or a nucleic acid sequence substantially identical (e.g., having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) at least thereto.

[0489] In some embodiments, the parent AAV capsid nucleotide sequence is a K449R variant of SEQ ID NO: 137, wherein the codon encoding a lysine (e.g., AAA or AAG) at position 449 in the amino acid sequence (nucleotides 1345-1347) is exchanged for one encoding an arginine (CGT, CGC, CGA, CGG, AGA, AGG). In some embodiments, the K449R variant has the same function as wild-type AAV9.

[0490] In some embodiments, the parent AAV capsid amino acid sequence, e.g., a parental amino acid sequence, is as set forth in SEQ ID NO: 138.

MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPNGLDKGEVFNAA
DAAALEHDKAYDQQLKAGDNFYLYKNHADAEEFQERLKEDTSFGGNLGRAVFOAKKRLLEPLGLVEEAA
KTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVPDFQPIGEPFAAPSGVGSITMA
SGGGAPVADNNEGADGVGSSSGNWHCDSSQWLGDVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDN
AYFGYSTPWGYFDENRFHCHFSPRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIANNLTS
TVQVFTDSQYQLPYVLGSAHEGCLPPFPADVEMI PQYGYLTLDNGSQAVGRSSFYCLEYFSPQMLRTG
NNFQFSYEFENVFPFHSSYAHSSQSLDRLMNPFLIDQYLYLSKTINGSGQNQQTLLKFSVAGPSNMAVQGR
NYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFG
KQGTGRDNDVADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDRDV
YLQGGPIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPADPPTAFNKKLNSFITQYSTGGQVS
VEIEWELQKENS KRWNPEIQYTSNYYKSNVFEAVNTEGVYSEPRPIGTRYLTRNL (SEQ ID NO:
138)

[0491] In some embodiments, the parental sequence comprises an amino acid sequence comprising at least one, two, or three modifications but no more than 30, 20, or 10 modifications, e.g., substitutions, relative to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the parental sequence comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the parental sequence comprises substitution at position K449, e.g., a K449R substitution.

[0492] In some embodiments, the parent AAV capsid amino acid sequence, e.g., a parental amino acid sequence, is as set forth in SEQ ID NO: 11. In some embodiments, the parental sequence comprises an amino acid sequence comprising at least one, two, or three modifications but no more than 30, 20, or 10 modifications, e.g., substitutions, relative to the amino acid sequence of SEQ ID NO: 11. In some embodiments, the parental sequence comprises the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0493] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid 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 of a parent AAV capsid described herein is PHP.B or AAV9. In

some embodiments, the AAV serotype of a parent AAV capsid or AAV capsid variant is paired with a synapsin promoter to enhance neuronal transduction, as compared to when more ubiquitous promoters are used (e.g., CBA or CMV).

[0494] In some embodiments the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid is AAV9, or a variant thereof. In some embodiments, the AAV9 capsid comprises the amino acid sequence SEQ ID NO: 138. In some embodiments, the AAV9 amino acid sequence is encoded by a nucleotide sequence comprising SEQ ID NO: 137. In some embodiments, the AAV9 capsid comprises an amino acid sequence at least 70% identical to SEQ ID NO: 138, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%. In some embodiments, the AAV9 capsid comprises a nucleotide sequence at least 70% identical to SEQ ID NO: 137, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0495] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid is AAV9 K449R, or a variant thereof. In some embodiments, the AAV9 K449R capsid comprises the amino acid sequence SEQ ID NO: 11. In some embodiments, the AAV9 K449R capsid comprises an amino acid sequence at least 70% identical to SEQ ID NO: 11, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0496] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid comprises an AAVDJ sequence. In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid comprises an AAVDJ8 sequence. In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid comprises an AAVrh10 sequence. In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid comprises an AAVI sequence. In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid comprises AAVF7/HSC7 (SEQ ID NO: 8 and 27 of WO2016049230). In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid comprises AAVF15/HSC15 (SEQ ID NO: 16 and 33 of WO2016049230). In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid comprises AAVF17/HSC17 (SEQ ID NO: 13 and 35 of WO2016049230). In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid comprises an AAV5 sequence. As a non-limiting example, the AAV5 sequence is SEQ ID NO: 4 of U.S. Patent No. 6,984,517, the contents of which are herein incorporated by reference in their entirety.

[0497] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, allows for blood brain barrier penetration following intravenous administration. In some embodiments, the AAV capsid, e.g., AAV capsid variant, allows for blood brain barrier penetration following focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or

MRI-guided FUS coupled with intravenous administration. In some embodiments the AAV capsid, e.g., AAV capsid variant allows for increased distribution to a brain region. In some embodiments, the brain region comprises a frontal cortex, sensory cortex, motor cortex, caudate, dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus, putamen, or a combination thereof. In some embodiments, the AAV capsid, e.g., AAV capsid variant allows for preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG).

[0498] In some embodiments the AAV capsid polypeptide, e.g., AAV capsid variant allows for increased distribution to a spinal cord region. In some embodiments, the spinal region comprises a cervical spinal cord region, thoracic spinal cord region, and/or lumbar spinal cord region.

[0499] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, is suitable for intramuscular administration and/or transduction of muscle fibers. In some embodiments the AAV capsid polypeptide, e.g., AAV capsid variant, allows for increased distribution to a muscle region. In some embodiments, the muscle region comprises a heart muscle, quadriceps muscle, a diaphragm muscle region, or a combination thereof. In some embodiments, the muscle region comprises a heart muscle region, e.g., a heart atrium muscle region or a heart ventricle muscle region.

[0500] In some embodiments, one or more targeting sequence is inserted into a parent AAV capsid sequence or an AAV capsid polypeptide, e.g., AAV capsid variant, sequence. As a non-limiting example, one targeting sequence may be inserted into a parent AAV capsid sequence or an AAV capsid variant sequence. As a non-limiting example, two targeting sequences may be inserted into a parent AAV capsid sequence or an AAV capsid variant sequence. As a non-limiting example, three targeting sequences may be inserted into a parent AAV capsid sequence or an AAV capsid variant sequence. As a non-limiting example, more than three targeting sequences may be inserted into a parent AAV capsid sequence or an AAV capsid variant sequence.

[0501] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises a parental AAV capsid sequence having an insert, e.g., an amino acid sequence as described in Table 1 or 2. In some embodiments, the parental sequence may comprise at least 1, 2, 3 or more insert sequences.

[0502] While not wishing to be bound by theory, it is understood that a parent AAV capsid sequence or an AAV capsid polypeptide, e.g., an AAV capsid variant, comprises a VP1 region. In some embodiments, a parent AAV capsid sequence or an AAV capsid variant comprises a VP1, VP2 and/or VP3 region, or any combination thereof.

[0503] In some embodiments, the initiation codon for translation of the AAV VP1 capsid protein, e.g., a capsid variant, may be CTG, TTG, or GTG as described in US Patent No. US8163543, the contents of which are herein incorporated by reference in its entirety.

[0504] The present disclosure refers to structural capsid proteins (including VP1, VP2 and VP3) which are encoded by capsid (Cap) genes. These capsid proteins form an outer protein structural shell

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

[0505] Where the Met/AA-clipping is incomplete, a mixture of one or more (one, two or three) VP capsid proteins comprising the viral capsid may be produced, some of which may include a Met1/AA1 amino acid (Met+/AA+) and some of which may lack a Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-). For further discussion regarding Met/AA-clipping in capsid proteins, see Jin, et al. Direct Liquid Chromatography/Mass Spectrometry Analysis for Complete Characterization of Recombinant Adeno-Associated Virus Capsid Proteins. *Hum Gene Ther Methods*. 2017 Oct. 28(5):255-267; Hwang, et al. N-Terminal Acetylation of Cellular Proteins Creates Specific Degradation Signals. *Science*. 2010 February 19. 327(5968): 973-977; the contents of which are each incorporated herein by reference in its entirety.

[0506] According to the present disclosure, references to capsid proteins, e.g., AAV capsid variants, is not limited to either clipped (Met-/AA-) or unclipped (Met+/AA+) and may, in context, refer to independent capsid proteins, viral capsids comprised of a mixture of capsid proteins, and/or polynucleotide sequences (or fragments thereof) which encode, describe, produce or result in capsid proteins of the present disclosure. A direct reference to a capsid protein or capsid polypeptide (such as VP1, VP2 or VP2) may also comprise VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) as well as corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-).

[0507] Further according to the present disclosure, a reference to a specific SEQ ID NO: (whether a protein or nucleic acid) which comprises or encodes, respectively, one or more capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) should be understood to teach the VP capsid proteins which lack the Met1/AA1 amino acid as upon review of the sequence, it is readily apparent any sequence which merely lacks the first listed amino acid (whether or not Met1/AA1).

[0508] As a non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length and which includes a "Met1" amino acid (Met+) encoded by the AUG/ATG start codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length and which does not include the "Met1" amino acid (Met-) of the 736 amino acid Met+ sequence. As a second non-limiting example, reference to a VP1 polypeptide sequence which is 736

amino acids in length and which includes an "AA1" amino acid (AA1+) encoded by any NNN initiator codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length and which does not include the "AA1" amino acid (AA1-) of the 736 amino acid AA1+ sequence.

[0509] References to viral capsids formed from VP capsid proteins (such as reference to specific AAV capsid serotypes), can incorporate VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA1+), corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA1-clipping (Met-/AA1-), and combinations thereof (Met+/AA1+ and Met-/AA1-).

[0510] As a non-limiting example, an AAV capsid serotype can include VP1 (Met+/AA1+), VP1 (Met-/AA1-), or a combination of VP1 (Met+/AA1+) and VP1 (Met-/AA1-). An AAV capsid serotype can also include VP3 (Met+/AA1+), VP3 (Met-/AA1-), or a combination of VP3 (Met+/AA1+) and VP3 (Met-/AA1-); and can also include similar optional combinations of VP2 (Met+/AA1) and VP2 (Met-/AA1-).

Additional AAV Sequences

[0511] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, comprises, or the parent AAV capsid is modified such that, immediately subsequent to position 586, 588, or 589 numbered relative to SEQ ID NO: 138, the AAV capsid variant or the parent AAV capsid polypeptide comprises at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids of any of SEQ ID NOs: 1725-3622 or 3648-3659.

[0512] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid described herein does not comprise an insert sequence present immediately subsequent to position 586, 588, or 589 numbered relative to SEQ ID NO: 138, having at least 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, of any of SEQ ID NOs: 1-1724, e.g., as described in Table 6.

[0513] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may comprise at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, an amino acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of those described herein.

[0514] In any of the embodiments described herein, a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138 can be identified by providing an alignment of a reference sequence and a query sequence, wherein the reference

sequence is SEQ ID NO: 138, and identifying the residues corresponding to the positions in the query sequence that correspond to positions 586 to 594 in the reference sequence.

[0515] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be encoded by a nucleic acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of those described herein, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138.

[0516] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be an AAV9, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138. In some embodiments, In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, an AAV9hu.14 (SEQ ID NO: 137 or 138). In some embodiments, In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, an AAV9 K449R (SEQ ID NO: 11). In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a PHP.B (SEQ ID NO: 5 or 6). In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a PHP.N (SEQ ID NO: 4). In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a VOY101 (SEQ ID NO: 1 or 2). In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a VOY201 (SEQ ID NO: 3 or 1724).

[0517] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, an AAV5.

[0518] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, selected from any of the following VOY101, VOY201, AAVPHP.B (PHP.B), AAVPHP.A (PHP.A), AAVG2B-26, AAVG2B-13,

AAVTH1.1-32, AAVTH1.1-35, AAVPHP.B2 (PHP.B2), AAVPHP.B3 (PHP.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 (G2A3), AAVG2B4 (G2B4), AAVG2B5
(G2B5), PHP.S, 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 K449R,
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/rh.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, AAV, BAAV, caprine AAV, bovine 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, and/or AAVF9/HSC9 and variants thereof.

[0519] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0520] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0521] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding

to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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 US 7198951).

[0522] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0523] In some embodiments, the AAV serotype, the parent AAV capsid polypeptide, or the AAV capsid variant may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0524] In some embodiments, the AAV serotype, the parent AAV capsid polypeptide, or the AAV capsid variant may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0525] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a AAVDJ or a variant thereof, such as AAVDJ8 (or AAV-DJ8), as described by Grimm et al. (Journal of Virology 82(12): 5887-5911 (2008), herein incorporated by reference in its entirety). In some embodiments, the amino acid sequence of AAVDJ8 may comprise two or more mutations in order to remove the heparin binding domain (HBD). In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may comprise, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0526] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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).

[0527] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a mutation in the AAV2 sequence to generate AAV2G9 as described in International Publication No. WO2014144229 and herein incorporated by reference in its entirety.

[0528] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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, AAVrh.4. 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.

[0529] In some embodiments, the AAV serotype, the parent AAV capsid polypeptide, or the AAV capsid variant may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0530] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0531] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0532] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0533] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0534] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0535] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0536] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0537] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0538] According to the present disclosure, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid, may be selected or derived from a variety of species. In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid, may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, an avian AAV (AAAV). In some embodiments, the AAV serotype, the parent AAV capsid polypeptide, or the AAV capsid variant may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a sequence as described in United States Patent No. US 9,238,800, 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.

[0539] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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 9,193,769), or variants thereof. In some embodiments, the AAV serotype, the parent AAV capsid polypeptide, or the AAV capsid variant may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a BAAV serotype comprising 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.

[0540] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be a caprine AAV. In some embodiments, the AAV serotype, the parent AAV capsid polypeptide, or the AAV capsid variant may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, may be a caprine AAV serotype comprising 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.

[0541] In other embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be engineered as a hybrid AAV from two or more serotypes, e.g., parental serotypes. In some embodiments, the AAV serotype, the parent AAV capsid polypeptide, or the AAV capsid variant may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, may be a AAV2G9, which comprises sequences from AAV2 and AAV9, e.g., wherein 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.

[0542] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138 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; F411H), 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).

[0543] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0544] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a sequence as described in United States Patent No. US 8734809, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV CBr-E1 (SEQ ID NO: 13 and 87 of US8734809), AAV CBr-E2 (SEQ ID NO: 14 and 88 of US8734809), AAV CBr-E3 (SEQ ID NO: 15 and 89 of US8734809), AAV CBr-E4 (SEQ ID NO: 16 and 90 of US8734809), AAV CBr-E5 (SEQ ID NO: 17 and 91 of US8734809), AAV CBr-e5 (SEQ ID NO: 18 and 92 of US8734809), AAV CBr-E6 (SEQ ID NO: 19 and 93 of US8734809), AAV CBr-E7 (SEQ ID NO: 20 and 94 of US8734809), AAV CBr-E8 (SEQ ID NO: 21 and 95 of US8734809), AAV CLv-D1 (SEQ ID NO: 22 and 96 of US8734809), AAV CLv-D2 (SEQ ID NO: 23 and 97 of US8734809), AAV CLv-D3 (SEQ ID NO: 24 and 98 of US8734809), AAV CLv-D4 (SEQ ID NO: 25 and 99 of US8734809), AAV CLv-D5 (SEQ ID NO: 26 and 100 of US8734809), AAV CLv-D6 (SEQ ID NO: 27 and 101 of US8734809), AAV CLv-D7 (SEQ ID NO: 28 and 102 of US8734809), AAV CLv-D8 (SEQ ID NO: 29 and 103 of US8734809), AAV CLv-E1 (SEQ ID NO: 13 and 87 of US8734809), AAV CLv-R1 (SEQ ID NO: 30 and 104 of US8734809), AAV CLv-R2 (SEQ ID NO: 31 and 105 of US8734809), AAV CLv-R3 (SEQ ID NO: 32 and 106 of US8734809), AAV CLv-R4 (SEQ ID NO: 33 and 107 of US8734809), AAV CLv-R5 (SEQ ID NO: 34 and 108 of US8734809), AAV CLv-R6 (SEQ ID NO: 35 and 109 of US8734809),

AAV CLv-R7 (SEQ ID NO: 36 and 110 of US8734809), AAV CLv-R8 (SEQ ID NO: X and X of US8734809), AAV CLv-R9 (SEQ ID NO: X and X of US8734809), AAV CLg-F1 (SEQ ID NO: 39 and 113 of US8734809), AAV CLg-F2 (SEQ ID NO: 40 and 114 of US8734809), AAV CLg-F3 (SEQ ID NO: 41 and 115 of US8734809), AAV CLg-F4 (SEQ ID NO: 42 and 116 of US8734809), AAV CLg-F5 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F6 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F7 (SEQ ID NO: 44 and 118 of US8734809), AAV CLg-F8 (SEQ ID NO: 43 and 117 of US8734809), AAV CSp-1 (SEQ ID NO: 45 and 119 of US8734809), AAV CSp-10 (SEQ ID NO: 46 and 120 of US8734809), AAV CSp-11 (SEQ ID NO: 47 and 121 of US8734809), AAV CSp-2 (SEQ ID NO: 48 and 122 of US8734809), AAV CSp-3 (SEQ ID NO: 49 and 123 of US8734809), AAV CSp-4 (SEQ ID NO: 50 and 124 of US8734809), AAV CSp-6 (SEQ ID NO: 51 and 125 of US8734809), AAV CSp-7 (SEQ ID NO: 52 and 126 of US8734809), AAV CSp-8 (SEQ ID NO: 53 and 127 of US8734809), AAV CSp-9 (SEQ ID NO: 54 and 128 of US8734809), AAV CHt-2 (SEQ ID NO: 55 and 129 of US8734809), AAV CHt-3 (SEQ ID NO: 56 and 130 of US8734809), AAV CKd-1 (SEQ ID NO: 57 and 131 of US8734809), AAV CKd-10 (SEQ ID NO: 58 and 132 of US8734809), AAV CKd-2 (SEQ ID NO: 59 and 133 of US8734809), AAV CKd-3 (SEQ ID NO: 60 and 134 of US8734809), AAV CKd-4 (SEQ ID NO: 61 and 135 of US8734809), AAV CKd-6 (SEQ ID NO: 62 and 136 of US8734809), AAV CKd-7 (SEQ ID NO: 63 and 137 of US8734809), AAV CKd-8 (SEQ ID NO: 64 and 138 of US8734809), AAV CLv-1 (SEQ ID NO: 35 and 139 of US8734809), AAV CLv-12 (SEQ ID NO: 66 and 140 of US8734809), AAV CLv-13 (SEQ ID NO: 67 and 141 of US8734809), AAV CLv-2 (SEQ ID NO: 68 and 142 of US8734809), AAV CLv-3 (SEQ ID NO: 69 and 143 of US8734809), AAV CLv-4 (SEQ ID NO: 70 and 144 of US8734809), AAV CLv-6 (SEQ ID NO: 71 and 145 of US8734809), AAV CLv-8 (SEQ ID NO: 72 and 146 of US8734809), AAV CKd-B1 (SEQ ID NO: 73 and 147 of US8734809), AAV CKd-B2 (SEQ ID NO: 74 and 148 of US8734809), AAV CKd-B3 (SEQ ID NO: 75 and 149 of US8734809), AAV CKd-B4 (SEQ ID NO: 76 and 150 of US8734809), AAV CKd-B5 (SEQ ID NO: 77 and 151 of US8734809), AAV CKd-B6 (SEQ ID NO: 78 and 152 of US8734809), AAV CKd-B7 (SEQ ID NO: 79 and 153 of US8734809), AAV CKd-B8 (SEQ ID NO: 80 and 154 of US8734809), AAV CKd-H1 (SEQ ID NO: 81 and 155 of US8734809), AAV CKd-H2 (SEQ ID NO: 82 and 156 of US8734809), AAV CKd-H3 (SEQ ID NO: 83 and 157 of US8734809), AAV CKd-H4 (SEQ ID NO: 84 and 158 of US8734809), AAV CKd-H5 (SEQ ID NO: 85 and 159 of US8734809), AAV CKd-H6 (SEQ ID NO: 77 and 151 of US8734809), AAV CHt-1 (SEQ ID NO: 86 and 160 of US8734809), AAV CLv1-1 (SEQ ID NO: 171 of US8734809), AAV CLv1-2 (SEQ ID NO: 172 of US8734809), AAV CLv1-3 (SEQ ID NO: 173 of US8734809), AAV CLv1-4 (SEQ ID NO: 174 of US8734809), AAV Clv1-7 (SEQ ID NO: 175 of US8734809), AAV Clv1-8 (SEQ ID NO: 176 of US8734809), AAV Clv1-9 (SEQ ID NO: 177 of US8734809), AAV Clv1-10 (SEQ ID NO: 178 of US8734809), AAV.VR-355

(SEQ ID NO: 181 of US8734809), AAV.hu.48R3 (SEQ ID NO: 183 of US8734809), or variants or derivatives thereof.

[0545] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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.

[0546] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a serotype selected from any of those found in Table 6.

[0547] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a sequence, fragment or variant thereof, of any of the sequences in Table 6.

[0548] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be encoded by, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a sequence, fragment or variant as described in Table 6.

Table 6. AAV Sequences

Serotype	SEQ ID NO:	Reference Information
VOY101	1	-
VOY101	2	-
VOY201	3	-
VOY201	1724	-
PHP.N/PHP.B-DGT	4	WO2017100671 SEQ ID NO: 46
AAVPHP.B or G2B-26	5	WO2015038958 SEQ ID NO: 8 and 13
AAVPHP.B	6	WO2015038958 SEQ ID NO: 9
AAVG2B-13	7	WO2015038958 SEQ ID NO: 12
AAVTH1.1-32	8	WO2015038958 SEQ ID NO: 14
AAVTH1.1-35	9	WO2015038958 SEQ ID NO: 15
PHP.S/G2A12	10	WO2017100671 SEQ ID NO: 47
AAV9/hu.14 K449R	11	WO2017100671 SEQ ID NO: 45
AAV1	12	US20150159173 SEQ ID NO: 11, US20150315612 SEQ ID NO: 202
AAV1	13	US20160017295 SEQ ID NO: 1, US20030138772 SEQ ID NO: 64, US20150159173 SEQ ID NO: 27, US20150315612 SEQ ID NO: 219, US7198951 SEQ ID NO: 5
AAV1	14	US20030138772 SEQ ID NO: 6
AAV1.3	15	US20030138772 SEQ ID NO: 14
AAV10	16	US20030138772 SEQ ID NO: 117
AAV10	17	WO2015121501 SEQ ID NO: 9
AAV10	18	WO2015121501 SEQ ID NO: 8
AAV11	19	US20030138772 SEQ ID NO: 118
AAV12	20	US20030138772 SEQ ID NO: 119
AAV2	21	US20150159173 SEQ ID NO: 7, US20150315612 SEQ ID NO: 211
AAV2	22	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	23	US6156303 SEQ ID NO: 8
AAV2	24	US20030138772 SEQ ID NO: 7
AAV2	25	US6156303 SEQ ID NO: 3
AAV2.5T	26	US9233131 SEQ ID NO: 42
AAV223.10	27	US20030138772 SEQ ID NO: 75
AAV223.2	28	US20030138772 SEQ ID NO: 49
AAV223.2	29	US20030138772 SEQ ID NO: 76
AAV223.4	30	US20030138772 SEQ ID NO: 50
AAV223.4	31	US20030138772 SEQ ID NO: 73
AAV223.5	32	US20030138772 SEQ ID NO: 51
AAV223.5	33	US20030138772 SEQ ID NO: 74
AAV223.6	34	US20030138772 SEQ ID NO: 52
AAV223.6	35	US20030138772 SEQ ID NO: 78
AAV223.7	36	US20030138772 SEQ ID NO: 53
AAV223.7	37	US20030138772 SEQ ID NO: 77
AAV29.3	38	US20030138772 SEQ ID NO: 82
AAV29.4	39	US20030138772 SEQ ID NO: 12
AAV29.5	40	US20030138772 SEQ ID NO: 83
AAV29.5 (AAVbb.2)	41	US20030138772 SEQ ID NO: 13
AAV3	42	US20150159173 SEQ ID NO: 12
AAV3	43	US20030138772 SEQ ID NO: 71, US20150159173 SEQ ID NO: 28, US20160017295 SEQ ID NO: 3, US7198951 SEQ ID NO: 6
AAV3	44	US20030138772 SEQ ID NO: 8
AAV3.3b	45	US20030138772 SEQ ID NO: 72
AAV3-3	46	US20150315612 SEQ ID NO: 200
AAV3-3	47	US20150315612 SEQ ID NO: 217
AAV3a	48	US6156303 SEQ ID NO: 5
AAV3a	49	US6156303 SEQ ID NO: 9
AAV3b	50	US6156303 SEQ ID NO: 6
AAV3b	51	US6156303 SEQ ID NO: 10
AAV3b	52	US6156303 SEQ ID NO: 1
AAV4	53	US20140348794 SEQ ID NO: 17
AAV4	54	US20140348794 SEQ ID NO: 5
AAV4	55	US20140348794 SEQ ID NO: 3
AAV4	56	US20140348794 SEQ ID NO: 14
AAV4	57	US20140348794 SEQ ID NO: 15
AAV4	58	US20140348794 SEQ ID NO: 19
AAV4	59	US20140348794 SEQ ID NO: 12
AAV4	60	US20140348794 SEQ ID NO: 13
AAV4	61	US20140348794 SEQ ID NO: 7
AAV4	62	US20140348794 SEQ ID NO: 8
AAV4	63	US20140348794 SEQ ID NO: 9
AAV4	64	US20140348794 SEQ ID NO: 2
AAV4	65	US20140348794 SEQ ID NO: 10
AAV4	66	US20140348794 SEQ ID NO: 11
AAV4	67	US20140348794 SEQ ID NO: 18
AAV4	68	US20030138772 SEQ ID NO: 63, US20160017295 SEQ ID NO: 4, US20140348794 SEQ ID NO: 4
AAV4	69	US20140348794 SEQ ID NO: 16
AAV4	70	US20140348794 SEQ ID NO: 20
AAV4	71	US20140348794 SEQ ID NO: 6
AAV4	72	US20140348794 SEQ ID NO: 1
AAV42.2	73	US20030138772 SEQ ID NO: 9
AAV42.2	74	US20030138772 SEQ ID NO: 102
AAV42.3b	75	US20030138772 SEQ ID NO: 36
AAV42.3B	76	US20030138772 SEQ ID NO: 107
AAV42.4	77	US20030138772 SEQ ID NO: 33

AAV42.4	78	US20030138772 SEQ ID NO: 88
AAV42.8	79	US20030138772 SEQ ID NO: 27
AAV42.8	80	US20030138772 SEQ ID NO: 85
AAV43.1	81	US20030138772 SEQ ID NO: 39
AAV43.1	82	US20030138772 SEQ ID NO: 92
AAV43.12	83	US20030138772 SEQ ID NO: 41
AAV43.12	84	US20030138772 SEQ ID NO: 93
AAV43.20	85	US20030138772 SEQ ID NO: 42
AAV43.20	86	US20030138772 SEQ ID NO: 99
AAV43.21	87	US20030138772 SEQ ID NO: 43
AAV43.21	88	US20030138772 SEQ ID NO: 96
AAV43.23	89	US20030138772 SEQ ID NO: 44
AAV43.23	90	US20030138772 SEQ ID NO: 98
AAV43.25	91	US20030138772 SEQ ID NO: 45
AAV43.25	92	US20030138772 SEQ ID NO: 97
AAV43.5	93	US20030138772 SEQ ID NO: 40
AAV43.5	94	US20030138772 SEQ ID NO: 94
AAV44	95	US20150315612 SEQ ID NO: 201
AAV44	96	US20150315612 SEQ ID NO: 218
AAV44.1	97	US20030138772 SEQ ID NO: 46
AAV44.1	98	US20030138772 SEQ ID NO: 79
AAV44.5	99	US20030138772 SEQ ID NO: 47
AAV44.5	100	US20030138772 SEQ ID NO: 80
AAV4407	101	US20150315612 SEQ ID NO: 90
AAV5	102	US7427396 SEQ ID NO: 1
AAV5	103	US20030138772 SEQ ID NO: 114
AAV5	104	US20160017295 SEQ ID NO: 5, US7427396 SEQ ID NO: 2, US20150315612 SEQ ID NO: 216
AAV5	105	US20150315612 SEQ ID NO: 199
AAV6	106	US20150159173 SEQ ID NO: 13
AAV6	107	US20030138772 SEQ ID NO: 65, US20150159173 SEQ ID NO: 29, US20160017295 SEQ ID NO: 6, US6156303 SEQ ID NO: 7
AAV6	108	US6156303 SEQ ID NO: 11
AAV6	109	US6156303 SEQ ID NO: 2
AAV6	110	US20150315612 SEQ ID NO: 203
AAV6	111	US20150315612 SEQ ID NO: 220
AAV6.1	112	US20150159173
AAV6.12	113	US20150159173
AAV6.2	114	US20150159173
AAV7	115	US20150159173 SEQ ID NO: 14
AAV7	116	US20150315612 SEQ ID NO: 183
AAV7	117	US20030138772 SEQ ID NO: 2, US20150159173 SEQ ID NO: 30, US20150315612 SEQ ID NO: 181, US20160017295 SEQ ID NO: 7
AAV7	118	US20030138772 SEQ ID NO: 3
AAV7	119	US20030138772 SEQ ID NO: 1, US20150315612 SEQ ID NO: 180
AAV7	120	US20150315612 SEQ ID NO: 213
AAV7	121	US20150315612 SEQ ID NO: 222
AAV8	122	US20150159173 SEQ ID NO: 15
AAV8	123	US20150376240 SEQ ID NO: 7
AAV8	124	US20030138772 SEQ ID NO: 4, US20150315612 SEQ ID NO: 182
AAV8	125	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	126	US20150376240 SEQ ID NO: 8
AAV8	127	US20150315612 SEQ ID NO: 214
AAV-8b	128	US20150376240 SEQ ID NO: 5
AAV-8b	129	US20150376240 SEQ ID NO: 3

AAV-8h	130	US20150376240 SEQ ID NO: 6
AAV-8h	131	US20150376240 SEQ ID NO: 4
AAV9	132	US20030138772 SEQ ID NO: 5
AAV9	133	US7198951 SEQ ID NO: 1
AAV9	134	US20160017295 SEQ ID NO: 9
AAV9	135	US20030138772 SEQ ID NO: 100, US7198951 SEQ ID NO: 2
AAV9	136	US7198951 SEQ ID NO: 3
AAV9 (AAVhu.14)	137	US7906111 SEQ ID NO: 3; WO2015038958 SEQ ID NO: 11
AAV9 (AAVhu.14)	138	US7906111 SEQ ID NO: 123, WO2015038958 SEQ ID NO: 2
AAVA3.1	139	US20030138772 SEQ ID NO: 120
AAVA3.3	140	US20030138772 SEQ ID NO: 57
AAVA3.3	141	US20030138772 SEQ ID NO: 66
AAVA3.4	142	US20030138772 SEQ ID NO: 54
AAVA3.4	143	US20030138772 SEQ ID NO: 68
AAVA3.5	144	US20030138772 SEQ ID NO: 55
AAVA3.5	145	US20030138772 SEQ ID NO: 69
AAVA3.7	146	US20030138772 SEQ ID NO: 56
AAVA3.7	147	US20030138772 SEQ ID NO: 67
AAV29.3 (AAVbb.1)	148	US20030138772 SEQ ID NO: 11
AAVC2	149	US20030138772 SEQ ID NO: 61
AAVCh.5	150	US20150159173 SEQ ID NO: 46, US20150315612 SEQ ID NO: 234
AAVcy.2 (AAV13.3)	151	US20030138772 SEQ ID NO: 15
AAV24.1	152	US20030138772 SEQ ID NO: 101
AAVcy.3 (AAV24.1)	153	US20030138772 SEQ ID NO: 16
AAV27.3	154	US20030138772 SEQ ID NO: 104
AAVcy.4 (AAV27.3)	155	US20030138772 SEQ ID NO: 17
AAVcy.5	156	US20150315612 SEQ ID NO: 227
AAV7.2	157	US20030138772 SEQ ID NO: 103
AAVcy.5 (AAV7.2)	158	US20030138772 SEQ ID NO: 18
AAV16.3	159	US20030138772 SEQ ID NO: 105
AAVcy.6 (AAV16.3)	160	US20030138772 SEQ ID NO: 10
AAVcy.5	161	US20150159173 SEQ ID NO: 8
AAVcy.5	162	US20150159173 SEQ ID NO: 24
AAVCy.5R1	163	US20150159173
AAVCy.5R2	164	US20150159173
AAVCy.5R3	165	US20150159173
AAVCy.5R4	166	US20150159173
AAVDJ	167	US20140359799 SEQ ID NO: 3, US7588772 SEQ ID NO: 2
AAVDJ	168	US20140359799 SEQ ID NO: 2, US7588772 SEQ ID NO: 1
AAVDJ-8	169	US7588772; Grimm et al 2008
AAVDJ-8	170	US7588772; Grimm et al 2008
AAVF5	171	US20030138772 SEQ ID NO: 110
AAVH2	172	US20030138772 SEQ ID NO: 26
AAVH6	173	US20030138772 SEQ ID NO: 25
AAVhEr1.1	174	US9233131 SEQ ID NO: 44
AAVhEr1.14	175	US9233131 SEQ ID NO: 46
AAVhEr1.16	176	US9233131 SEQ ID NO: 48
AAVhEr1.18	177	US9233131 SEQ ID NO: 49
AAVhEr1.23 (AAVhEr2.29)	178	US9233131 SEQ ID NO: 53
AAVhEr1.35	179	US9233131 SEQ ID NO: 50
AAVhEr1.36	180	US9233131 SEQ ID NO: 52
AAVhEr1.5	181	US9233131 SEQ ID NO: 45
AAVhEr1.7	182	US9233131 SEQ ID NO: 51
AAVhEr1.8	183	US9233131 SEQ ID NO: 47
AAVhEr2.16	184	US9233131 SEQ ID NO: 55
AAVhEr2.30	185	US9233131 SEQ ID NO: 56

AAVhEr2.31	186	US9233131 SEQ ID NO: 58
AAVhEr2.36	187	US9233131 SEQ ID NO: 57
AAVhEr2.4	188	US9233131 SEQ ID NO: 54
AAVhEr3.1	189	US9233131 SEQ ID NO: 59
AAVhu.1	190	US20150315612 SEQ ID NO: 46
AAVhu.1	191	US20150315612 SEQ ID NO: 144
AAVhu.10 (AAV16.8)	192	US20150315612 SEQ ID NO: 56
AAVhu.10 (AAV16.8)	193	US20150315612 SEQ ID NO: 156
AAVhu.11 (AAV16.12)	194	US20150315612 SEQ ID NO: 57
AAVhu.11 (AAV16.12)	195	US20150315612 SEQ ID NO: 153
AAVhu.12	196	US20150315612 SEQ ID NO: 59
AAVhu.12	197	US20150315612 SEQ ID NO: 154
AAVhu.13	198	US20150159173 SEQ ID NO: 16, US20150315612 SEQ ID NO: 71
AAVhu.13	199	US20150159173 SEQ ID NO: 32, US20150315612 SEQ ID NO: 129
AAVhu.136.1	200	US20150315612 SEQ ID NO: 165
AAVhu.140.1	201	US20150315612 SEQ ID NO: 166
AAVhu.140.2	202	US20150315612 SEQ ID NO: 167
AAVhu.145.6	203	US20150315612 SEQ ID NO: 178
AAVhu.15	204	US20150315612 SEQ ID NO: 147
AAVhu.15 (AAV33.4)	205	US20150315612 SEQ ID NO: 50
AAVhu.156.1	206	US20150315612 SEQ ID NO: 179
AAVhu.16	207	US20150315612 SEQ ID NO: 148
AAVhu.16 (AAV33.8)	208	US20150315612 SEQ ID NO: 51
AAVhu.17	209	US20150315612 SEQ ID NO: 83
AAVhu.17 (AAV33.12)	210	US20150315612 SEQ ID NO: 4
AAVhu.172.1	211	US20150315612 SEQ ID NO: 171
AAVhu.172.2	212	US20150315612 SEQ ID NO: 172
AAVhu.173.4	213	US20150315612 SEQ ID NO: 173
AAVhu.173.8	214	US20150315612 SEQ ID NO: 175
AAVhu.18	215	US20150315612 SEQ ID NO: 52
AAVhu.18	216	US20150315612 SEQ ID NO: 149
AAVhu.19	217	US20150315612 SEQ ID NO: 62
AAVhu.19	218	US20150315612 SEQ ID NO: 133
AAVhu.2	219	US20150315612 SEQ ID NO: 48
AAVhu.2	220	US20150315612 SEQ ID NO: 143
AAVhu.20	221	US20150315612 SEQ ID NO: 63
AAVhu.20	222	US20150315612 SEQ ID NO: 134
AAVhu.21	223	US20150315612 SEQ ID NO: 65
AAVhu.21	224	US20150315612 SEQ ID NO: 135
AAVhu.22	225	US20150315612 SEQ ID NO: 67
AAVhu.22	226	US20150315612 SEQ ID NO: 138
AAVhu.23	227	US20150315612 SEQ ID NO: 60
AAVhu.23.2	228	US20150315612 SEQ ID NO: 137
AAVhu.24	229	US20150315612 SEQ ID NO: 66
AAVhu.24	230	US20150315612 SEQ ID NO: 136
AAVhu.25	231	US20150315612 SEQ ID NO: 49
AAVhu.25	232	US20150315612 SEQ ID NO: 146
AAVhu.26	233	US20150159173 SEQ ID NO: 17, US20150315612 SEQ ID NO: 61
AAVhu.26	234	US20150159173 SEQ ID NO: 33, US20150315612 SEQ ID NO: 139
AAVhu.27	235	US20150315612 SEQ ID NO: 64
AAVhu.27	236	US20150315612 SEQ ID NO: 140
AAVhu.28	237	US20150315612 SEQ ID NO: 68
AAVhu.28	238	US20150315612 SEQ ID NO: 130
AAVhu.29	239	US20150315612 SEQ ID NO: 69

AAVhu.29	240	US20150159173 SEQ ID NO: 42, US20150315612 SEQ ID NO: 132
AAVhu.29	241	US20150315612 SEQ ID NO: 225
AAVhu.29R	242	US20150159173
AAVhu.3	243	US20150315612 SEQ ID NO: 44
AAVhu.3	244	US20150315612 SEQ ID NO: 145
AAVhu.30	245	US20150315612 SEQ ID NO: 70
AAVhu.30	246	US20150315612 SEQ ID NO: 131
AAVhu.31	247	US20150315612 SEQ ID NO: 1
AAVhu.31	248	US20150315612 SEQ ID NO: 121
AAVhu.32	249	US20150315612 SEQ ID NO: 2
AAVhu.32	250	US20150315612 SEQ ID NO: 122
AAVhu.33	251	US20150315612 SEQ ID NO: 75
AAVhu.33	252	US20150315612 SEQ ID NO: 124
AAVhu.34	253	US20150315612 SEQ ID NO: 72
AAVhu.34	254	US20150315612 SEQ ID NO: 125
AAVhu.35	255	US20150315612 SEQ ID NO: 73
AAVhu.35	256	US20150315612 SEQ ID NO: 164
AAVhu.36	257	US20150315612 SEQ ID NO: 74
AAVhu.36	258	US20150315612 SEQ ID NO: 126
AAVhu.37	259	US20150159173 SEQ ID NO: 34, US20150315612 SEQ ID NO: 88
AAVhu.37 (AAV106.1)	260	US20150315612 SEQ ID NO: 10, US20150159173 SEQ ID NO: 18
AAVhu.38	261	US20150315612 SEQ ID NO: 161
AAVhu.39	262	US20150315612 SEQ ID NO: 102
AAVhu.39 (AAVLG-9)	263	US20150315612 SEQ ID NO: 24
AAVhu.4	264	US20150315612 SEQ ID NO: 47
AAVhu.4	265	US20150315612 SEQ ID NO: 141
AAVhu.40	266	US20150315612 SEQ ID NO: 87
AAVhu.40 (AAV114.3)	267	US20150315612 SEQ ID NO: 11
AAVhu.41	268	US20150315612 SEQ ID NO: 91
AAVhu.41 (AAV127.2)	269	US20150315612 SEQ ID NO: 6
AAVhu.42	270	US20150315612 SEQ ID NO: 85
AAVhu.42 (AAV127.5)	271	US20150315612 SEQ ID NO: 8
AAVhu.43	272	US20150315612 SEQ ID NO: 160
AAVhu.43	273	US20150315612 SEQ ID NO: 236
AAVhu.43 (AAV128.1)	274	US20150315612 SEQ ID NO: 80
AAVhu.44	275	US20150159173 SEQ ID NO: 45, US20150315612 SEQ ID NO: 158
AAVhu.44 (AAV128.3)	276	US20150315612 SEQ ID NO: 81
AAVhu.44R1	277	US20150159173
AAVhu.44R2	278	US20150159173
AAVhu.44R3	279	US20150159173
AAVhu.45	280	US20150315612 SEQ ID NO: 76
AAVhu.45	281	US20150315612 SEQ ID NO: 127
AAVhu.46	282	US20150315612 SEQ ID NO: 82
AAVhu.46	283	US20150315612 SEQ ID NO: 159
AAVhu.46	284	US20150315612 SEQ ID NO: 224
AAVhu.47	285	US20150315612 SEQ ID NO: 77
AAVhu.47	286	US20150315612 SEQ ID NO: 128
AAVhu.48	287	US20150159173 SEQ ID NO: 38
AAVhu.48	288	US20150315612 SEQ ID NO: 157
AAVhu.48 (AAV130.4)	289	US20150315612 SEQ ID NO: 78
AAVhu.48R1	290	US20150159173
AAVhu.48R2	291	US20150159173
AAVhu.48R3	292	US20150159173
AAVhu.49	293	US20150315612 SEQ ID NO: 209
AAVhu.49	294	US20150315612 SEQ ID NO: 189

AAVhu.5	295	US20150315612 SEQ ID NO: 45
AAVhu.5	296	US20150315612 SEQ ID NO: 142
AAVhu.51	297	US20150315612 SEQ ID NO: 208
AAVhu.51	298	US20150315612 SEQ ID NO: 190
AAVhu.52	299	US20150315612 SEQ ID NO: 210
AAVhu.52	300	US20150315612 SEQ ID NO: 191
AAVhu.53	301	US20150159173 SEQ ID NO: 19
AAVhu.53	302	US20150159173 SEQ ID NO: 35
AAVhu.53 (AAV145.1)	303	US20150315612 SEQ ID NO: 176
AAVhu.54	304	US20150315612 SEQ ID NO: 188
AAVhu.54 (AAV145.5)	305	US20150315612 SEQ ID NO: 177
AAVhu.55	306	US20150315612 SEQ ID NO: 187
AAVhu.56	307	US20150315612 SEQ ID NO: 205
AAVhu.56 (AAV145.6)	308	US20150315612 SEQ ID NO: 168
AAVhu.56 (AAV145.6)	309	US20150315612 SEQ ID NO: 192
AAVhu.57	310	US20150315612 SEQ ID NO: 206
AAVhu.57	311	US20150315612 SEQ ID NO: 169
AAVhu.57	312	US20150315612 SEQ ID NO: 193
AAVhu.58	313	US20150315612 SEQ ID NO: 207
AAVhu.58	314	US20150315612 SEQ ID NO: 194
AAVhu.6 (AAV3.1)	315	US20150315612 SEQ ID NO: 5
AAVhu.6 (AAV3.1)	316	US20150315612 SEQ ID NO: 84
AAVhu.60	317	US20150315612 SEQ ID NO: 184
AAVhu.60 (AAV161.10)	318	US20150315612 SEQ ID NO: 170
AAVhu.61	319	US20150315612 SEQ ID NO: 185
AAVhu.61 (AAV161.6)	320	US20150315612 SEQ ID NO: 174
AAVhu.63	321	US20150315612 SEQ ID NO: 204
AAVhu.63	322	US20150315612 SEQ ID NO: 195
AAVhu.64	323	US20150315612 SEQ ID NO: 212
AAVhu.64	324	US20150315612 SEQ ID NO: 196
AAVhu.66	325	US20150315612 SEQ ID NO: 197
AAVhu.67	326	US20150315612 SEQ ID NO: 215
AAVhu.67	327	US20150315612 SEQ ID NO: 198
AAVhu.7	328	US20150315612 SEQ ID NO: 226
AAVhu.7	329	US20150315612 SEQ ID NO: 150
AAVhu.7 (AAV7.3)	330	US20150315612 SEQ ID NO: 55
AAVhu.71	331	US20150315612 SEQ ID NO: 79
AAVhu.8	332	US20150315612 SEQ ID NO: 53
AAVhu.8	333	US20150315612 SEQ ID NO: 12
AAVhu.8	334	US20150315612 SEQ ID NO: 151
AAVhu.9 (AAV3.1)	335	US20150315612 SEQ ID NO: 58
AAVhu.9 (AAV3.1)	336	US20150315612 SEQ ID NO: 155
AAV-LK01	337	US20150376607 SEQ ID NO: 2
AAV-LK01	338	US20150376607 SEQ ID NO: 29
AAV-LK02	339	US20150376607 SEQ ID NO: 3
AAV-LK02	340	US20150376607 SEQ ID NO: 30
AAV-LK03	341	US20150376607 SEQ ID NO: 4
AAV-LK03	342	WO2015121501 SEQ ID NO: 12, US20150376607 SEQ ID NO: 31
AAV-LK04	343	US20150376607 SEQ ID NO: 5
AAV-LK04	344	US20150376607 SEQ ID NO: 32
AAV-LK05	345	US20150376607 SEQ ID NO: 6
AAV-LK05	346	US20150376607 SEQ ID NO: 33
AAV-LK06	347	US20150376607 SEQ ID NO: 7
AAV-LK06	348	US20150376607 SEQ ID NO: 34
AAV-LK07	349	US20150376607 SEQ ID NO: 8
AAV-LK07	350	US20150376607 SEQ ID NO: 35
AAV-LK08	351	US20150376607 SEQ ID NO: 9

AAV-LK08	352	US20150376607 SEQ ID NO: 36
AAV-LK09	353	US20150376607 SEQ ID NO: 10
AAV-LK09	354	US20150376607 SEQ ID NO: 37
AAV-LK10	355	US20150376607 SEQ ID NO: 11
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AAV-LK11	357	US20150376607 SEQ ID NO: 12
AAV-LK11	358	US20150376607 SEQ ID NO: 39
AAV-LK12	359	US20150376607 SEQ ID NO: 13
AAV-LK12	360	US20150376607 SEQ ID NO: 40
AAV-LK13	361	US20150376607 SEQ ID NO: 14
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AAV-LK15	365	US20150376607 SEQ ID NO: 16
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AAV-LK16	367	US20150376607 SEQ ID NO: 17
AAV-LK16	368	US20150376607 SEQ ID NO: 44
AAV-LK17	369	US20150376607 SEQ ID NO: 18
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AAV-PAEC2	383	US20150376607 SEQ ID NO: 21
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AAV-PAEC4	385	US20150376607 SEQ ID NO: 22
AAV-PAEC4	386	US20150376607 SEQ ID NO: 55
AAV-PAEC6	387	US20150376607 SEQ ID NO: 23
AAV-PAEC6	388	US20150376607 SEQ ID NO: 52
AAV-PAEC7	389	US20150376607 SEQ ID NO: 24
AAV-PAEC7	390	US20150376607 SEQ ID NO: 53
AAV-PAEC8	391	US20150376607 SEQ ID NO: 25
AAV-PAEC8	392	US20150376607 SEQ ID NO: 50
AAVpi.1	393	US20150315612 SEQ ID NO: 28
AAVpi.1	394	US20150315612 SEQ ID NO: 93
AAVpi.2	395	US20150315612 SEQ ID NO: 30
AAVpi.2	396	US20150315612 SEQ ID NO: 95
AAVpi.3	397	US20150315612 SEQ ID NO: 29
AAVpi.3	398	US20150315612 SEQ ID NO: 94
AAVrh.10	399	US20150159173 SEQ ID NO: 9
AAVrh.10	400	US20150159173 SEQ ID NO: 25
AAV44.2	401	US20030138772 SEQ ID NO: 59
AAVrh.10 (AAV44.2)	402	US20030138772 SEQ ID NO: 81
AAV42.1B	403	US20030138772 SEQ ID NO: 90
AAVrh.12 (AAV42.1b)	404	US20030138772 SEQ ID NO: 30
AAVrh.13	405	US20150159173 SEQ ID NO: 10
AAVrh.13	406	US20150159173 SEQ ID NO: 26
AAVrh.13	407	US20150315612 SEQ ID NO: 228
AAVrh.13R	408	US20150159173

AAV42.3A	409	US20030138772 SEQ ID NO: 87
AAVrh.14 (AAV42.3a)	410	US20030138772 SEQ ID NO: 32
AAV42.5A	411	US20030138772 SEQ ID NO: 89
AAVrh.17 (AAV42.5a)	412	US20030138772 SEQ ID NO: 34
AAV42.5B	413	US20030138772 SEQ ID NO: 91
AAVrh.18 (AAV42.5b)	414	US20030138772 SEQ ID NO: 29
AAV42.6B	415	US20030138772 SEQ ID NO: 112
AAVrh.19 (AAV42.6b)	416	US20030138772 SEQ ID NO: 38
AAVrh.2	417	US20150159173 SEQ ID NO: 39
AAVrh.2	418	US20150315612 SEQ ID NO: 231
AAVrh.20	419	US20150159173 SEQ ID NO: 1
AAV42.10	420	US20030138772 SEQ ID NO: 106
AAVrh.21 (AAV42.10)	421	US20030138772 SEQ ID NO: 35
AAV42.11	422	US20030138772 SEQ ID NO: 108
AAVrh.22 (AAV42.11)	423	US20030138772 SEQ ID NO: 37
AAV42.12	424	US20030138772 SEQ ID NO: 113
AAVrh.23 (AAV42.12)	425	US20030138772 SEQ ID NO: 58
AAV42.13	426	US20030138772 SEQ ID NO: 86
AAVrh.24 (AAV42.13)	427	US20030138772 SEQ ID NO: 31
AAV42.15	428	US20030138772 SEQ ID NO: 84
AAVrh.25 (AAV42.15)	429	US20030138772 SEQ ID NO: 28
AAVrh.2R	430	US20150159173
AAVrh.31 (AAV223.1)	431	US20030138772 SEQ ID NO: 48
AAVC1	432	US20030138772 SEQ ID NO: 60
AAVrh.32 (AAVC1)	433	US20030138772 SEQ ID NO: 19
AAVrh.32/33	434	US20150159173 SEQ ID NO: 2
AAVrh.33 (AAVC3)	435	US20030138772 SEQ ID NO: 20
AAVC5	436	US20030138772 SEQ ID NO: 62
AAVrh.34 (AAVC5)	437	US20030138772 SEQ ID NO: 21
AAVF1	438	US20030138772 SEQ ID NO: 109
AAVrh.35 (AAVF1)	439	US20030138772 SEQ ID NO: 22
AAVF3	440	US20030138772 SEQ ID NO: 111
AAVrh.36 (AAVF3)	441	US20030138772 SEQ ID NO: 23
AAVrh.37	442	US20030138772 SEQ ID NO: 24
AAVrh.37	443	US20150159173 SEQ ID NO: 40
AAVrh.37	444	US20150315612 SEQ ID NO: 229
AAVrh.37R2	445	US20150159173
AAVrh.38 (AAVLG-4)	446	US20150315612 SEQ ID NO: 7
AAVrh.38 (AAVLG-4)	447	US20150315612 SEQ ID NO: 86
AAVrh.39	448	US20150159173 SEQ ID NO: 20, US20150315612 SEQ ID NO: 13
AAVrh.39	449	US20150159173 SEQ ID NO: 3, US20150159173 SEQ ID NO: 36, US20150315612 SEQ ID NO: 89
AAVrh.40	450	US20150315612 SEQ ID NO: 92
AAVrh.40 (AAVLG-10)	451	US20150315612 SEQ ID NO: 14
AAVrh.43 (AAVN721-8)	452	US20150315612 SEQ ID NO: 43, US20150159173 SEQ ID NO: 21
AAVrh.43 (AAVN721-8)	453	US20150315612 SEQ ID NO: 163, US20150159173 SEQ ID NO: 37
AAVrh.44	454	US20150315612 SEQ ID NO: 34
AAVrh.44	455	US20150315612 SEQ ID NO: 111
AAVrh.45	456	US20150315612 SEQ ID NO: 41
AAVrh.45	457	US20150315612 SEQ ID NO: 109
AAVrh.46	458	US20150159173 SEQ ID NO: 22, US20150315612 SEQ ID NO: 19
AAVrh.46	459	US20150159173 SEQ ID NO: 4, US20150315612 SEQ ID NO: 101
AAVrh.47	460	US20150315612 SEQ ID NO: 38
AAVrh.47	461	US20150315612 SEQ ID NO: 118
AAVrh.48	462	US20150159173 SEQ ID NO: 44, US20150315612 SEQ ID NO: 115

AAVrh.48.1	463	US20150159173
AAVrh.48.1.2	464	US20150159173
AAVrh.48.2	465	US20150159173
AAVrh.48 (AAV1-7)	466	US20150315612 SEQ ID NO: 32
AAVrh.49 (AAV1-8)	467	US20150315612 SEQ ID NO: 25
AAVrh.49 (AAV1-8)	468	US20150315612 SEQ ID NO: 103
AAVrh.50 (AAV2-4)	469	US20150315612 SEQ ID NO: 23
AAVrh.50 (AAV2-4)	470	US20150315612 SEQ ID NO: 108
AAVrh.51 (AAV2-5)	471	US20150315612 SEQ ID No: 22
AAVrh.51 (AAV2-5)	472	US20150315612 SEQ ID NO: 104
AAVrh.52 (AAV3-9)	473	US20150315612 SEQ ID NO: 18
AAVrh.52 (AAV3-9)	474	US20150315612 SEQ ID NO: 96
AAVrh.53	475	US20150315612 SEQ ID NO: 97
AAVrh.53 (AAV3-11)	476	US20150315612 SEQ ID NO: 17
AAVrh.53 (AAV3-11)	477	US20150315612 SEQ ID NO: 186
AAVrh.54	478	US20150315612 SEQ ID NO: 40
AAVrh.54	479	US20150159173 SEQ ID NO: 49, US20150315612 SEQ ID NO: 116
AAVrh.55	480	US20150315612 SEQ ID NO: 37
AAVrh.55 (AAV4-19)	481	US20150315612 SEQ ID NO: 117
AAVrh.56	482	US20150315612 SEQ ID NO: 54
AAVrh.56	483	US20150315612 SEQ ID NO: 152
AAVrh.57	484	US20150315612 SEQ ID NO: 26
AAVrh.57	485	US20150315612 SEQ ID NO: 105
AAVrh.58	486	US20150315612 SEQ ID NO: 27
AAVrh.58	487	US20150159173 SEQ ID NO: 48, US20150315612 SEQ ID NO: 106
AAVrh.58	488	US20150315612 SEQ ID NO: 232
AAVrh.59	489	US20150315612 SEQ ID NO: 42
AAVrh.59	490	US20150315612 SEQ ID NO: 110
AAVrh.60	491	US20150315612 SEQ ID NO: 31
AAVrh.60	492	US20150315612 SEQ ID NO: 120
AAVrh.61	493	US20150315612 SEQ ID NO: 107
AAVrh.61 (AAV2-3)	494	US20150315612 SEQ ID NO: 21
AAVrh.62 (AAV2-15)	495	US20150315612 SEQ ID No: 33
AAVrh.62 (AAV2-15)	496	US20150315612 SEQ ID NO: 114
AAVrh.64	497	US20150315612 SEQ ID No: 15
AAVrh.64	498	US20150159173 SEQ ID NO: 43, US20150315612 SEQ ID NO: 99
AAVrh.64	499	US20150315612 SEQ ID NO: 233
AAVrh.64R1	500	US20150159173
AAVrh.64R2	501	US20150159173
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AAVrh.65	503	US20150315612 SEQ ID NO: 112
AAVrh.67	504	US20150315612 SEQ ID NO: 36
AAVrh.67	505	US20150315612 SEQ ID NO: 230
AAVrh.67	506	US20150159173 SEQ ID NO: 47, US20150315612 SEQ ID NO: 113
AAVrh.68	507	US20150315612 SEQ ID NO: 16
AAVrh.68	508	US20150315612 SEQ ID NO: 100
AAVrh.69	509	US20150315612 SEQ ID NO: 39
AAVrh.69	510	US20150315612 SEQ ID NO: 119
AAVrh.70	511	US20150315612 SEQ ID NO: 20
AAVrh.70	512	US20150315612 SEQ ID NO: 98
AAVrh.71	513	US20150315612 SEQ ID NO: 162
AAVrh.72	514	US20150315612 SEQ ID NO: 9
AAVrh.73	515	US20150159173 SEQ ID NO: 5
AAVrh.74	516	US20150159173 SEQ ID NO: 6

AAVrh.8	517	US20150159173 SEQ ID NO: 41
AAVrh.8	518	US20150315612 SEQ ID NO: 235
AAVrh.8R	519	US20150159173, WO2015168666 SEQ ID NO: 9
AAVrh.8R A586R mutant	520	WO2015168666 SEQ ID NO: 10
AAVrh.8R R533A mutant	521	WO2015168666 SEQ ID NO: 11
BAAV (bovine AAV)	522	US9193769 SEQ ID NO: 8
BAAV (bovine AAV)	523	US9193769 SEQ ID NO: 10
BAAV (bovine AAV)	524	US9193769 SEQ ID NO: 4
BAAV (bovine AAV)	525	US9193769 SEQ ID NO: 2
BAAV (bovine AAV)	526	US9193769 SEQ ID NO: 6
BAAV (bovine AAV)	527	US9193769 SEQ ID NO: 1
BAAV (bovine AAV)	528	US9193769 SEQ ID NO: 5
BAAV (bovine AAV)	529	US9193769 SEQ ID NO: 3
BAAV (bovine AAV)	530	US9193769 SEQ ID NO: 11
BAAV (bovine AAV)	531	US7427396 SEQ ID NO: 5
BAAV (bovine AAV)	532	US7427396 SEQ ID NO: 6
BAAV (bovine AAV)	533	US9193769 SEQ ID NO: 7
BAAV (bovine AAV)	534	US9193769 SEQ ID NO: 9
BNP61 AAV	535	US20150238550 SEQ ID NO: 1
BNP61 AAV	536	US20150238550 SEQ ID NO: 2
BNP62 AAV	537	US20150238550 SEQ ID NO: 3
BNP63 AAV	538	US20150238550 SEQ ID NO: 4
caprine AAV	539	US7427396 SEQ ID NO: 3
caprine AAV	540	US7427396 SEQ ID NO: 4
true type AAV (ttAAV)	541	WO2015121501 SEQ ID NO: 2
AAAV (Avian AAV)	542	US9238800 SEQ ID NO: 12
AAAV (Avian AAV)	543	US9238800 SEQ ID NO: 2
AAAV (Avian AAV)	544	US9238800 SEQ ID NO: 6
AAAV (Avian AAV)	545	US9238800 SEQ ID NO: 4
AAAV (Avian AAV)	546	US9238800 SEQ ID NO: 8
AAAV (Avian AAV)	547	US9238800 SEQ ID NO: 14
AAAV (Avian AAV)	548	US9238800 SEQ ID NO: 10
AAAV (Avian AAV)	549	US9238800 SEQ ID NO: 15
AAAV (Avian AAV)	550	US9238800 SEQ ID NO: 5
AAAV (Avian AAV)	551	US9238800 SEQ ID NO: 9
AAAV (Avian AAV)	552	US9238800 SEQ ID NO: 3
AAAV (Avian AAV)	553	US9238800 SEQ ID NO: 7
AAAV (Avian AAV)	554	US9238800 SEQ ID NO: 11
AAAV (Avian AAV)	555	US9238800 SEQ ID NO: 13
AAAV (Avian AAV)	556	US9238800 SEQ ID NO: 1
AAV Shuffle 100-1	557	US20160017295 SEQ ID NO: 23
AAV Shuffle 100-1	558	US20160017295 SEQ ID NO: 11
AAV Shuffle 100-2	559	US20160017295 SEQ ID NO: 37
AAV Shuffle 100-2	560	US20160017295 SEQ ID NO: 29
AAV Shuffle 100-3	561	US20160017295 SEQ ID NO: 24
AAV Shuffle 100-3	562	US20160017295 SEQ ID NO: 12
AAV Shuffle 100-7	563	US20160017295 SEQ ID NO: 25
AAV Shuffle 100-7	564	US20160017295 SEQ ID NO: 13
AAV Shuffle 10-2	565	US20160017295 SEQ ID NO: 34
AAV Shuffle 10-2	566	US20160017295 SEQ ID NO: 26
AAV Shuffle 10-6	567	US20160017295 SEQ ID NO: 35
AAV Shuffle 10-6	568	US20160017295 SEQ ID NO: 27
AAV Shuffle 10-8	569	US20160017295 SEQ ID NO: 36
AAV Shuffle 10-8	570	US20160017295 SEQ ID NO: 28
AAV SM 100-10	571	US20160017295 SEQ ID NO: 41
AAV SM 100-10	572	US20160017295 SEQ ID NO: 33
AAV SM 100-3	573	US20160017295 SEQ ID NO: 40

AAV SM 100-3	574	US20160017295 SEQ ID NO: 32
AAV SM 10-1	575	US20160017295 SEQ ID NO: 38
AAV SM 10-1	576	US20160017295 SEQ ID NO: 30
AAV SM 10-2	577	US20160017295 SEQ ID NO: 10
AAV SM 10-2	578	US20160017295 SEQ ID NO: 22
AAV SM 10-8	579	US20160017295 SEQ ID NO: 39
AAV SM 10-8	580	US20160017295 SEQ ID NO: 31
AAVF1/HSC1	581	WO2016049230 SEQ ID NO: 20
AAVF2/HSC2	582	WO2016049230 SEQ ID NO: 21
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AAVF5/HSC5	585	WO2016049230 SEQ ID NO: 25
AAVF6/HSC6	586	WO2016049230 SEQ ID NO: 24
AAVF7/HSC7	587	WO2016049230 SEQ ID NO: 27
AAVF8/HSC8	588	WO2016049230 SEQ ID NO: 28
AAVF9/HSC9	589	WO2016049230 SEQ ID NO: 29
AAVF11/HSC11	590	WO2016049230 SEQ ID NO: 26
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AAVF13/HSC13	592	WO2016049230 SEQ ID NO: 31
AAVF14/HSC14	593	WO2016049230 SEQ ID NO: 32
AAVF15/HSC15	594	WO2016049230 SEQ ID NO: 33
AAVF16/HSC16	595	WO2016049230 SEQ ID NO: 34
AAVF17/HSC17	596	WO2016049230 SEQ ID NO: 35
AAVF1/HSC1	597	WO2016049230 SEQ ID NO: 2
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AAV CBr-E3	615	US8734809 SEQ ID NO: 15
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AAV CBr-E5	617	US8734809 SEQ ID NO: 17
AAV CBr-e5	618	US8734809 SEQ ID NO: 18
AAV CBr-E6	619	US8734809 SEQ ID NO: 19
AAV CBr-E7	620	US8734809 SEQ ID NO: 20
AAV CBr-E8	621	US8734809 SEQ ID NO: 21
AAV CLv-D1	622	US8734809 SEQ ID NO: 22
AAV CLv-D2	623	US8734809 SEQ ID NO: 23
AAV CLv-D3	624	US8734809 SEQ ID NO: 24
AAV CLv-D4	625	US8734809 SEQ ID NO: 25
AAV CLv-D5	626	US8734809 SEQ ID NO: 26
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AAV CLv-D7	628	US8734809 SEQ ID NO: 28
AAV CLv-D8	629	US8734809 SEQ ID NO: 29
AAV CLv-E1	630	US8734809 SEQ ID NO: 13

AAV CLv-R1	631	US8734809 SEQ ID NO: 30
AAV CLv-R2	632	US8734809 SEQ ID NO: 31
AAV CLv-R3	633	US8734809 SEQ ID NO: 32
AAV CLv-R4	634	US8734809 SEQ ID NO: 33
AAV CLv-R5	635	US8734809 SEQ ID NO: 34
AAV CLv-R6	636	US8734809 SEQ ID NO: 35
AAV CLv-R7	637	US8734809 SEQ ID NO: 36
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AAV CLv-R9	639	US8734809 SEQ ID NO: 38
AAV CLg-F1	640	US8734809 SEQ ID NO: 39
AAV CLg-F2	641	US8734809 SEQ ID NO: 40
AAV CLg-F3	642	US8734809 SEQ ID NO: 41
AAV CLg-F4	643	US8734809 SEQ ID NO: 42
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AAV CSp-6	654	US8734809 SEQ ID NO: 51
AAV CSp-7	655	US8734809 SEQ ID NO: 52
AAV CSp-8	656	US8734809 SEQ ID NO: 53
AAV CSp-9	657	US8734809 SEQ ID NO: 54
AAV CHt-2	658	US8734809 SEQ ID NO: 55
AAV CHt-3	659	US8734809 SEQ ID NO: 56
AAV CKd-1	660	US8734809 SEQ ID NO: 57
AAV CKd-10	661	US8734809 SEQ ID NO: 58
AAV CKd-2	662	US8734809 SEQ ID NO: 59
AAV CKd-3	663	US8734809 SEQ ID NO: 60
AAV CKd-4	664	US8734809 SEQ ID NO: 61
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AAV CLv-1	668	US8734809 SEQ ID NO: 65
AAV CLv-12	669	US8734809 SEQ ID NO: 66
AAV CLv-13	670	US8734809 SEQ ID NO: 67
AAV CLv-2	671	US8734809 SEQ ID NO: 68
AAV CLv-3	672	US8734809 SEQ ID NO: 69
AAV CLv-4	673	US8734809 SEQ ID NO: 70
AAV CLv-6	674	US8734809 SEQ ID NO: 71
AAV CLv-8	675	US8734809 SEQ ID NO: 72
AAV CKd-B1	676	US8734809 SEQ ID NO: 73
AAV CKd-B2	677	US8734809 SEQ ID NO: 74
AAV CKd-B3	678	US8734809 SEQ ID NO: 75
AAV CKd-B4	679	US8734809 SEQ ID NO: 76
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AAV CKd-B7	682	US8734809 SEQ ID NO: 79
AAV CKd-B8	683	US8734809 SEQ ID NO: 80
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AAV CKd-H2	685	US8734809 SEQ ID NO: 82
AAV CKd-H3	686	US8734809 SEQ ID NO: 83
AAV CKd-H4	687	US8734809 SEQ ID NO: 84

AAV CKd-H5	688	US8734809 SEQ ID NO: 85
AAV CKd-H6	689	US8734809 SEQ ID NO: 77
AAV CHt-1	690	US8734809 SEQ ID NO: 86
AAV CLv1-1	691	US8734809 SEQ ID NO: 171
AAV CLv1-2	692	US8734809 SEQ ID NO: 172
AAV CLv1-3	693	US8734809 SEQ ID NO: 173
AAV CLv1-4	694	US8734809 SEQ ID NO: 174
AAV Clv1-7	695	US8734809 SEQ ID NO: 175
AAV Clv1-8	696	US8734809 SEQ ID NO: 176
AAV Clv1-9	697	US8734809 SEQ ID NO: 177
AAV Clv1-10	698	US8734809 SEQ ID NO: 178
AAV VR-355	699	US8734809 SEQ ID NO: 181
AAV hu.48R3	700	US8734809 SEQ ID NO: 183
AAV CBr-E1	701	US8734809 SEQ ID NO: 87
AAV CBr-E2	702	US8734809 SEQ ID NO: 88
AAV CBr-E3	703	US8734809 SEQ ID NO: 89
AAV CBr-E4	704	US8734809 SEQ ID NO: 90
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AAV CBr-e5	706	US8734809 SEQ ID NO: 92
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AAV CBr-E7	708	US8734809 SEQ ID NO: 94
AAV CBr-E8	709	US8734809 SEQ ID NO: 95
AAV CLv-D1	710	US8734809 SEQ ID NO: 96
AAV CLv-D2	711	US8734809 SEQ ID NO: 97
AAV CLv-D3	712	US8734809 SEQ ID NO: 98
AAV CLv-D4	713	US8734809 SEQ ID NO: 99
AAV CLv-D5	714	US8734809 SEQ ID NO: 100
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AAV CLv-D7	716	US8734809 SEQ ID NO: 102
AAV CLv-D8	717	US8734809 SEQ ID NO: 103
AAV CLv-E1	718	US8734809 SEQ ID NO: 87
AAV CLv-R1	719	US8734809 SEQ ID NO: 104
AAV CLv-R2	720	US8734809 SEQ ID NO: 105
AAV CLv-R3	721	US8734809 SEQ ID NO: 106
AAV CLv-R4	722	US8734809 SEQ ID NO: 107
AAV CLv-R5	723	US8734809 SEQ ID NO: 108
AAV CLv-R6	724	US8734809 SEQ ID NO: 109
AAV CLv-R7	725	US8734809 SEQ ID NO: 110
AAV CLv-R8	726	US8734809 SEQ ID NO: 111
AAV CLv-R9	727	US8734809 SEQ ID NO: 112
AAV CLg-F1	728	US8734809 SEQ ID NO: 113
AAV CLg-F2	729	US8734809 SEQ ID NO: 114
AAV CLg-F3	730	US8734809 SEQ ID NO: 115
AAV CLg-F4	731	US8734809 SEQ ID NO: 116
AAV CLg-F5	732	US8734809 SEQ ID NO: 117
AAV CLg-F6	733	US8734809 SEQ ID NO: 117
AAV CLg-F7	734	US8734809 SEQ ID NO: 118
AAV CLg-F8	735	US8734809 SEQ ID NO: 117
AAV CSp-1	736	US8734809 SEQ ID NO: 119
AAV CSp-10	737	US8734809 SEQ ID NO: 120
AAV CSp-11	738	US8734809 SEQ ID NO: 121
AAV CSp-2	739	US8734809 SEQ ID NO: 122
AAV CSp-3	740	US8734809 SEQ ID NO: 123
AAV CSp-4	741	US8734809 SEQ ID NO: 124
AAV CSp-6	742	US8734809 SEQ ID NO: 125
AAV CSp-7	743	US8734809 SEQ ID NO: 126
AAV CSp-8	744	US8734809 SEQ ID NO: 127

AAV CSp-9	745	US8734809 SEQ ID NO: 128
AAV CHi-2	746	US8734809 SEQ ID NO: 129
AAV CHi-3	747	US8734809 SEQ ID NO: 130
AAV CKd-1	748	US8734809 SEQ ID NO: 131
AAV CKd-10	749	US8734809 SEQ ID NO: 132
AAV CKd-2	750	US8734809 SEQ ID NO: 133
AAV CKd-3	751	US8734809 SEQ ID NO: 134
AAV CKd-4	752	US8734809 SEQ ID NO: 135
AAV CKd-6	753	US8734809 SEQ ID NO: 136
AAV CKd-7	754	US8734809 SEQ ID NO: 137
AAV CKd-8	755	US8734809 SEQ ID NO: 138
AAV CLv-1	756	US8734809 SEQ ID NO: 139
AAV CLv-12	757	US8734809 SEQ ID NO: 140
AAV CLv-13	758	US8734809 SEQ ID NO: 141
AAV CLv-2	759	US8734809 SEQ ID NO: 142
AAV CLv-3	760	US8734809 SEQ ID NO: 143
AAV CLv-4	761	US8734809 SEQ ID NO: 144
AAV CLv-6	762	US8734809 SEQ ID NO: 145
AAV CLv-8	763	US8734809 SEQ ID NO: 146
AAV CKd-B1	764	US8734809 SEQ ID NO: 147
AAV CKd-B2	765	US8734809 SEQ ID NO: 148
AAV CKd-B3	766	US8734809 SEQ ID NO: 149
AAV CKd-B4	767	US8734809 SEQ ID NO: 150
AAV CKd-B5	768	US8734809 SEQ ID NO: 151
AAV CKd-B6	769	US8734809 SEQ ID NO: 152
AAV CKd-B7	770	US8734809 SEQ ID NO: 153
AAV CKd-B8	771	US8734809 SEQ ID NO: 154
AAV CKd-H1	772	US8734809 SEQ ID NO: 155
AAV CKd-H2	773	US8734809 SEQ ID NO: 156
AAV CKd-H3	774	US8734809 SEQ ID NO: 157
AAV CKd-H4	775	US8734809 SEQ ID NO: 158
AAV CKd-H5	776	US8734809 SEQ ID NO: 159
AAV CKd-H6	777	US8734809 SEQ ID NO: 151
AAV CHi-1	778	US8734809 SEQ ID NO: 160
AAV CHi-P2	779	WO2016065001 SEQ ID NO: 1
AAV CHi-P5	780	WO2016065001 SEQ ID NO: 2
AAV CHi-P9	781	WO2016065001 SEQ ID NO: 3
AAV CBr-7.1	782	WO2016065001 SEQ ID NO: 4
AAV CBr-7.2	783	WO2016065001 SEQ ID NO: 5
AAV CBr-7.3	784	WO2016065001 SEQ ID NO: 6
AAV CBr-7.4	785	WO2016065001 SEQ ID NO: 7
AAV CBr-7.5	786	WO2016065001 SEQ ID NO: 8
AAV CBr-7.7	787	WO2016065001 SEQ ID NO: 9
AAV CBr-7.8	788	WO2016065001 SEQ ID NO: 10
AAV CBr-7.10	789	WO2016065001 SEQ ID NO: 11
AAV CKd-N3	790	WO2016065001 SEQ ID NO: 12
AAV CKd-N4	791	WO2016065001 SEQ ID NO: 13
AAV CKd-N9	792	WO2016065001 SEQ ID NO: 14
AAV CLv-L4	793	WO2016065001 SEQ ID NO: 15
AAV CLv-L5	794	WO2016065001 SEQ ID NO: 16
AAV CLv-L6	795	WO2016065001 SEQ ID NO: 17
AAV CLv-K1	796	WO2016065001 SEQ ID NO: 18
AAV CLv-K3	797	WO2016065001 SEQ ID NO: 19
AAV CLv-K6	798	WO2016065001 SEQ ID NO: 20
AAV CLv-M1	799	WO2016065001 SEQ ID NO: 21
AAV CLv-M11	800	WO2016065001 SEQ ID NO: 22
AAV CLv-M2	801	WO2016065001 SEQ ID NO: 23

AAV CLv-M5	802	WO2016065001 SEQ ID NO: 24
AAV CLv-M6	803	WO2016065001 SEQ ID NO: 25
AAV CLv-M7	804	WO2016065001 SEQ ID NO: 26
AAV CLv-M8	805	WO2016065001 SEQ ID NO: 27
AAV CLv-M9	806	WO2016065001 SEQ ID NO: 28
AAV CHt-P1	807	WO2016065001 SEQ ID NO: 29
AAV CHt-P6	808	WO2016065001 SEQ ID NO: 30
AAV CHt-P8	809	WO2016065001 SEQ ID NO: 31
AAV CHt-6.1	810	WO2016065001 SEQ ID NO: 32
AAV CHt-6.10	811	WO2016065001 SEQ ID NO: 33
AAV CHt-6.5	812	WO2016065001 SEQ ID NO: 34
AAV CHt-6.6	813	WO2016065001 SEQ ID NO: 35
AAV CHt-6.7	814	WO2016065001 SEQ ID NO: 36
AAV CHt-6.8	815	WO2016065001 SEQ ID NO: 37
AAV CSp-8.10	816	WO2016065001 SEQ ID NO: 38
AAV CSp-8.2	817	WO2016065001 SEQ ID NO: 39
AAV CSp-8.4	818	WO2016065001 SEQ ID NO: 40
AAV CSp-8.5	819	WO2016065001 SEQ ID NO: 41
AAV CSp-8.6	820	WO2016065001 SEQ ID NO: 42
AAV CSp-8.7	821	WO2016065001 SEQ ID NO: 43
AAV CSp-8.8	822	WO2016065001 SEQ ID NO: 44
AAV CSp-8.9	823	WO2016065001 SEQ ID NO: 45
AAV CBr-B7.3	824	WO2016065001 SEQ ID NO: 46
AAV CBr-B7.4	825	WO2016065001 SEQ ID NO: 47
AAV3B	826	WO2016065001 SEQ ID NO: 48
AAV4	827	WO2016065001 SEQ ID NO: 49
AAV5	828	WO2016065001 SEQ ID NO: 50
AAV CHt-P2	829	WO2016065001 SEQ ID NO: 51
AAV CHt-P5	830	WO2016065001 SEQ ID NO: 52
AAV CHt-P9	831	WO2016065001 SEQ ID NO: 53
AAV CBr-7.1	832	WO2016065001 SEQ ID NO: 54
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AAV CBr-7.3	834	WO2016065001 SEQ ID NO: 56
AAV CBr-7.4	835	WO2016065001 SEQ ID NO: 57
AAV CBr-7.5	836	WO2016065001 SEQ ID NO: 58
AAV CBr-7.7	837	WO2016065001 SEQ ID NO: 59
AAV CBr-7.8	838	WO2016065001 SEQ ID NO: 60
AAV CBr-7.10	839	WO2016065001 SEQ ID NO: 61
AAV CKd-N3	840	WO2016065001 SEQ ID NO: 62
AAV CKd-N4	841	WO2016065001 SEQ ID NO: 63
AAV CKd-N9	842	WO2016065001 SEQ ID NO: 64
AAV CLv-L4	843	WO2016065001 SEQ ID NO: 65
AAV CLv-L5	844	WO2016065001 SEQ ID NO: 66
AAV CLv-L6	845	WO2016065001 SEQ ID NO: 67
AAV CLv-K1	846	WO2016065001 SEQ ID NO: 68
AAV CLv-K3	847	WO2016065001 SEQ ID NO: 69
AAV CLv-K6	848	WO2016065001 SEQ ID NO: 70
AAV CLv-M1	849	WO2016065001 SEQ ID NO: 71
AAV CLv-M11	850	WO2016065001 SEQ ID NO: 72
AAV CLv-M2	851	WO2016065001 SEQ ID NO: 73
AAV CLv-M5	852	WO2016065001 SEQ ID NO: 74
AAV CLv-M6	853	WO2016065001 SEQ ID NO: 75
AAV CLv-M7	854	WO2016065001 SEQ ID NO: 76
AAV CLv-M8	855	WO2016065001 SEQ ID NO: 77
AAV CLv-M9	856	WO2016065001 SEQ ID NO: 78
AAV CHt-P1	857	WO2016065001 SEQ ID NO: 79
AAV CHt-P6	858	WO2016065001 SEQ ID NO: 80

AAV CHt-P8	859	WO2016065001 SEQ ID NO: 81
AAV CHt-6.1	860	WO2016065001 SEQ ID NO: 82
AAV CHt-6.10	861	WO2016065001 SEQ ID NO: 83
AAV CHt-6.5	862	WO2016065001 SEQ ID NO: 84
AAV CHt-6.6	863	WO2016065001 SEQ ID NO: 85
AAV CHt-6.7	864	WO2016065001 SEQ ID NO: 86
AAV CHt-6.8	865	WO2016065001 SEQ ID NO: 87
AAV CSp-8.10	866	WO2016065001 SEQ ID NO: 88
AAV CSp-8.2	867	WO2016065001 SEQ ID NO: 89
AAV CSp-8.4	868	WO2016065001 SEQ ID NO: 90
AAV CSp-8.5	869	WO2016065001 SEQ ID NO: 91
AAV CSp-8.6	870	WO2016065001 SEQ ID NO: 92
AAV CSp-8.7	871	WO2016065001 SEQ ID NO: 93
AAV CSp-8.8	872	WO2016065001 SEQ ID NO: 94
AAV CSp-8.9	873	WO2016065001 SEQ ID NO: 95
AAV CBr-B7.3	874	WO2016065001 SEQ ID NO: 96
AAV CBr-B7.4	875	WO2016065001 SEQ ID NO: 97
AAV3B	876	WO2016065001 SEQ ID NO: 98
AAV4	877	WO2016065001 SEQ ID NO: 99
AAV5	878	WO2016065001 SEQ ID NO: 100
GPV	879	US9624274B2 SEQ ID NO: 192
B19	880	US9624274B2 SEQ ID NO: 193
MVM	881	US9624274B2 SEQ ID NO: 194
FPV	882	US9624274B2 SEQ ID NO: 195
CPV	883	US9624274B2 SEQ ID NO: 196
AAV6	884	US9546112B2 SEQ ID NO: 5
AAV6	885	US9457103B2 SEQ ID NO: 1
AAV2	886	US9457103B2 SEQ ID NO: 2
ShH10	887	US9457103B2 SEQ ID NO: 3
ShH13	888	US9457103B2 SEQ ID NO: 4
ShH10	889	US9457103B2 SEQ ID NO: 5
ShH10	890	US9457103B2 SEQ ID NO: 6
ShH10	891	US9457103B2 SEQ ID NO: 7
ShH10	892	US9457103B2 SEQ ID NO: 8
ShH10	893	US9457103B2 SEQ ID NO: 9
rh74	894	US9434928B2 SEQ ID NO: 1, US2015023924A1 SEQ ID NO: 2
rh74	895	US9434928B2 SEQ ID NO: 2, US2015023924A1 SEQ ID NO: 1
AAV8	896	US9434928B2 SEQ ID NO: 4
rh74	897	US9434928B2 SEQ ID NO: 5
rh74 (RHM4-1)	898	US2015023924A1 SEQ ID NO: 5, US20160375110A1 SEQ ID NO: 4
rh74 (RHM15-1)	899	US2015023924A1 SEQ ID NO: 6, US20160375110A1 SEQ ID NO: 5
rh74 (RHM15-2)	900	US2015023924A1 SEQ ID NO: 7, US20160375110A1 SEQ ID NO: 6
rh74 (RHM15-3/RHM15-5)	901	US2015023924A1 SEQ ID NO: 8, US20160375110A1 SEQ ID NO: 7
rh74 (RHM15-4)	902	US2015023924A1 SEQ ID NO: 9, US20160375110A1 SEQ ID NO: 8
rh74 (RHM15-6)	903	US2015023924A1 SEQ ID NO: 10, US20160375110A1 SEQ ID NO: 9
rh74 (RHM4-1)	904	US2015023924A1 SEQ ID NO: 11
rh74 (RHM15-1)	905	US2015023924A1 SEQ ID NO: 12
rh74 (RHM15-2)	906	US2015023924A1 SEQ ID NO: 13
rh74 (RHM15-3/RHM15-5)	907	US2015023924A1 SEQ ID NO: 14
rh74 (RHM15-4)	908	US2015023924A1 SEQ ID NO: 15
rh74 (RHM15-6)	909	US2015023924A1 SEQ ID NO: 16

AAV2 (comprising lung specific polypeptide)	910	US20160175389A1 SEQ ID NO: 9
AAV2 (comprising lung specific polypeptide)	911	US20160175389A1 SEQ ID NO: 10
Anc80	912	US20170051257A1 SEQ ID NO: 1
Anc80	913	US20170051257A1 SEQ ID NO: 2
Anc81	914	US20170051257A1 SEQ ID NO: 3
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Anc94	922	US20170051257A1 SEQ ID NO: 11
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Anc113	924	US20170051257A1 SEQ ID NO: 13
Anc113	925	US20170051257A1 SEQ ID NO: 14
Anc126	926	US20170051257A1 SEQ ID NO: 15
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Anc80L62	933	US20170051257A1 SEQ ID NO: 22
Anc80L65	934	US20170051257A1 SEQ ID NO: 23
Anc80L33	935	US20170051257A1 SEQ ID NO: 24
Anc80L36	936	US20170051257A1 SEQ ID NO: 25
Anc80L44	937	US20170051257A1 SEQ ID NO: 26
Anc80L1	938	US20170051257A1 SEQ ID NO: 35
Anc80L1	939	US20170051257A1 SEQ ID NO: 36
AAV-X1	940	US8283151B2 SEQ ID NO: 11
AAV-X1b	941	US8283151B2 SEQ ID NO: 12
AAV-X5	942	US8283151B2 SEQ ID NO: 13
AAV-X19	943	US8283151B2 SEQ ID NO: 14
AAV-X21	944	US8283151B2 SEQ ID NO: 15
AAV-X22	945	US8283151B2 SEQ ID NO: 16
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AAV-X25	948	US8283151B2 SEQ ID NO: 19
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AAV-X1	950	US8283151B2 SEQ ID NO: 21
AAV-X1b	951	US8283151B2 SEQ ID NO: 22
AAV-X5	952	US8283151B2 SEQ ID NO: 23
AAV-X19	953	US8283151B2 SEQ ID NO: 24
AAV-X21	954	US8283151B2 SEQ ID NO: 25
AAV-X22	955	US8283151B2 SEQ ID NO: 26
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AAV-X26	959	US8283151B2 SEQ ID NO: 30
AAVrh8	960	WO2016054554A1 SEQ ID NO: 8
AAVrh8VP2FC5	961	WO2016054554A1 SEQ ID NO: 9
AAVrh8VP2FC44	962	WO2016054554A1 SEQ ID NO: 10
AAVrh8VP2ApoB100	963	WO2016054554A1 SEQ ID NO: 11
AAVrh8VP2RVG	964	WO2016054554A1 SEQ ID NO: 12

AAVrh8VP2Angiopep-2 VP2	965	WO2016054554A1 SEQ ID NO: 13
AAV9.47VP1.3	966	WO2016054554A1 SEQ ID NO: 14
AAV9.47VP2ICAMg3	967	WO2016054554A1 SEQ ID NO: 15
AAV9.47VP2RVG	968	WO2016054554A1 SEQ ID NO: 16
AAV9.47VP2Angiopep-2	969	WO2016054554A1 SEQ ID NO: 17
AAV9.47VP2A-string	970	WO2016054554A1 SEQ ID NO: 18
AAVrh8VP2FC5 VP2	971	WO2016054554A1 SEQ ID NO: 19
AAVrh8VP2FC44 VP2	972	WO2016054554A1 SEQ ID NO: 20
AAVrh8VP2ApoB100 VP2	973	WO2016054554A1 SEQ ID NO: 21
AAVrh8VP2RVG VP2	974	WO2016054554A1 SEQ ID NO: 22
AAVrh8VP2Angiopep-2 VP2	975	WO2016054554A1 SEQ ID NO: 23
AAV9.47VP2ICAMg3 VP2	976	WO2016054554A1 SEQ ID NO: 24
AAV9.47VP2RVG VP2	977	WO2016054554A1 SEQ ID NO: 25
AAV9.47VP2Angiopep-2 VP2	978	WO2016054554A1 SEQ ID NO: 26
AAV9.47VP2A-string VP2	979	WO2016054554A1 SEQ ID NO: 27
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rAAV-L1	992	WO2016054557A1 SEQ ID NO: 13
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rAAV-L4	995	WO2016054557A1 SEQ ID NO: 16
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rAAV	1020	WO2016081811A1 SEQ ID NO: 24
rAAV	1021	WO2016081811A1 SEQ ID NO: 25

rAAV	1022	WO2016081811A1 SEQ ID NO: 26
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rAAV	1078	WO2016081811A1 SEQ ID NO: 82

rAAV	1079	WO2016081811A1 SEQ ID NO: 83
rAAV	1080	WO2016081811A1 SEQ ID NO: 84
rAAV	1081	WO2016081811A1 SEQ ID NO: 85
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rAAV	1092	WO2016081811A1 SEQ ID NO: 96
rAAV	1093	WO2016081811A1 SEQ ID NO: 97
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rAAV	1098	WO2016081811A1 SEQ ID NO: 102
rAAV	1099	WO2016081811A1 SEQ ID NO: 103
rAAV	1100	WO2016081811A1 SEQ ID NO: 104
rAAV	1101	WO2016081811A1 SEQ ID NO: 105
rAAV	1102	WO2016081811A1 SEQ ID NO: 106
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rAAV	1122	WO2016081811A1 SEQ ID NO: 126
rAAV	1123	WO2016081811A1 SEQ ID NO: 127
rAAV	1124	WO2016081811A1 SEQ ID NO: 128
AAV8 E532K	1125	WO2016081811A1 SEQ ID NO: 133
AAV8 E532K	1126	WO2016081811A1 SEQ ID NO: 134
rAAV4	1127	WO2016115382A1 SEQ ID NO: 2
rAAV4	1128	WO2016115382A1 SEQ ID NO: 3
rAAV4	1129	WO2016115382A1 SEQ ID NO: 4
rAAV4	1130	WO2016115382A1 SEQ ID NO: 5
rAAV4	1131	WO2016115382A1 SEQ ID NO: 6
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rAAV4	1133	WO2016115382A1 SEQ ID NO: 8
rAAV4	1134	WO2016115382A1 SEQ ID NO: 9
rAAV4	1135	WO2016115382A1 SEQ ID NO: 10

rAAV4	1136	WO2016115382A1 SEQ ID NO: 11
rAAV4	1137	WO2016115382A1 SEQ ID NO: 12
rAAV4	1138	WO2016115382A1 SEQ ID NO: 13
rAAV4	1139	WO2016115382A1 SEQ ID NO: 14
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AAV11	1147	WO2016115382A1 SEQ ID NO: 22
AAV12	1148	WO2016115382A1 SEQ ID NO: 23
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rAAV4	1157	WO2016115382A1 SEQ ID NO: 33
AAV2/8	1158	WO2016131981A1 SEQ ID NO: 47
AAV2/8	1159	WO2016131981A1 SEQ ID NO: 48
ancestral AAV	1160	WO2016154344A1 SEQ ID NO: 7
ancestral AAV variant C4	1161	WO2016154344A1 SEQ ID NO: 13
ancestral AAV variant C7	1162	WO2016154344A1 SEQ ID NO: 14
ancestral AAV variant G4	1163	WO2016154344A1 SEQ ID NO: 15
consensus amino acid sequence of ancestral AAV variants, C4, C7 and G4	1164	WO2016154344A1 SEQ ID NO: 16
consensus amino acid sequence of ancestral AAV variants, C4 and C7	1165	WO2016154344A1 SEQ ID NO: 17
AAV8 (with a AAV2 phospholipase domain)	1166	WO2016150403A1 SEQ ID NO: 13
AAV VR-942n	1167	US20160289275A1 SEQ ID NO: 10
AAV5-A (M569V)	1168	US20160289275A1 SEQ ID NO: 13
AAV5-A (M569V)	1169	US20160289275A1 SEQ ID NO: 14
AAV5-A (Y585V)	1170	US20160289275A1 SEQ ID NO: 16
AAV5-A (Y585V)	1171	US20160289275A1 SEQ ID NO: 17
AAV5-A (L587T)	1172	US20160289275A1 SEQ ID NO: 19
AAV5-A (L587T)	1173	US20160289275A1 SEQ ID NO: 20
AAV5-A (Y585V/L587T)	1174	US20160289275A1 SEQ ID NO: 22
AAV5-A (Y585V/L587T)	1175	US20160289275A1 SEQ ID NO: 23
AAV5-B (D652A)	1176	US20160289275A1 SEQ ID NO: 25
AAV5-B (D652A)	1177	US20160289275A1 SEQ ID NO: 26
AAV5-B (T362M)	1178	US20160289275A1 SEQ ID NO: 28
AAV5-B (T362M)	1179	US20160289275A1 SEQ ID NO: 29
AAV5-B (Q359D)	1180	US20160289275A1 SEQ ID NO: 31
AAV5-B (Q359D)	1181	US20160289275A1 SEQ ID NO: 32
AAV5-B (E350Q)	1182	US20160289275A1 SEQ ID NO: 34
AAV5-B (E350Q)	1183	US20160289275A1 SEQ ID NO: 35
AAV5-B (P533S)	1184	US20160289275A1 SEQ ID NO: 37
AAV5-B (P533S)	1185	US20160289275A1 SEQ ID NO: 38
AAV5-B (P533G)	1186	US20160289275A1 SEQ ID NO: 40
AAV5-B (P533G)	1187	US20160289275A1 SEQ ID NO: 41

AAV5-mutation in loop VII	1188	US20160289275A1 SEQ ID NO: 43
AAV5-mutation in loop VII	1189	US20160289275A1 SEQ ID NO: 44
AAV8	1190	US20160289275A1 SEQ ID NO: 47
Mut A (LK03/AAV8)	1191	WO2016181123A1 SEQ ID NO: 1
Mut B (LK03/AAV5)	1192	WO2016181123A1 SEQ ID NO: 2
Mut C (AAV8/AAV3B)	1193	WO2016181123A1 SEQ ID NO: 3
Mut D (AAV5/AAV3B)	1194	WO2016181123A1 SEQ ID NO: 4
Mut E (AAV8/AAV3B)	1195	WO2016181123A1 SEQ ID NO: 5
Mut F (AAV3B/AAV8)	1196	WO2016181123A1 SEQ ID NO: 6
AAV44.9	1197	WO2016183297A1 SEQ ID NO: 4
AAV44.9	1198	WO2016183297A1 SEQ ID NO: 5
AAVrh8	1199	WO2016183297A1 SEQ ID NO: 6
AAV44.9 (S470N)	1200	WO2016183297A1 SEQ ID NO: 9
rh74 VP1	1201	US20160375110A1 SEQ ID NO: 1
AAV-LK03 (L125I)	1202	WO2017015102A1 SEQ ID NO: 5
AAV3B (S663V+T492V)	1203	WO2017015102A1 SEQ ID NO: 6
Anc80	1204	WO2017019994A2 SEQ ID NO: 1
Anc80	1205	WO2017019994A2 SEQ ID NO: 2
Anc81	1206	WO2017019994A2 SEQ ID NO: 3
Anc81	1207	WO2017019994A2 SEQ ID NO: 4
Anc82	1208	WO2017019994A2 SEQ ID NO: 5
Anc82	1209	WO2017019994A2 SEQ ID NO: 6
Anc83	1210	WO2017019994A2 SEQ ID NO: 7
Anc83	1211	WO2017019994A2 SEQ ID NO: 8
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Anc80L62	1225	WO2017019994A2 SEQ ID NO: 22
Anc80L65	1226	WO2017019994A2 SEQ ID NO: 23
Anc80L33	1227	WO2017019994A2 SEQ ID NO: 24
Anc80L36	1228	WO2017019994A2 SEQ ID NO: 25
Anc80L44	1229	WO2017019994A2 SEQ ID NO: 26
Anc80L1	1230	WO2017019994A2 SEQ ID NO: 35
Anc80L1	1231	WO2017019994A2 SEQ ID NO: 36
AAVrh10	1232	WO2017019994A2 SEQ ID NO: 41
Anc110	1233	WO2017019994A2 SEQ ID NO: 42
Anc110	1234	WO2017019994A2 SEQ ID NO: 43
AAVrh32.33	1235	WO2017019994A2 SEQ ID NO: 45
AAVrh74	1236	WO2017049031A1 SEQ ID NO: 1
AAV2	1237	WO2017053629A2 SEQ ID NO: 49
AAV2	1238	WO2017053629A2 SEQ ID NO: 50
AAV2	1239	WO2017053629A2 SEQ ID NO: 82
Parvo-like virus	1240	WO2017070476A2 SEQ ID NO: 1
Parvo-like virus	1241	WO2017070476A2 SEQ ID NO: 2
Parvo-like virus	1242	WO2017070476A2 SEQ ID NO: 3
Parvo-like virus	1243	WO2017070476A2 SEQ ID NO: 4
Parvo-like virus	1244	WO2017070476A2 SEQ ID NO: 5

Parvo-like virus	1245	WO2017070476A2 SEQ ID NO: 6
AAVrh.10	1246	WO2017070516A1 SEQ ID NO: 7
AAVrh.10	1247	WO2017070516A1 SEQ ID NO: 14
AAV2iYF	1248	WO2017070491A1 SEQ ID NO: 1
AAV-SPK	1249	WO2017075619A1 SEQ ID NO:28
AAV2.5	1250	US20170128528A1 SEQ ID NO: 13
AAV1.1	1251	US20170128528A1 SEQ ID NO: 15
AAV6.1	1252	US20170128528A1 SEQ ID NO: 17
AAV6.3.1	1253	US20170128528A1 SEQ ID NO: 18
AAV2i8	1254	US20170128528A1 SEQ ID NO: 28
AAV2i8	1255	US20170128528A1 SEQ ID NO: 29
ttAAV	1256	US20170128528A1 SEQ ID NO: 30
ttAAV-S312N	1257	US20170128528A1 SEQ ID NO: 32
ttAAV-S312N	1258	US20170128528A1 SEQ ID NO: 33
AAV6 (Y705, Y731, and T492)	1259	WO2016134337A1 SEQ ID NO: 24
AAV2	1260	WO2016134375A1 SEQ ID NO: 9
AAV2	1261	WO2016134375A1 SEQ ID NO: 10

[0549] Each of the patents, applications and or publications listed in Table 6 are hereby incorporated by reference in their entirety.

[0550] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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: 138 and 137 respectively herein), PHP.B (SEQ ID NO: 8 and 9 of WO2015038958, herein SEQ ID NO: 5 and 6), G2B-13 (SEQ ID NO: 12 of WO2015038958, herein SEQ ID NO: 7), G2B-26 (SEQ ID NO: 13 of WO2015038958, herein SEQ ID NO: 5), TH1.1-32 (SEQ ID NO: 14 of WO2015038958, herein SEQ ID NO: 8), TH1.1-35 (SEQ ID NO: 15 of WO2015038958, herein SEQ ID NO: 9) or variants thereof.

[0551] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid described herein does not comprise an insert sequence present immediately subsequent to position 586, 588, or 589 numbered relative to SEQ ID NO: 138, having at least 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, of any of the following amino acid sequences, TLAVPFK (SEQ ID NO: 1262), KFPVALT (SEQ ID NO: 1263), LAVPFK (SEQ ID NO: 1264), AVPFK (SEQ ID NO: 1265), VPFK (SEQ ID NO: 1266), TLAVPF (SEQ ID NO: 1267), TLAVP (SEQ ID NO: 1268), TLAV (SEQ ID NO: 1269), SVSKPFL (SEQ ID NO: 1270), FTLTPPK (SEQ ID NO: 1271), MNATKNV (SEQ ID NO: 1272), QSSQTPR (SEQ ID NO: 1273), ILGTGTS (SEQ ID NO: 1274), TRTNPEA (SEQ ID NO: 1275), NGGTSSS (SEQ ID NO: 1276), or YTLSQGW (SEQ ID NO: 1277); or encoded by a nucleotide sequence of any of SEQ ID NO: 1278, SEQ ID NO: 1279, SEQ ID NO: 1280, SEQ ID NO: 1281,

SEQ ID NO: 1282, SEQ ID NO: 1283, SEQ ID NO: 1284, SEQ ID NO: 1285, SEQ ID NO: 1286, or SEQ ID NO: 1287.

[0552] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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: 11), PHP.N (SEQ ID NO: 4), PHP.S (SEQ ID NO: 10), or variants thereof.

[0553] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid described herein does not comprise an insert sequence present immediately subsequent to position 586, 588, or 589 numbered relative to SEQ ID NO: 138, having at least 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, of the targeting peptides or amino acid inserts described in WO2017100671.

[0554] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid described herein does not comprise an insert sequence present immediately subsequent to position 586, 588, or 589 numbered relative to SEQ ID NO: 138, having at least 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, of any of the following amino acid sequences, AQLAVPFKAQ (SEQ ID NO: 1288), AQSVPFLAQ (SEQ ID NO: 1289), AQFTLTTPKAQ (SEQ ID NO: 1290), DGTAVPFKAQ (SEQ ID NO: 1291), ESTLAVPFKAQ (SEQ ID NO: 1292), GGTAVPFKAQ (SEQ ID NO: 1293), AQLATPFKAQ (SEQ ID NO: 1294), ATLATPFKAQ (SEQ ID NO: 1295), DGLATPFKAQ (SEQ ID NO: 1296), GGLATPFKAQ (SEQ ID NO: 1297), SGSLAVPFKAQ (SEQ ID NO: 1298), AQLAQPFKAQ (SEQ ID NO: 1299), AQLQPFKAQ (SEQ ID NO: 1300), AQLSNPFKAQ (SEQ ID NO: 1301), AQLAVPFSNP (SEQ ID NO: 1302), QGTAVPFKAQ (SEQ ID NO: 1303), NQLAVPFKAQ (SEQ ID NO: 1304), EGSLAVPFKAQ (SEQ ID NO: 1305), SGNLAVPFKAQ (SEQ ID NO: 1306), EGTAVPFKAQ (SEQ ID NO: 1307), DSTAVPFKAQ (SEQ ID NO: 1308), AVTLAVPFKAQ (SEQ ID NO: 1309), AQLSTPFKAQ (SEQ ID NO: 1310), AQLPQPFKAQ (SEQ ID NO: 1311), AQLSQPFKAQ (SEQ ID NO: 1312), AQLQLPFKAQ (SEQ ID NO: 1313), AQLTMPFKAQ (SEQ ID NO: 1314), AQLTTPFKAQ (SEQ ID NO: 1315), AQYLSQGW (SEQ ID NO: 1316), AQMNATKNVAQ (SEQ ID NO: 1317), AQVSGGHSAQ (SEQ ID NO: 1318), AQLTAPFKAQ (SEQ ID NO: 1319), AQLSKPFKAQ (SEQ ID NO: 1320), QAVRTSL (SEQ ID NO: 1321), YTLSQGW (SEQ ID NO: 1277), LAKERLS (SEQ ID NO: 1322), TLAVPFK (SEQ ID NO: 1262), SVSKPFL (SEQ ID NO: 1270), FTLTTPK (SEQ ID NO: 1271), MNSTKNV (SEQ ID NO: 1323), VSGGHHS (SEQ ID NO: 1324), SAQLAVPFKAQ (SEQ ID NO: 1325), SXXXLAVPFKAQ (wherein X may be any amino acid; SEQ ID NO: 1326), SAQXXXVPFKAQ (wherein X may be any amino acid; SEQ ID NO: 1327),

SAQTLXXXFKAQAAQ (wherein X may be any amino acid; SEQ ID NO: 1328),
 SAQTLAVXXXAQAQ (wherein X may be any amino acid; SEQ ID NO: 1329),
 SAQTLAVPFXXXAQAQ (wherein X may be any amino acid; SEQ ID NO: 1330), TNHQSAQ (SEQ ID NO: 1331), AQAQTGW (SEQ ID NO: 1332), DGTLATPFK (SEQ ID NO: 1333), DGTLATPFKXX (wherein X may be any amino acid; SEQ ID NO: 1334), LAVPFKAQ (SEQ ID NO: 1335), VPFKAQ (SEQ ID NO: 1336), FKAQ (SEQ ID NO: 1337), AQTAV (SEQ ID NO: 1338), AQTAVPF (SEQ ID NO: 1339), QAVR (SEQ ID NO: 1340), AVRT (SEQ ID NO: 1341), VRTS (SEQ ID NO: 1342), RTSL (SEQ ID NO: 1343), QAVRT (SEQ ID NO: 1344), AVRTS (SEQ ID NO: 1345), VRTSL (SEQ ID NO: 1346), QAVRTS (SEQ ID NO: 1347), or AVRTSL (SEQ ID NO: 1348); or encoded by a nucleotide sequence of any of SEQ ID NO: 1349, SEQ ID NO: 1350, SEQ ID NO: 1351, SEQ ID NO: 1352, SEQ ID NO: 1353, SEQ ID NO: 1354, SEQ ID NO: 1355, SEQ ID NO: 1356, SEQ ID NO: 1357, SEQ ID NO: 1358 (wherein N may be A, C, T, or G), SEQ ID NO: 1359 (wherein N may be A, C, T, or G), SEQ ID NO: 1360 (wherein N may be A, C, T, or G), SEQ ID NO: 1361 (wherein N may be A, C, T, or G), SEQ ID NO: 1362 (wherein N may be A, C, T, or G), SEQ ID NO: 1279, SEQ ID NO: 1280, SEQ ID NO: 1281, SEQ ID NO: 1287, or SEQ ID NO: 1363.

[0555] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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: 879), B19 (SEQ ID NO: 193 of US9624274; herein SEQ ID NO: 880), MVM (SEQ ID NO: 194 of US9624274; herein SEQ ID NO: 881), FPV (SEQ ID NO: 195 of US9624274; herein SEQ ID NO: 882), CPV (SEQ ID NO: 196 of US9624274; herein SEQ ID NO: 883) or variants thereof.

[0556] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid described herein does not comprise an insert sequence present immediately subsequent to position 586, 588, or 589 numbered relative to SEQ ID NO: 138, having at least 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, of any of the structural protein inserts described in US 9624274 or any of the following amino acid sequences, VNLTWSRASG (SEQ ID NO: 1364), EFCINHRGYWVCGD (SEQ ID NO: 1365), EDGQVMDVDLS (SEQ ID NO: 1366), EKQRNGTLT (SEQ ID NO: 1367), TYQCRVTHPHLPRALMR (SEQ ID NO: 1368), RHSTTQPRKTKGSG (SEQ ID NO: 1369),

DSNPRGVSAAYLSR (SEQ ID NO: 1370), TITCLWDLAPSK (SEQ ID NO: 1371), KTKGSGFFVF (SEQ ID NO: 1372), THPHLPRLMRS (SEQ ID NO: 1373), GETYQCRVTHPHLPRLMRSTTK (SEQ ID NO: 1374), LPRALMRS (SEQ ID NO: 1375), INHRGYWV (SEQ ID NO: 1376), CDAGSVRTNAPD (SEQ ID NO: 1377), AKAVSNLTESRSESLS (SEQ ID NO: 1378), SLTGDEFKKVLET (SEQ ID NO: 1379), REAVAYRFEED (SEQ ID NO: 1380), INPEITLDG (SEQ ID NO: 1381), DISVTGAPVITATYL (SEQ ID NO: 1382), DISVTGAPVITA (SEQ ID NO: 1383), PKTVSNLTESSESVSQS (SEQ ID NO: 1384), SLMGDEFKAVLET (SEQ ID NO: 1385), QHSVAYTFEED (SEQ ID NO: 1386), INPEITRDG (SEQ ID NO: 1387), DISLTGDPVITASYL (SEQ ID NO: 1388), DISLTGDPVITA (SEQ ID NO: 1389), DQSIDFEIDSA (SEQ ID NO: 1390), KNVSEDLPLPTFSPTLLGDS (SEQ ID NO: 1391), KNVSEDLPLPT (SEQ ID NO: 1392), CDSGRVRTDAPD (SEQ ID NO: 1393), FPEHLLVDFLQSL (SEQ ID NO: 1394), DAEFRHDSG (SEQ ID NO: 1395), HYAAAQWDFGNTMCQL (SEQ ID NO: 1396), YAAQWDFGNTMCQ (SEQ ID NO: 1397), RSQKEGLHYT (SEQ ID NO: 1398), SSRTPSDKPVAHWANPQAE (SEQ ID NO: 1399), SRTPSDKPVAHWANP (SEQ ID NO: 1400), SSRTPSDKP (SEQ ID NO: 1401), NADGNVDYHMNSVP (SEQ ID NO: 1402), DGNVDYHMNSV (SEQ ID NO: 1403), RSFKEFLQSSLRALRQ (SEQ ID NO: 1404), FKEFLQSSLRA (SEQ ID NO: 1405), or QMWAPQWGP (SEQ ID NO: 1406).

[0557] In some embodiments, the AAV serotype, the parent AAV capsid polypeptide, or the AAV capsid variant may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, a sequence as described in United States Patent No. US9475845, the contents of which are herein incorporated by reference in their entirety.

[0558] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid described herein does not comprise an insert sequence present immediately subsequent to position 586, 588, or 589 numbered relative to SEQ ID NO: 138, having at least 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, of any of the amino acid sequences of RGNRQA (SEQ ID NO: 1407), SSSTDP (SEQ ID NO: 1408), SSNTAP (SEQ ID NO: 1409), SNSNLP (SEQ ID NO: 1410), SSTTAP (SEQ ID NO: 1411), AANTAA (SEQ ID NO: 1412), QQNTAP (SEQ ID NO: 1413), SAQAQA (n SEQ ID NO: 1414), QANTGP (SEQ ID NO: 1415), NATTAP (SEQ ID NO: 1416), SSTAGP (SEQ ID NO: 1417), QQNTAA (SEQ ID NO: 1418), PSTAGP (SEQ ID NO: 1419), NQNTAP (SEQ ID NO: 1420), QAANAP (SEQ ID NO: 1421), SIVGLP (SEQ ID NO: 1422), AASTAA (SEQ ID NO: 1423), SQNTTA (SEQ ID NO: 1424), QQDTAP (SEQ ID NO: 1425), QTNTGP (SEQ ID NO: 1426), QTNGAP (SEQ ID NO: 1427), QQNAAP (SEQ ID NO: 1428), or AANTQA (SEQ ID NO: 1429).

[0559] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid described herein may further comprise an amino acid modification, e.g., a

substitution or insertion, at amino acid positions 262 through 265, numbered according to the AAV2 capsid protein or the corresponding position in the capsid protein of another AAV with a targeting sequence, e.g., of any of the amino acid sequences of, NGRAHA (SEQ ID NO: 1430), QPEHSST (SEQ ID NO: 1431), VNTANST (SEQ ID NO: 1432), HGPMQKS (SEQ ID NO: 1433), PHKPPLA (SEQ ID NO: 1434), IKNNEMW (SEQ ID NO: 1435), RNLDTPM (SEQ ID NO: 1436), VDSHRQS (SEQ ID NO: 1437), YDSKTKT (SEQ ID NO: 1438), SQLPHQK (SEQ ID NO: 1439), STMQQNT (SEQ ID NO: 1440), TERYMTQ (SEQ ID NO: 1441), DASLSTS (SEQ ID NO: 1442), DLPNKKT (SEQ ID NO: 1443), DLTAARL (SEQ ID NO: 1444), EPHQFNY (SEQ ID NO: 1445), EPQSNHT (SEQ ID NO: 1446), MSSWPSQ (SEQ ID NO: 1447), NPKHNAT (SEQ ID NO: 1448), PDGMRTT (SEQ ID NO: 1449), PNNNKTT (SEQ ID NO: 1450), QSTTHDS (SEQ ID NO: 1451), TGSKQKQ (SEQ ID NO: 1452), SLKHQAL (SEQ ID NO: 1453), SPIDGEQ (SEQ ID NO: 1454), WIFPWQL (SEQ ID NO: 1455), CDCRGDCFC (SEQ ID NO: 1456), CNGRC (SEQ ID NO: 1457), CPRECE (SEQ ID NO: 1458), CTTHWGFTLC (SEQ ID NO: 1459), CGRRAGGSC (SEQ ID NO: 1460), CKGGRKDC (SEQ ID NO: 1461), CVPGLGHEC (SEQ ID NO: 1462), CRRETAWAK (SEQ ID NO: 1463), VSWFSHRYSPFAVS (SEQ ID NO: 1464), GYRDGYAGPILYN (SEQ ID NO: 1465), XXXYXXX (SEQ ID NO: 1466), YXNW (SEQ ID NO: 1467), RPLPLP (SEQ ID NO: 1468), APPLPPR (SEQ ID NO: 1469), DVFYPPYASGS (SEQ ID NO: 1470), MYWYPY (SEQ ID NO: 1471), DITWDQLWDLMK (SEQ ID NO: 1472), CWDDXWLC (SEQ ID NO: 1473), EWCEYLGGYLRCYA (SEQ ID NO: 1474), YXCXXGPXTWXCXP (SEQ ID NO: 1475), IEGPTLRQWLAARA (SEQ ID NO: 1476), LWXXX (SEQ ID NO: 1477), XFXXYLW (SEQ ID NO: 1478), SSIISHFRWGLCD (SEQ ID NO: 1479), MSRPACPPNDKYE (SEQ ID NO: 1480), CLRSRGRC (SEQ ID NO: 1481), CHWMFSPWC (SEQ ID NO: 1482), WXXF (SEQ ID NO: 1483), CSSRLDAC (SEQ ID NO: 1484), CLPVASC (SEQ ID NO: 1485), CGFECVRQCPERC (SEQ ID NO: 1486), CVALCREACGEGC (SEQ ID NO: 1487), SWCEPGWCR (SEQ ID NO: 1488), YSGKWWG (SEQ ID NO: 1489), GLSGGRS (SEQ ID NO: 1490), LMLPRAD (SEQ ID NO: 1491), CSCFRDVCC (SEQ ID NO: 1492), CRDVVSVC (SEQ ID NO: 1493), MARSG (SEQ ID NO: 1494), MARAKE (SEQ ID NO: 1495), MSRTMS (SEQ ID NO: 1496), KCCYSL (SEQ ID NO: 1497), MYWGDSHWLQYWYE (SEQ ID NO: 1498), MQLPLAT (SEQ ID NO: 1499), EWLS (SEQ ID NO: 1500), SNEW (SEQ ID NO: 1501), TNYL (SEQ ID NO: 1502), WDLAWMFRLPVG (SEQ ID NO: 1503), CTVALPGGYVRVC (SEQ ID NO: 1504), CVAYCIEHHCWTC (SEQ ID NO: 1505), CVFAHNYDYLCV (SEQ ID NO: 1506), CVFTSNYAFC (SEQ ID NO: 1507), VHSPNKK (SEQ ID NO: 1508), CRGDGWC (SEQ ID NO: 1509), XRGCDX (SEQ ID NO: 1510), PXXX (SEQ ID NO: 1511), SGKGPRQITAL (SEQ ID NO: 1512), AAAAAAAAAAXXXXX (SEQ ID NO: 1513), VYMSPF (SEQ ID NO: 1514), ATWLPPR (SEQ ID NO: 1515), HTMYHHYQHHL (SEQ ID NO: 1516), SEVGCRAGPLQWLCEKYFG (SEQ ID NO: 1517), CGLLPVGRPDNRNVWRWLC (SEQ ID NO: 1518), CKGQCDRFKGLPWEC (SEQ ID NO: 1519), SGRSA (SEQ ID NO: 1520), WGFP

(SEQ ID NO: 1521), AEPMPHSLNFSQYLWYT (SEQ ID NO: 1522), WAYXSP (SEQ ID NO: 1523), IELLQAR (SEQ ID NO: 1524), AYTKCSRQWRTCMTH (SEQ ID NO: 1525), PQNSKIPGPTFLDPH (SEQ ID NO: 1526), SMEPALPDWWWKMFK (SEQ ID NO: 1527), ANTPCGPYTHDCPVKR (SEQ ID NO: 1528), TACHQHVRMVRP (SEQ ID NO: 1529), VPWMEPAYQRFL (SEQ ID NO: 1530), DPRATPGS (SEQ ID NO: 1531), FRPNRAQDYNTN (SEQ ID NO: 1532), CTKNSYLMC (SEQ ID NO: 1533), CXXTXXXGXGC (SEQ ID NO: 1534), CPIEDRPMC (SEQ ID NO: 1535), HEWSYLAPYPWF (SEQ ID NO: 1536), MCPKHPLGC (SEQ ID NO: 1537), RMWPSSTVNLSAGRR (SEQ ID NO: 1538), SAKTAVSQRVWLPSHRGGEP (SEQ ID NO: 1539), KSREHVNNACPSKRITAAL (SEQ ID NO: 1540), EGFR (SEQ ID NO: 1541), AGLGVR (SEQ ID NO: 1542), GTRQGHTMRLGVSDG (SEQ ID NO: 1543), IAGLATPGWSHWLAL (SEQ ID NO: 1544), SMSIARL (SEQ ID NO: 1545), HTFEPGV (SEQ ID NO: 1546), NTSCLKRISNKRIRRK (SEQ ID NO: 1547), LRIKRKRKRKKKTRK (SEQ ID NO: 1548), GGG, GFS, LWS, EGG, LLV, LSP, LBS, AGG, GRR, GGH and GTV.

[0560] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may be or have, at a position other than 5 consecutive amino acids corresponding to positions 586 to 594 numbered relative to SEQ ID NO: 138, 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: 1549) or variants thereof, wherein the specific site is at least one site selected from sites R447, G453, and/or S662 of a VP1 or a fragment thereof.

[0561] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may further comprise any of the mutated sequences described in US 20160369298, e.g., any of the following sequences SDSGASN (SEQ ID NO: 1550), SPSGASN (SEQ ID NO: 1551), SHSGASN (SEQ ID NO: 1552), SRSGASN (SEQ ID NO: 1553), SKSGASN (SEQ ID NO: 1554), SNSGASN (SEQ ID NO: 1555), SGSGASN (SEQ ID NO: 1556), SASGASN (SEQ ID NO: 1557), SESGTSN (SEQ ID NO: 1558), STTGGSN (SEQ ID NO: 1559), SSAGSTN (SEQ ID NO: 1560), NNDSQA (SEQ ID NO: 1561), NNRNQA (SEQ ID NO: 1562), NNNKQA (SEQ ID NO: 1563), NAKRQA (SEQ ID NO: 1564), NDEHQA (SEQ ID NO: 1565), NTSQKA (SEQ ID NO: 1566), YYLSRTNTPSGTDTQSRLVFSQAGA (SEQ ID NO: 1567), YYLSRTNTDSGTETQSGLDIFSQAGA (SEQ ID NO: 1568), YYLSRTNTESGTPTQSALEFSQAGA (SEQ ID NO: 1569), YYLSRTNTHSGTHTQSPLHFSQAGA (SEQ ID NO: 1570), YYLSRTNTSSGTITISHLIFSQAGA (SEQ ID NO: 1571), YYLSRTNTRSGIMTKSSLMFSQAGA (SEQ ID NO: 1572), YYLSRTNTKSGRKTLNLSFSQAGA (SEQ ID NO: 1573), YYLSRTNDGSGPVTPSKLRFSQAGA (SEQ ID NO: 1574), YYLSRTNAASGHATHSDLKFSQPGA (SEQ ID NO: 1575),

YYLSRTNGQAGSLTMSELGFSQVGA (SEQ ID NO: 1576),
YYLSRTNSTGGNQTTSQLLFSQLSA (SEQ ID NO: 1577),
YFLSRTNNNTGLNTNSTLNFSQGRA (SEQ ID NO: 1578), SKTGADNNNNSEYSWTG (SEQ ID NO: 1579), SKTDADNNNNSEYSWTG (SEQ ID NO: 1580), SKTEADNNNNSEYSWTG (SEQ ID NO: 1581), SKTPADNNNNSEYSWTG (SEQ ID NO: 1582), SKTHADNNNNSEYSWTG (SEQ ID NO: 1583), SKTQADNNNNSEYSWTG (SEQ ID NO: 1584), SKTIADNNNNSEYSWTG (SEQ ID NO: 1585), SKTMADNNNNSEYSWTG (SEQ ID NO: 1586), SKTRADNNNNSEYSWTG (SEQ ID NO: 1587), SKTNADNNNNSEYSWTG (SEQ ID NO: 1588), SKTVGRNNNNSEYSWTG (SEQ ID NO: 1589), SKTADRNNNNSEYSWTG (SEQ ID NO: 1590), SKKLSQNNNNSKYSWQG (SEQ ID NO: 1591), SKPTTGNNNSDYSWPG (SEQ ID NO: 1592), STQKNENNNNSNYSWPG (SEQ ID NO: 1593), HKDDEGKF (SEQ ID NO: 1594), HKDDNRKF (SEQ ID NO: 1595), HKDDTNKF (SEQ ID NO: 1596), HEDSDKNF (SEQ ID NO: 1597), HRDGADSF (SEQ ID NO: 1598), HGDNKSFR (SEQ ID NO: 1599), KQGSEKTNVDFFEV (SEQ ID NO: 1600), KQGSEKTNVDSEEV (SEQ ID NO: 1601), KQGSEKTNVDVEEV (SEQ ID NO: 1602), KQGSCKTNVD DAGV (SEQ ID NO: 1603), KQGSSKTNVDPREV (SEQ ID NO: 1604), KQGSRKTNVDHKQV (SEQ ID NO: 1605), KQGSKGGNVD TNRV (SEQ ID NO: 1606), KQGSGEANVDNGDV (SEQ ID NO: 1607), KQDAAADNIDYDHV (SEQ ID NO: 1608), KQSGTRSNA AASSV (SEQ ID NO: 1609), KENTNTNDEL TNV (SEQ ID NO: 1610), QRGNNVAATADVNT (SEQ ID NO: 1611), QRGNNEAATADVNT (SEQ ID NO: 1612), QRGNNPAATADVNT (SEQ ID NO: 1613), QRGNNHAATADVNT (SEQ ID NO: 1614), QEENNIAATPGVNT (SEQ ID NO: 1615), QPPNNMAATHEVNT (SEQ ID NO: 1616), QHHNNSAATTIVNT (SEQ ID NO: 1617), QTTNNRAAFNMVET (SEQ ID NO: 1618), QKKNNNAASKKVAT (SEQ ID NO: 1619), QGGNNKAADDAVKT (SEQ ID NO: 1620), QAAKGGAADDAVKT (SEQ ID NO: 1621), QDDRAAAANESVD T (SEQ ID NO: 1622), QQQHDDAAYQRVHT (SEQ ID NO: 1623), QSSSSLA AVSTVQT (SEQ ID NO: 1624), QNNQTAAIRNVTT (SEQ ID NO: 1625), NYNKKSDNVDFT (SEQ ID NO: 1626), NYNKKSENV DFT (SEQ ID NO: 1627), NYNKKSLNVDFT (SEQ ID NO: 1628), NYNKKSPNVDFT (SEQ ID NO: 1629), NYSKKSHCV DFT (SEQ ID NO: 1630), NYRKTIIYVDFT (SEQ ID NO: 1631), NYKEKKDVHFT (SEQ ID NO: 1632), NYGHRAIVQFT (SEQ ID NO: 1633), NYANHQFVVCT (SEQ ID NO: 1634), NYDDDP TGVL LT (SEQ ID NO: 1635), NYDDPTGVLLT (SEQ ID NO: 1636), NFEQQNSVEWT (SEQ ID NO: 1637), SQSGASN (SEQ ID NO: 1638), NNGSQA (SEQ ID NO: 1639), YYLSRTNTPSGTTTWSRLQFSQAGA (SEQ ID NO: 1640), SKTSADNNNNSEYSWTG (SEQ ID NO: 1641), HKDDEEF (SEQ ID NO: 1642), KQGSEKTNVDIEEV (SEQ ID NO: 1643), QRGNNQAATADVNT (SEQ ID NO: 1644), NYNKKSVNVDFT (SEQ ID NO: 1645), SQSGASNYNTPSGTTTQSR LQFST SADNNNNSEYSWTGATKYH (SEQ ID NO: 1646), SASGASNFNSEGGSLTQSSLGFST DGENNNSDFS WTGATKYH (SEQ ID NO: 1647),

SQSGASNYNTPSGTTTQSRLQFSTDGENNNSDFS WTGATKYH (SEQ ID NO: 1648), SASGASNYNTPSGTTTQSRLQFSTSADNNNSEFSWPGATTYH (SEQ ID NO: 1649), SQSGASNFNFSEGGSLTQSSLGFSTDGENNNSDFS WTGATKYH (SEQ ID NO: 1650), SASGASNYNTPSGSLTQSSLGFSTDGENNNSDFS WTGATKYH (SEQ ID NO: 1651), SQSGASNYNTPSGTTTQSRLQFSTSADNNNSDFS WTGATKYH (SEQ ID NO: 1652), SGAGASNFNFSEGGSLTQSSLGFSTDGENNNSDFS WTGATKYH (SEQ ID NO: 1653), SGAGASN (SEQ ID NO: 1654), NSEGGSLTQSSLGFS (SEQ ID NO: 1655), TDGENNNSDFS (SEQ ID NO: 1656), SEFSWPGATT (SEQ ID NO: 1657), TSADNNNSDFS WT (SEQ ID NO: 1658), SQSGASNY (SEQ ID NO: 1659), NTPSGTTTQSRLQFS (SEQ ID NO: 1660), TSADNNNSEYS WTGATKYH (SEQ ID NO: 1661), SASGASNF (SEQ ID NO: 1662), TDGENNNSDFS WTGATKYH (SEQ ID NO: 1663), SASGASNY (SEQ ID NO: 1664), TSADNNNSEFSWPGATTYH (SEQ ID NO: 1665), NTPSGSLTQSSLGFS (SEQ ID NO: 1666), TSADNNNSDFS WTGATKYH (SEQ ID NO: 1667), SGAGASNF (SEQ ID NO: 1668), CTCCAGVVSVVSMRSRVCVNSGCAGCTDHCVVSRNSGTCVMSACACAA (SEQ ID NO: 1669), CTCCAGAGAGGCAACAGACAAGCAGCTACCGCAGATGTCAACACACAA (SEQ ID NO: 1670), SAAGASN (SEQ ID NO: 1671), YFLSRTNTESGSTTQSTLRFSQAG (SEQ ID NO: 1672), SKTSADNNNSDFS (SEQ ID NO: 1673), KQGSEKTDVDIDKV (SEQ ID NO: 1674), STAGASN (SEQ ID NO: 1675), YFLSRTNTTSGIETQSTLRFSQAG (SEQ ID NO: 1676), SKTDGENNNSDFS (SEQ ID NO: 1677), KQGAAADDVEIDGV (SEQ ID NO: 1678), SEAGASN (SEQ ID NO: 1679), YYLSRTNTPSGTTTQSRLQFSQAG (SEQ ID NO: 1680), SKTSADNNNSEYS (SEQ ID NO: 1681), KQGSEKTNVDIEKV (SEQ ID NO: 1682), YFLSRTNDASGSDTKSTLLFSQAG (SEQ ID NO: 1683), STTPSENNNSEYS (SEQ ID NO: 1684), SAAGATN (SEQ ID NO: 1685), YFLSRTNGEAGSATLSELRFSSQAG (SEQ ID NO: 1686), HGDDADRF (SEQ ID NO: 1687), KQGAEKSDVEVDRV (SEQ ID NO: 1688), KQDSGGDNIDIDQV (SEQ ID NO: 1689), SDAGASN (SEQ ID NO: 1690), YFLSRTNTEGGHDTQSTLRFSQAG (SEQ ID NO: 1691), KEDGGGSDVAIDV (SEQ ID NO: 1692), SNAGASN (SEQ ID NO: 1693), and YFLSRTNGEAGSATLSELRFSSQPG (SEQ ID NO: 1694); or a nucleotide sequence that may encode the amino acid mutated sites of any of the following SEQ ID NO: 1695, SEQ ID NO: 1696, SEQ ID NO: 1697, SEQ ID NO: 1698, SEQ ID NO: 1699, SEQ ID NO: 1700, SEQ ID NO: 1701, SEQ ID NO: 1702, SEQ ID NO: 1703, SEQ ID NO: 1704, SEQ ID NO: 1705, SEQ ID NO: 1706, SEQ ID NO: 1707, SEQ ID NO: 1708, SEQ ID NO: 1709, SEQ ID NO: 1710, SEQ ID NO: 1711, SEQ ID NO: 1712, SEQ ID NO: 1713, SEQ ID NO: 1714, SEQ ID NO: 1715, SEQ ID NO: 1716, and SEQ ID NO: 1717.

[0562] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid may further comprise an ocular cell targeting peptide, e.g., 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 capsid sequence, such as, but not limited to, AAV2 (SEQ ID NO:8 of WO2016134375; herein SEQ ID NO: 1718), or AAV9 (SEQ ID NO: 11 of WO2016134375; herein SEQ ID NO: 1719). The ocular cell targeting peptide may be, but is not limited to, any of the following amino acid sequences, GSTPPPM (SEQ ID NO: 1720), or GETRAPL (SEQ ID NO: 1721).

[0563] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid 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).

[0564] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid 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, AAV5(Y436+693+719F), AAV6 (VP3 variant Y705F/Y731F/T492V), AAV8 (Y733F), AAV9, AAV9 (VP3 variant Y731F), and AAV10 (Y733F).

[0565] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid 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: 1722) or NKDKLN (SEQ ID NO:2 of WO2017015102; herein SEQ ID NO: 1723). 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).

[0566] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid 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, 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 some embodiments, the AAV may comprise an amino acid substitution at residues 256L, 258K, 259Q,

261S, 263A, 264S, 265T, 266G, 272H, 385S, 386Q, S472R, V473D, N500E 547S, 709A, 710N, 716D, 717N, 718N, 720L, A456T, Q457T, N458Q, K459S, T492S, K493A, S586R, S587G, S588N, T589R and/or 722T of AAV1 (SEQ ID NO: 1 of WO2017058892) in any combination, 244N, 246Q, 248R, 249E, 250I, 251K, 252S, 253G, 254S, 255V, 256D, 263Y, 377E, 378N, 453L, 456R, 532Q, 533P, 535N, 536P, 537G, 538T, 539T, 540A, 541T, 542Y, 543L, 546N, 653V, 654P, 656S, 697Q, 698F, 704D, 705S, 706T, 707G, 708E, 709Y and/or 710R of AAV5 (SEQ ID NO: 5 of WO2017058892) in any combination, 248R, 316V, 317Q, 318D, 319S, 443N, 530N, 531S, 532Q, 533P, 534A, 535N, 540A, 541 T, 542Y, 543L, 545G, 546N, 697Q, 704D, 706T, 708E, 709Y and/or 710R of AAV5 (SEQ ID NO: 5 of WO2017058892) in any combination, 264S, 266G, 269N, 272H, and/or 457Q, of AAV6 (SEQ ID NO: 6 of WO2017058892) in any combination, 457T, 459N, 496G, 499N, and/or 500N, of AAV8 (SEQ ID NO: 8 of WO2017058892) in any combination, 451I, 452N, 453G, 454S, 455G, 456Q, 457N and/or 458Q of AAV9 (SEQ ID NO: 9 of WO2017058892) in any combination.

[0567] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid 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.

[0568] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, or the parent AAV capsid further comprise one or more components 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 some embodiments, AAV serotypes generated in this manner have improved CNS transduction and/or neuronal and astrocytic tropism, as compared to other AAV serotypes.

Promoters

[0569] In some embodiments, an AAV particle comprising a novel capsid of the present disclosure, which may hereinafter also be referred to as an AAV particle comprising an AAV capsid polypeptide, e.g., AAV capsid variant (e.g., a TRACER AAV particle), comprises at least one element to enhance 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 an element to enhance the 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.

[0570] A person skilled in the art may recognize that expression of the polypeptides 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).

[0571] In some embodiments, the promoter is deemed to be efficient when it drives expression of the polypeptide(s) encoded by AAV capsid mRNA described herein. In some embodiments, the promoter is deemed to be efficient when it drives expression of the polypeptide(s) encoded by viral genomes encapsulated within a capsid described herein.

[0572] In some embodiments, the promoter drives expression of the polypeptides (e.g., AAV capsid polypeptides) 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.

[0573] In some embodiments, the promoter drives expression of the polypeptides (e.g., AAV capsid polypeptides) 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.

[0574] 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.

[0575] Promoters which drive or promote expression in most tissues include, but are not limited to, human elongation factor 1 α -subunit (EF1 α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β -actin (CBA; such as, but not limited to, a CBA promoter as described in Miyazaki et al. (Gene. 1989 Jul 15;79(2):269-77, the contents of which are herein incorporated by reference in its entirety)) 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.

[0576] 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 US20110212529, the contents of which are herein incorporated by reference in their entirety). Muscle specific promoters may also include Mb promoter, myosin promoter, dystrophin promoter, dMCK and tMCK. As a non-limiting example, the muscle-specific promoter may be used to drive or promote expression in certain cell types, such as, but not limited to, myocytes and muscle stem cells.

[0577] Non-limiting examples of blood-specific promoters include B29 promoter, immunoglobulin heavy chain promoter, CD45 promoter, mouse INF- β promoter, CD45 SV40 / CD45 promoter, WASP promoter, CD43 promoter, CD43 SV40 / CD43 promoter, CD68 promoter, GPIIb promoter, CD14 promoter, and CD2 promoter. As a non-limiting example, the blood-specific promoter may be used to drive or promote expression in certain cell types, such as, but not limited to, in B cells, hematopoietic cells, leukocytes, platelets, macrophages, megakaryocytes, monocytes and/or T cells.

[0578] Non-limiting examples of bone-specific promoters include osteocalcin, bone sialoprotein, and OG-2 promoter. As a non-limiting example, the bone-specific promoter may be used to drive or promote expression in certain cell types, such as, but not limited to, osteoblasts and odontoblasts.

[0579] Non-limiting examples of eye-specific promoters include Chx10, PrP, Dkk3, Math5, Ptf1a, Pcp2, Nefh, gamma-synuclein gene (SNCG), Grik4, Pdgfra, Chat, Thy1.2, hVmd2, Thy1, Modified α A-crystallin, hRgp, mMo, Opn4, RLBP1, Glst, Foxg1, hVmd2, Trp1, Six3, cx36, Grm6 - SV40 eukaryotic promoter, hVmd2, Dct, Rpe65, mRho, Irbp, hRho, Pcp2, Rhodopsin, and mSo. As a non-limiting example, the eye-specific promoter may be used to drive or promote expression in

certain cell types, such as, but not limited, to retinal neurons, horizontal cells, bipolar cells, ganglion cells (GCs), ONL Müller cells, amacrine cells, lens cells, S-cone cells, M-cone cells, melanopsin-expressing GCs, neurons, ON bipolar, optic nerve cells, pigmented cells, retinal pigment epithelial cells, rod cells, rod bipolar cells, and rod photoreceptors.

[0580] Non-limiting examples of heart-specific promoters include MLC2v promoter, α MHC promoter, rat troponin T (Tnt2), Tie2, and Tcf21. As a non-limiting example, the heart-specific promoter may be used to drive or promote expression in certain cell types, such as, but not limited to, cardiomyocytes, endothelial cells, and fibroblasts.

[0581] Non-limiting examples of kidney-specific promoters include, ECAD, NKCC2, KSPC, NPHS1, and SGLT2. As a non-limiting example, the kidney-specific promoter may be used to drive or promote expression in certain cell types, such as, but not limited to, collecting duct cells, loop of Henle cells, nephron cells, podocytes and proximal tubular cells.

[0582] Non-limiting examples of liver-specific promoters include, SV40/bAlb promoter, SV40 / hAlb promoter, Hepatitis B virus core promoter, and Alpha fetoprotein. As a non-limiting example, the liver-specific promoter may be used to drive or promote expression in certain cell types, such as, but not limited to, hepatocytes.

[0583] Non-limiting examples of lung-specific promoters include Surfactant protein B promoter and Surfactant protein C promoter. As a non-limiting example, the lung-specific promoter may be used to drive or promote expression in certain cell types, such as, but not limited to, AT II cells and Clara cells.

[0584] Non-limiting examples of pancreas-specific promoters include elastase-1 promoter, PDX1 promoter, and insulin promoter. As a non-limiting example, the pancreas-specific promoter may be used to drive or promote expression in certain cell types, such as, but not limited to, acinar cells, beta cells, and Langerhans cells.

[0585] Non-limiting examples of vascular- or vasculature-specific promoters include Slco1c1, tie, cadherin, ICAM-2, claudin 1, Cldn5, Flt-1 promoter, and Endoglin promoter. As a non-limiting example, the vascular-specific promoter may be used to drive or promote expression in certain cell types, such as, endothelial cells. As a non-limiting example, the endothelial cell is a blood-brain barrier endothelial cell.

[0586] 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 or Syn1), 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) chain, β -globin minigene n β 2, preproenkephalin (PPE), enkephalin (Enk), VGF, and excitatory amino acid transporter 2 (EAAT2) promoters. A non-limiting examples of tissue-specific expression elements for neuroectodermal stem cells is nestin.

[0587] Non-limiting examples of tissue-specific expression elements for astrocytes include glial fibrillary acidic protein (GFAP, GFAPc1D) and EAAT2 promoters. A non-limiting example of a tissue-specific expression element for oligodendrocytes includes the myelin basic protein (MBP) promoter.

[0588] In some embodiments, the promoter may be less than 1 kb. The promoter may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, or more than 800 nucleotides. The promoter may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800, or 700-800.

[0589] In some embodiments, the promoter may be a combination of two or more components of the same or different starting or parental promoters such as, but not limited to, CMV and CBA. Each component may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, or more than 800. Each component may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800 or 700-800. In some embodiments, the promoter is a combination of a 382 nucleotide CMV-enhancer sequence and a 260 nucleotide CBA-promoter sequence.

[0590] In some embodiments, the AAV particle comprises a ubiquitous promoter. Non-limiting examples of ubiquitous promoters include CMV, CBA (including derivatives CAG, CB6, CBh, etc.), EF-1 α , PGK, UBC, GUSB (hGBp), and UCOE (promoter of HNRPA2B1-CBX3).

[0591] 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, EF1 α , 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 EF1 α 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 H β H

construct with a hGUSB promoter, an HSV-1LAT promoter and an NSE promoter and found that the H β H 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 H β H 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 650nucleotide 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 entirety).

[0592] Any of promoters taught by the aforementioned Yu, Soderblom, Gill, Husain, Passini, Xu, Drews, or Raymond may be used in the present disclosures.

[0593] In some embodiments, the promoter is ubiquitous. In some embodiments, the promoter is not cell specific.

[0594] In some embodiments, the promoter is a 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.

[0595] In some embodiments, 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.

[0596] In some embodiments, 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.

[0597] In some embodiments, 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.

- [0598] In some embodiments, 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.
- [0599] In some embodiments, the promoter is a phosphoglycerate kinase 1 (PGK) promoter.
- [0600] In some embodiments, the promoter is a chicken β -actin (CBA) promoter, or a variant thereof.
- [0601] In some embodiments, the promoter is a CB6 promoter.
- [0602] In some embodiments, the promoter is a minimal CB promoter.
- [0603] In some embodiments, the promoter is a P40 promoter. In some embodiments, the P40 promoter is located in the 3' of the AAV capsid REP gene.
- [0604] In some embodiments, the promoter is a cytomegalovirus (CMV) promoter.
- [0605] In some embodiments, the CMV promoter is a hybrid CMV enhancer/Chicken beta-actin promoter sequence such as described by Niwa et al., 1991, the contents of which are incorporated herein by reference in their entirety.
- [0606] In some embodiments, the promoter is a CAG promoter.
- [0607] In some embodiments, the promoter is a GFAP promoter.
- [0608] In some embodiments, the promoter is a synapsin (syn or syn1) promoter.
- [0609] In some embodiments, the promoter is a liver or a skeletal muscle promoter. Non-limiting examples of liver promoters include human α -1-antitrypsin (hAAT) and thyroxine binding globulin (TBG). Non-limiting examples of skeletal muscle promoters include Desmin, MCK or synthetic C5-12.
- [0610] In some embodiments, the promoter is an 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.
- [0611] In some embodiments, the promoter may be selected depending on the desired tropism. Non-limiting examples of promoters are described in WO2020072683, the contents of which are herein incorporated by reference in their entirety.
- [0612] In some embodiments, the promoter drives capsid mRNA expression in the absence of helper virus co-infection.
- [0613] In some embodiments, the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant described herein) comprises two promoters. As a non-limiting example, the promoters are an P40 promoter and a CMV promoter. As another non-limiting example, the promoters are an P40 promoter and a cell-type specific promoter (e.g. synapsin).
- [0614] In some embodiments, the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant described herein) comprises an engineered promoter.

[0615] In another embodiment, the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., AAV capsid variant described herein) comprises a promoter from a naturally expressed protein.

[0616] In some embodiments, a portion of the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., AAV capsid variant described herein) REP gene is deleted to accommodate the promoter insertion. The promoter may be inserted upstream or downstream of the AAV particle CAP gene.

[0617] In some embodiments, the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., AAV capsid variant described herein) comprises a cell type-specific promoter to drive capsid mRNA expression. As a non-limiting example, the promoter is cell-type specific. The cell-type specific promoter may be synapsin. The cell-type specific promoter may be glial fibrillary acidic protein (GFAP). The AAV particle may comprise a P40 promoter and a cell-type specific promoter.

[0618] In some embodiments, the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., AAV capsid variant described herein) comprises a structure as shown in FIG 4. In some embodiments, an alternate backbone may be used for generation of the capsid libraries. In the alternate backbone, the forward version is changed into reverse, which can avoid the expression of capsid proteins and possible immune response to these foreign capsid proteins during in vivo evolution. In some embodiments, one or more additional WPRE elements may also be added to the backbone to improve RNA yield during viral library RNA recovery. In some embodiments, the backbone for the TRACER approach is as shown in FIG. 5.

AAV selection

[0619] The present disclosure provides methods of AAV selection for tissue- and/or cell type-specific transduction, whereby AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein) with high tropism for a tissue(s) and/or cell type(s) are identified and selected for use. In some embodiments, the AAV selection comprises administration of the AAV particles to a cell and/or a subject by standard methods known in the art (e.g. intravenously). In some embodiments, the AAV selection may comprise extraction of polynucleotides, e.g., capsid RNA, encoded by AAV particles, from a specific tissue and/or cell type. In some embodiments, the tissue may be non-nervous system tissue such as, but not limited to, liver, spleen and heart. The cells type may be, e.g., hepatocytes, islets of Langerhans cells, and cardiomyocytes. In some embodiments, the tissue may be nervous system tissue such as, but not limited to, brain tissue, spinal cord tissue, and dorsal root ganglion tissue. The cell type may be, e.g., neurons, astrocytes, or oligodendrocytes. In some embodiments, the extracted RNA is enriched, reverse transcribed, and/or amplified. In some embodiments, the extracted RNA allows for recovery

of full-length capsid “amplicon(s)” from a specific tissue and/or cell type, using various production methods, e.g., reverse transcription polymerase chain reaction (RT-PCR). As used herein, amplicon may refer to any piece of RNA or DNA formed as the product of amplification events, e.g. PCR. In some embodiments, full-length capsid amplicons may be used as templates for next generation sequencing (NGS) library generation. Full-length capsid amplicons may be used for cloning into a DNA library for the generation of AAV TRACER particles for any number of additional rounds of AAV selection as described above. In some embodiments, the AAV selection may be performed iteratively, or repeated, any number of times, or rounds. The above-described selection of AAV particles may also be more generally referred to herein as biopanning.

[0620] In some embodiments, the AAV selection comprises administration of the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., AAV capsid variant, described herein) to a cell by standard methods known in the art (e.g. infection). As a non-limiting example, the cell is a HEK293 cell. As another non-limiting example, the cell is a nervous system cell such as, but not limited to, a neuron and/or a glial cell. As yet another non-limiting example, the cell is a brain microvascular endothelial cells (BMVEC). The BMVEC may be a human BMVEC (hBMVEC). The BMVEC may be a non-human primate (NHP) BMVEC.

[0621] In some embodiments, the AAV selection comprises administration of the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., AAV capsid variant, described herein) to a rodent by standard methods known in the art (e.g. intravenously). The rodent may be a transgenic rodent or a non-transgenic (e.g., wild type) rodent. As a non-limiting example, the rodent is a rat or a mouse. Non-limiting examples of rats include Sprague Dawley, Wistar Albino, and Long Evans rats. Non-limiting examples of mice include BALB/C, FVB and C57BL/6 mice.

[0622] In some embodiments, the AAV selection comprises administration of the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein) to a non-human primate (NHP) by standard methods known in the art (e.g. intravenously). Non-limiting examples of NHPs include rhesus macaques (*Macaca mulatta*) and cynomolgus macaques (*Macaca fascicularis*).

[0623] In some embodiments, the AAV selection comprises administration of AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein) to a rodent, non-human primate, and/or human cells. In some embodiments, the AAV selection comprises administration of AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein) to a rodent, non-human primate, and/or human subjects.

[0624] In some embodiments, the AAV selection may be performed iteratively, or repeated, any number of times, or rounds, within a single cell- or subject-type, wherein the single cell- or subject-type may remain unchanged, or the same, across AAV selection rounds. Cell types may be, e.g.,

HEK293 cells, hBMVECs, and NHP BMVECs. Subject types may be, e.g., Sprague Dawley rats, Wistar Albino rats, Long-Evans rats, BALB/C mice, FVB mice, C57BL/6 mice, rhesus macaques, cynomolgus macaques, and humans. As a non-limiting example, AAV selection is performed across one, two and/or three or more AAV selection rounds in the hBMVEC cell. As a non-limiting example, AAV selection is performed across one, two and/or three or more rounds in a mouse such as, but not limited to, a BALB/C mouse. As a non-limiting example, AAV selection is performed across one, two and/or three or more rounds in an NHP such as, but not limited to, a cynomolgus macaque, as represented in FIG. 1A and FIG. 1B.

[0625] AAV selection may be performed iteratively, or repeated, any number of times, or rounds, within any number of cell- and/or subject-types, wherein the cell- and or subject-type may change, or differ, across AAV selection rounds. As a non-limiting example, the AAV selection is performed a first round in a rhesus macaque, and an additional, e.g., subsequent, one, two, and/or three or more rounds in a Sprague-Dawley rat.

[0626] AAV selection may be performed iteratively, or repeated, any number of times, or rounds, within any number of cell- and/or subject-types, and may additionally comprise the combination and/or comparison of any AAV capsid serotype as disclosed herein, or variants or derivatives thereof, with the AAV particle pool, at any AAV selection round. As a non-limiting example, the AAV capsid serotype comprises AAVF7/HSC7 (SEQ ID NO: 8 and 27 of WO2016049230). As another non-limiting example, the AAV capsid serotype comprises AAVF15/HSC15 (SEQ ID NO: 16 and 33 of WO2016049230). As yet another non-limiting example, the AAV capsid serotype AAVF17/HSC17 (SEQ ID NO: 13 and 35 of WO2016049230). The AAV selection round may be the first, second, third, or fourth AAV selection round.

Orthogonal evolution

[0627] Methods of AAV selection of the present disclosure may comprise orthogonal evolution. In some embodiments, orthogonal evolution is a method wherein AAV particles are administered for a first round of AAV selection as described herein across a set of any number of cell- and/or subject-types that may be from different species and/or strains, and wherein any number of additional, e.g., subsequent, AAV selection rounds are performed either across a set of any number of cell- and/or subject-types that may be from different species and/or strains, or across a set of any number of cell- and/or subject-types that may be from the same species and/or strains, as represented in FIG 2. Cell types may be, e.g., HEK293 cells, hBMVECs, and NHP BMVECs. Subject types may be, e.g., Sprague Dawley rats, Wistar Albino rats, Long-Evans rats, BALB/C mice, FVB mice, C57BL/6 mice, rhesus macaques, cynomolgus macaques, and humans.

Viral Genome of the AAV particle

[0628] AAV particle as described herein, comprising a peptide, e.g., a targeting peptide and/or selected by the TRACER methods (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid polypeptide, e.g., AAV capsid variant, described herein), may be used for the delivery of a viral genome to a tissue, e.g., a target tissue (e.g., CNS, DRG, and/or muscle). In some embodiments, an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein can be used for delivery of a viral genome to a tissue or cell, e.g., CNS, DRG, or muscle cell or tissue. In some embodiments, an AAV particle of the present disclosure is a recombinant AAV particle. In some embodiments, an AAV particle of the present disclosure is an isolated AAV particle.

[0629] The viral genome may encode any payload, such as but not limited to a polypeptide (e.g., a therapeutic polypeptide), an antibody, an enzyme, an RNAi agent and/or components of a gene editing system. In one embodiment, the AAV particles described herein are used to deliver a payload to cells of the CNS, after intravenous delivery. In another embodiment, the AAV particles described herein are used to deliver a payload to cells of the DRG, after intravenous delivery. In some embodiments, the AAV particles described herein are used to deliver a payload to cells of a muscle, e.g., a heart muscle, after intravenous delivery.

[0630] A viral genome of an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, as described herein, comprises a nucleic acid sequence with at least one payload region encoding a payload, and at least one ITR. A viral genome typically comprises two ITR sequences, one at each of the 5' and 3' ends. Further, a viral genome of the AAV particles described herein may comprise nucleic acid sequences for additional components, such as, but not limited to, a regulatory element (e.g., promoter), untranslated regions (UTR), a polyadenylation sequence (polyA), a filler or stuffer sequence, an intron, and/or a linker sequence for enhanced expression.

[0631] These viral genome components can be selected and/or engineered to further tailor the specificity and efficiency of expression of a given payload in a target tissue (e.g., CNS, muscle, or DRG).

Viral Genome Component: Inverted Terminal Repeats (ITRs)

[0632] In some embodiments, the AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises a viral genome with at least one ITR 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 as described herein may be comprised of naturally occurring polynucleotide sequences or recombinantly derived polynucleotide sequences.

[0633] The ITRs may be derived from the same serotype as the capsid polypeptide, e.g., capsid variant, selected from any of the known serotypes, or a derivative thereof. The ITR may be of a different serotype than 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.

[0634] 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, 105, 130, 140, 141, 142, 145 nucleotides in length. ITRs encompassed by the present disclosure include those with at least 90% identity, at least 95% identity, at least 98% identity, or at least 99% identity to a known AAV serotype ITR sequence.

Viral Genome Component: Promoters

[0635] In one embodiment, the payload region of the viral genome comprises at least one element to enhance the payload 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 their entirety). Non-limiting examples of elements to enhance payload 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.

[0636] A person skilled in the art may recognize that expression of a payload 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).

[0637] In one embodiment, the promoter is deemed to be efficient when it drives expression of the payload encoded by the viral genome of the AAV particle.

[0638] In one embodiment, the promoter is a promoter deemed to be efficient when it drives expression in a cell being targeted.

[0639] In one embodiment, the promoter is a promoter having a tropism for a cell being targeted.

[0640] 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. As a non-limiting example, the promoter is selected for sustained expression of a payload in tissues and/or cells of the central or peripheral nervous system.

[0641] Promoters may be naturally occurring or non-naturally occurring. Non-limiting examples of promoters include those derived from viruses, plants, mammals, or humans. In some embodiments, the promoters may be those derived from human cells or systems. In some embodiments, the promoter may be truncated or mutated.

[0642] Promoters which drive or promote expression in most tissues include, but are not limited to, the human elongation factor 1 α -subunit (EF1 α) promoter, the cytomegalovirus (CMV) immediate-early enhancer and/or promoter, the chicken β -actin (CBA) promoter and its derivative CAG, β glucuronidase (GUSB) promoter, or ubiquitin C (UBC) promoter. Tissue-specific promoters can be used to restrict expression to certain cell types such as, but not limited to, cells of the central or peripheral nervous systems, targeted regions within (e.g., frontal cortex), and/or sub-sets of cells therein (e.g., excitatory neurons). As non-limiting examples, cell-type specific promoters may be used to restrict expression of a payload to excitatory neurons (e.g., glutamatergic), inhibitory neurons (e.g., GABA-ergic), neurons of the sympathetic or parasympathetic nervous system, sensory neurons, neurons of the dorsal root ganglia, motor neurons, or supportive cells of the nervous systems such as microglia, astrocytes, oligodendrocytes, and/or Schwann cells.

[0643] Cell-type specific promoters also exist for other tissues of the body, with non-limiting examples including, liver promoters (e.g., hAAT, TBG), skeletal muscle specific promoters (e.g., desmin, MCK, C512), B cell promoters, monocyte promoters, leukocyte promoters, macrophage promoters, pancreatic acinar cell promoters, endothelial cell promoters, lung tissue promoters, and/or cardiac or cardiovascular promoters (e.g., α MHC, cTnT, and CMV-MLC2k).

[0644] Non-limiting examples of tissue-specific promoters for targeting payload expression to central nervous system tissues and cells include synapsin (Syn), glutamate vesicular transporter (VGLUT), vesicular GABA transporter (VGAT), parvalbumin (PV), sodium channel Na_v 1.8,

tyrosine hydroxylase (TH), choline acetyltransferase (ChAT), 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), neuron-specific enolase (NSE), β -globin minigene β 2, 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.

[0645] In some embodiments, the promoter of the viral genome used to drive expression of the payload in a target tissue may be any of those noted herein for use in AAV particles.

Viral Genome Component: Untranslated Regions (UTRs)

[0646] In some embodiments, 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.

[0647] Features typically found in abundantly expressed genes of specific target organs (e.g., CNS tissue, muscle, or DRG) may be engineered into UTRs to enhance stability and protein production. As a non-limiting example, a 5' UTR from mRNA normally expressed in the brain (e.g., huntingtin) may be used in the viral genomes of the AAV particles described herein to enhance expression in neuronal cells or other cells of the central nervous system.

[0648] 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'.

[0649] In one embodiment, the 5'UTR in the viral genome includes a Kozak sequence.

[0650] In one embodiment, the 5'UTR in the viral genome does not include a Kozak sequence.

[0651] 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- α , 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*.

[0652] Introduction, removal or modification of 3' UTR AU rich elements (AREs) can be used to modulate the stability of a polynucleotide. 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.

[0653] In one embodiment, the 3' UTR of the viral genome may include an oligo(dT) sequence for templated addition of a poly-A tail.

[0654] 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. In some embodiments, a microRNA sequence comprises a seed region, e.g., a sequence in the region of positions 2-8 of the mature microRNA, which has Watson-Crick sequence fully or partially complementarity to the miRNA target sequence of the nucleic acid.

[0655] In one embodiment, the viral genome may be engineered to include, alter or remove at least one miRNA binding site, full sequence or seed region.

[0656] 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.

[0657] In one embodiment, the viral genome of the AAV particle comprises at least one artificial UTR which is not a variant of a wild type UTR.

[0658] 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

[0659] The viral genome of the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein) may comprise at least one polyadenylation sequence. In one embodiment, the viral genome of the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein) comprises a polyadenylation sequence between the 3' end of the payload encoding region and the 5' end of the 3' ITR.

[0660] In one embodiment, the polyadenylation sequence or "polyA sequence" may range from absent to about 500 nucleotides in length. In some embodiments, the polyA sequence comprises a length of about 100-600 nucleotides, e.g., about 100-500 nucleotides, about 100-400 nucleotides, about 100-300 nucleotides, about 100-200 nucleotides, about 200-600 nucleotides, about 200-500 nucleotides, about 200-400 nucleotides, about 200-300 nucleotides, about 300-600 nucleotides, about 300-500 nucleotides, about 300-400 nucleotides, about 400-600 nucleotides, about 400-500 nucleotides, or about 500-600 nucleotides. In some embodiments, the polyA signal region comprises a length of about 100 to 150 nucleotides, e.g., about 127 nucleotides. In some embodiments, the polyA sequence comprises a length of about 450 to 500 nucleotides, e.g., about 477 nucleotides. In some embodiments, the polyA sequence comprises a length of about 520 to about 560 nucleotides, e.g., about 552 nucleotides. In some embodiments, the polyA sequence comprises a length of about 127 nucleotides.

Viral Genome Component: Introns

[0661] In one embodiment, the viral genome of the AAV particle as described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), comprises at least one element to enhance the payload target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, Discov. Med, 2015, 19(102): 49-57; the contents of which are herein incorporated by reference in their entirety) such as an intron. Non-limiting examples of introns include, MVM (67-97 bps), F.IX truncated intron 1 (300 bps), β -globin SD/immunoglobulin heavy chain splice acceptor (250 bps), adenovirus splice donor/immunoglobulin splice acceptor (500 bps), SV40 late splice donor/splice acceptor (19S/16S) (180 bps) and hybrid adenovirus splice donor/IgG splice acceptor (230 bps).

[0662] 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

nucleotides. 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 nucleotides.

Viral Genome Component: Stuffer sequences

[0663] In one embodiment, the viral genome of the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), comprises at least one element to improve packaging efficiency and expression, such as a stuffer or filler sequence. Non-limiting examples of stuffer sequences include albumin and/or alpha-1 antitrypsin. Any known viral, mammalian, or plant sequence may be manipulated for use as a stuffer sequence.

[0664] In one embodiment, the stuffer or filler sequence may be from about 100-3500 nucleotides in length. The stuffer sequence may have a length of about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900 or 3000 nucleotides.

Viral Genome Component: miRNA

[0665] In one embodiment, the viral genome comprises at least one sequence encoding a miRNA to reduce the expression of the payload in an "off-target" tissue. As used herein, "off-target" indicates a tissue or cell-type unintentionally targeted by the AAV particles described herein. miRNAs and their targeted tissues are well known in the art. As an example, an "off-target" tissue or cell when targeting the DRG (dorsal root ganglion), may be neurons of other ganglia, such as those of the sympathetic or parasympathetic nervous system. In some embodiments, a miRNA, e.g., a miR183, a miR182, and/or miR96, may be encoded in the viral genome to modulate, e.g., reduce the expression, of the viral genome in a DRG neuron. As another non-limiting example, a miR-122 miRNA may be encoded in the viral genome to modulate, e.g., reduce, the expression of the viral genome in the liver. In some embodiments, a miRNA, e.g., a miR-142-3p, may be encoded in the viral genome to modulate, e.g., reduce, the expression, of the viral genome in a cell or tissue of the hematopoietic lineage, including for example immune cells (e.g., antigen presenting cells or APC, including dendritic cells (DCs), macrophages, and B-lymphocytes).

Viral Genome Component: miR Binding Site

[0666] Tissue- or cell-specific expression of the AAV viral particles of the invention can be enhanced by introducing tissue- or cell-specific regulatory sequences, e.g., promoters, enhancers, microRNA binding sites, e.g., a detargeting site. Without wishing to be bound by theory, it is believed that a miR binding site can modulate, e.g., prevent, suppress, or otherwise inhibit, the expression of a gene of interest on the viral genome of the invention, based on the expression of the corresponding endogenous microRNA (miRNA) or a corresponding controlled exogenous miRNA in

a tissue or cell, e.g., a non-targeting cell or tissue. In some embodiments, a miR binding site modulates, e.g., reduces, expression of the payload encoded by a viral genome of an AAV particle described herein in a cell or tissue where the corresponding mRNA is expressed.

[0667] In some embodiments, the viral genome of an AAV particle described herein comprises a microRNA binding site, e.g., a detargeting site. In some embodiments, the viral genome of an AAV particle described herein comprises a coding sequence for a miR binding site, a microRNA binding site series (miR BSs), or a reverse complement thereof.

[0668] In some embodiments, the miR binding site series or the miR binding site is located in the 3'-UTR region of the viral genome (e.g., 3' relative to the nucleic acid sequence encoding a payload), e.g., before the polyA sequence, 5'-UTR region of the viral genome (e.g., 5' relative to the nucleic acid sequence encoding a payload), or both.

[0669] In some embodiments, the miR binding site series comprise at least 1-5 copies, e.g., at least 1-3, 2-4, 3-5, 1, 2, 3, 4, 5 or more copies of a miR binding site (miR BS). In some embodiments, all copies are identical, e.g., comprise the same miR binding site. In some embodiments, the miR binding sites within the miR binding site series are continuous and not separated by a spacer. In some embodiments, the miR binding sites within a miR binding site series are separated by a spacer, e.g., a non-coding sequence. In some embodiments, the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, nucleotides in length. In some embodiments, the spacer comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii).

[0670] In some embodiments, the miR binding site series comprise at least 1-5 copies, e.g., at least 1-3, 2-4, 3-5, 1, 2, 3, 4, 5 or more copies of a miR binding site (miR BS). In some embodiments, at least 1, 2, 3, 4, 5, or all of the copies are different, e.g., comprise a different miR binding site. In some embodiments, the miR binding sites within the miR binding site series are continuous and not separated by a spacer. In some embodiments, the miR binding sites within a miR binding site series are separated by a spacer, e.g., a non-coding sequence. In some embodiments, the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, in length. In some embodiments, the spacer comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii).

[0671] In some embodiments, the miR binding site is substantially identical (e.g., at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% identical), to the miR in the host cell. In some embodiments, the miR binding site comprises at least 1, 2, 3, 4, or 5 mismatches or no more than 6, 7, 8, 9, or 10 mismatches to a miR in the host cell. In some embodiments, the mismatched nucleotides are contiguous. In some embodiments, the mismatched nucleotides are non-contiguous. In some embodiments, the mismatched nucleotides occur outside the seed region-binding sequence of the miR binding site, such as at one or both ends of the miR binding site. In some embodiments, the miR binding site is 100% identical to the miR in the host cell.

[0672] In some embodiments, a miR binding site or sequence region is at least about 10 to about 125 nucleotides in length, e.g., at least about 10 to 50 nucleotides, 10 to 100 nucleotides, 50 to 100 nucleotides, 50 to 125 nucleotides, or 100 to 125 nucleotides in length. In some embodiments, a miR binding site or sequence region is at least about 7 to about 28 nucleotides in length, e.g., at least about 8-28 nucleotides, 7-28 nucleotides, 8-18 nucleotides, 12-28 nucleotides, 20-26 nucleotides, 22 nucleotides, 24 nucleotides, or 26 nucleotides in length, and optionally comprises at least one consecutive region (e.g., 7 or 8 nucleotides) complementary to the seed sequence of a miRNA (e.g., a miR122, a miR142, a miR183).

[0673] In some embodiments, the miR binding site is complementary to a miR expressed in liver or hepatocytes, such as miR122. In some embodiments, the miR binding site or miR binding site series comprises a miR122 binding site sequence. In some embodiments, the miR122 binding site comprises the nucleotide sequence of ACAACACCATTGTCACACTCCA (SEQ ID NO: 3672), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 3672, e.g., wherein the modification can result in a mismatch between the miR binding site and the corresponding miRNA. In some embodiments, the miR122 binding site comprises at least 3, 4, or 5 copies of a miR122 binding site, optionally comprising the nucleotide sequence of:

ACAAACACCATTGTCACACTCCACACAAACACCATTGTCACACTCCACACAAACACCATTGTCACACTCCA (SEQ ID NO: 3673), or a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 3673, e.g., wherein the modification can result in a mismatch between the miR binding site and the corresponding miRNA. In some embodiments, at least two of the miR122 binding sites are connected directly, e.g., without a spacer. In other embodiments, at least two of the miR122 binding sites are separated by a spacer, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive miR122 binding site sequences. In embodiments, the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8, in length. In some embodiments, the spacer comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or repeats thereof. In some embodiments, a miR binding site series comprises at least 3-5 copies, e.g., 4 copies, of a miR122 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, in length.

[0674] In some embodiments, the miR binding site is complementary to a miR expressed in hematopoietic lineage, including immune cells (e.g., antigen presenting cells or APC, including dendritic cells (DCs), macrophages, and B-lymphocytes). In some embodiments, the miR binding site complementary to a miR expressed in hematopoietic lineage comprises a nucleotide sequence

disclosed, e.g., in US 2018/0066279, the contents of which are incorporated by reference herein in its entirety.

[0675] In some embodiments, the miR binding site or miR binding site series comprises a miR-142-3p binding site sequence. In some embodiments, the miR-142-3p binding site comprises the nucleotide sequence of TCCATAAAGTAGGAAACACTACA (SEQ ID NO: 3674), a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 3674, e.g., wherein the modification can result in a mismatch between the miR binding site and the corresponding miRNA. In some embodiments, the miR-142-3p binding site comprises at least 3, 4, or 5 copies of a miR-142-3p binding site. In some embodiments, a miR binding site series comprises at least 3-5 copies, e.g., 4 copies, of a miR-142-3p binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, in length.

[0676] In some embodiments, the miR binding site is complementary to a miR expressed in a DRG (dorsal root ganglion) neuron, e.g., a miR183, a miR182, and/or miR96 binding site. In some embodiments, the miR binding site complementary to a miR expressed in expressed in a DRG neuron comprises a nucleotide sequence disclosed, e.g., in WO2020/132455, the contents of which are incorporated by reference herein in its entirety.

[0677] In some embodiments, the miR binding site or miR binding site series comprises a miR183 binding site sequence. In some embodiments, the miR183 binding site comprises the nucleotide sequence of AGTGAATTCTACCAGTGCCATA (SEQ ID NO: 3675), or a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 3675, e.g., wherein the modification can result in a mismatch between the miR binding site and the corresponding miRNA. In some embodiments, the sequence complementary to the seed sequence corresponds to the double underlined of the miR-183 binding site sequence. In some embodiments, the miR183 binding site comprises at least 3, 4, or 5 copies of a miR183 binding site. In some embodiments, a miR binding site series comprises at least 3-5 copies, e.g., 4 copies, of a miR183 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, in length.

[0678] In some embodiments, the miR binding site or miR binding site series comprises a miR182 binding site sequence. In some embodiments, the miR182 binding site comprises, the nucleotide sequence of AGTGTGAGTTCTACCATGCCAAA (SEQ ID NO: 3676), a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 3676, e.g., wherein the modification can result in a

mismatch between the miR binding site and the corresponding miRNA. In some embodiments, the miR182 binding site comprises at least 3, 4, or 5 copies of a miR182 binding site. In some embodiments, a miR binding site series comprises at least 3-5 copies, e.g., 4 copies, of a miR182 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, in length.

[0679] In certain embodiments, the miR binding site or miR binding site series comprises a miR96 binding site sequence. In some embodiments, the miR96 binding site comprises the nucleotide sequence of AGCAAAAATGTGCTAGTGCCAAA (SEQ ID NO: 3677), a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 3677, e.g., wherein the modification can result in a mismatch between the miR binding site and the corresponding miRNA. In some embodiments, the miR96 binding site comprises at least 3, 4, or 5 copies of a miR96 binding site. In some embodiments, a miR binding site series comprises at least 3-5 copies, e.g., 4 copies, of a miR96 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8, in length.

[0680] In some embodiments, the miR binding site series comprises a miR122 binding site, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR 96 binding site, or a combination thereof. In some embodiments, the miR binding site series comprises at least 3, 4, or 5 copies of a miR122 binding site, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR 96 binding site, or a combination thereof. In some embodiments, at least two of the miR binding sites are connected directly, e.g., without a spacer. In other embodiments, at least two of the miR binding sites are separated by a spacer, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive miR binding site sequences. In embodiments, the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, in length. In some embodiments, the spacer comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, a miR binding site series comprises at least 3-5 copies, e.g., 4 copies, of a combination of at least two, three, four, five, or all of a miR122 binding site, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR96 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, in length.

Viral Genome Component: Selectable marker

[0681] In some embodiments, the viral genome of the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), optionally encodes a selectable marker. The selectable marker may comprise a cell-surface marker, such as any

protein expressed on the surface of the cell including, but not limited to receptors, CD markers, lectins, integrins, or truncated versions thereof.

[0682] In some embodiments, selectable marker reporter genes are described in International Publication Nos. WO 1996023810 and WO 1996030540; Heim et al., Current Biology 2:178-182 (1996); Heim et al., Proc. Natl. Acad. Sci. USA (1995); or Heim et al., Science 373:663-664 (1995), the contents of each of which are incorporated herein by reference in their entirety.

Genome Size

[0683] In one embodiment, the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), may comprise a single-stranded or double-stranded viral genome. The size of the viral genome may be small, medium, large or the maximum size. As described above, the viral genome may comprise a promoter and a polyA tail.

[0684] In one embodiment, the viral genome may be a small single stranded viral genome. A small single stranded viral genome may be 2.1 to 3.5 kb in size such as, but not limited to, about 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, and 3.5 kb in size.

[0685] In one embodiment, the viral genome 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, but not limited to, about 1.3, 1.4, 1.5, 1.6, and 1.7 kb in size.

[0686] In one embodiment, the viral genome may be a medium single stranded viral genome. A medium single stranded viral genome may be 3.6 to 4.3 kb in size such as, but not limited to, about 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2 and 4.3 kb in size.

[0687] In one embodiment, the viral genome 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, but not limited to, about 1.8, 1.9, 2.0, and 2.1 kb in size.

[0688] In one embodiment, the viral genome 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, but not limited to, 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.

[0689] In one embodiment, the viral genome 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, but not limited to, about 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 and 3.0 kb in size.

Payloads

[0690] The AAV particles of the present disclosure (e.g. an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprise a viral genome with at least one payload region. In some embodiments, a payload region may be a nucleic acid sequence within the viral genome of an AAV particle described herein, which encodes a payload, wherein the payload is an

RNAi agent or a polypeptide. Payloads of the present disclosure may be, but are not limited to, peptides, polypeptides, proteins, antibodies, RNAi agents, etc.

[0691] In some embodiments, the payload region may comprise a combination of coding and non-coding nucleic acid sequences. In some embodiments, the payload region may encode a coding or non-coding RNA.

[0692] In one embodiment, the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein) comprises a viral genome with a payload region encoding more than one payload of interest. In such an embodiment, a viral genome encoding more than one payload may be replicated and packaged into a viral particle. A target cell transduced with a viral particle comprising more than one payload may express each of the payloads in a single cell.

[0693] In some embodiments, the AAV particles described herein, e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, comprises a nucleic acid encoding a payload. In some embodiments, the encoded payload comprises a therapeutic protein, an antibody, an enzyme, one or more components of a genome editing system, and/or an RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA). In some embodiments, the encoded payload modulates, e.g., increases or decreases, the presence, level, and/or activity of a gene, mRNA, protein, or a combination thereof, e.g., in a cell or a tissue.

Polypeptides

[0694] In some embodiments, the payload of AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises a polypeptide, e.g., a polypeptide described herein. Where the payload region encodes a polypeptide, the polypeptide may be a peptide or protein. The payload region may encode a product of any known gene and/or a recombinant version thereof. As a non-limiting example, the payload region may encode at least one allele of apolipoprotein E (APOE) such as, but not limited to ApoE2, ApoE3 and/or ApoE4. In one embodiment, the payload region encodes ApoE2 (cys112, cys158). In one embodiment, the payload region encodes ApoE3 (cys112, arg158). In one embodiment, the payload region encodes ApoE4 (arg112, arg158). As another non-limiting example, the payload region may encode aromatic L-amino acid decarboxylase (AADC). As another non-limiting example, the payload region may encode an antibody, or a fragment thereof. As another non-limiting example, the payload region may encode human survival of motor neuron (SMN) 1 or SMN2, or fragments or variants thereof. As another non-limiting example, the payload region may encode glucocerebrosidase (GBA1), or a fragment or variant thereof. As another non-limiting example, the payload region may encode granulin precursor or progranulin (GRN), or a fragment or variant thereof. As another non-limiting example, the payload

region may encode aspartoacylase (ASPA), or a fragment or variant thereof. As another non-limiting example, the payload region may encode tripeptidyl peptidase I (CLN2), or a fragment or variant thereof. As another non-limiting example, the payload region may encode beta-galactosidase (GLB1), or a fragment or variant thereof. As another non-limiting example, the payload region may encode N-sulphoglucosamine sulphohydrolase (SGSH), or a fragment or variant thereof. As another non-limiting example, the payload region may encode N-acetyl-alpha-glucosaminidase (NAGLU), or a fragment or variant thereof. As another non-limiting example, the payload region may encode iduronate 2-sulfatase (IDS), or a fragment or variant thereof. As another non-limiting example, the payload region may encode Intracellular cholesterol transporter (NPC1), or a fragment or variant thereof. As another non-limiting example, the payload region may encode gigaxonin (GAN), or a fragment or variant thereof. The AAV viral genomes encoding polypeptides described herein may be useful in the fields of human disease, viruses, infections veterinary applications and a variety of *in vivo* and *in vitro* settings.

[0695] Amino acid sequences encoded by payload regions of the viral genomes described herein, may be translated as a whole polypeptide, a plurality of polypeptides or fragments of polypeptides, which independently may be encoded by one or more nucleic acids, fragments of nucleic acids or variants of any of the aforementioned.

Antibodies and Antibody Binding Fragments

[0696] In some embodiments, the payload of AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises an antibody or antibody binding fragment. Where the payload region encodes an antibody, the “antibody” may be a full antibody, a fragment, or any derivative thereof, which forms a “functional antibody”, exhibiting the desired biological activity. As non-limiting examples, an antibody may be a native antibody (e.g., with two heavy and two light chains), a heavy chain variable region, a light chain variable region, a heavy chain constant region, a light chain constant region, Fab, Fab', F(ab')₂, Fv, or scFv fragments, a diabody, a linear antibody, a single-chain antibody, a multi-specific antibody, an intrabody, one or more heavy chain complementarity determining regions (CDR), one or more light chain CDRs, a bi-specific antibody, a monoclonal antibody, a polyclonal antibody, a humanized antibody, an antibody mimetic, an antibody variant, a miniaturized antibody, a unibody, a maxibody, and/or a chimeric antigen receptor.

[0697] A payload region of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may encode a polypeptide that forms or functions as any antibody, including antibodies that are known in the art and/or antibodies that are commercially available. The encoded antibody or antibody binding fragment may be therapeutic, diagnostic, or for research purposes. The encoded antibody or antibody binding fragment may be

useful in the treatment of a neurological disease, a neurodegenerative disorder, a muscular disease, a neuromuscular disorder, a neuro-oncological disorder, or any disorder associated with the central and/or peripheral nervous systems.

[0698] In some embodiments, the viral genome of the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant described herein) may comprise a nucleic acid which has been engineered to enable or enhance the expression of an antibody, or antibody binding fragment thereof.

[0699] In some embodiments, the encoded antibody of the payload of an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises at least one immunoglobulin variable domain sequence. An antibody may include, for example, full-length, mature antibodies and antigen-binding fragments of an antibody. For example, an antibody can include a heavy (H) chain variable domain sequence (VH), and a light (L) chain variable domain sequence (VL). In another example, an antibody includes two heavy (H) chain variable domain sequences and two light (L) chain variable domain sequence, thereby forming two antigen binding sites, such as Fab, Fab', F(ab')₂, Fc, Fd, Fd', Fv, single chain antibodies (scFv for example), single variable domain antibodies, diabodies (Dab) (bivalent and bispecific), and chimeric (e.g., humanized) antibodies, which may be produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. These functional antibody fragments, e.g., an antibody binding fragments, retain the ability to selectively bind with their respective antigen or receptor.

[0700] In some embodiments, the antibody binding fragment comprises at least one portion of an intact antibody, or recombinant variants thereof, and refers to the antigen binding domain, for example, an antigenic determining variable region of an intact antibody, that is sufficient to confer recognition and specific binding of the antibody fragment to a target, such as an antigen. Examples of antigen binding fragments include: (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a diabody (dAb) fragment, which consists of a VH domain; (vi) a camelid or camelized variable domain; (vii) a single chain Fv (scFv), see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883; and (viii) a single domain antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. An antibody fragment can also be incorporated into single domain antibodies, maxibodies, minibodies, nanobodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, for example, Hollinger and Hudson, Nature Biotechnology 23:1126-1136, 2005).

[0701] In some embodiments, the encoded antibody of the payload of an AAV particle described herein comprises a multispecific antibody, e.g., it comprises a plurality of immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In some embodiments, the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In some embodiments, the first and second epitopes overlap. In some embodiments, the first and second epitopes do not overlap. In some embodiments, the first and second epitopes are on different antigens, e.g., the different proteins (or different subunits of a multimeric protein). In some embodiments, a multispecific antibody comprises a third, fourth or fifth immunoglobulin variable domain. In some embodiments, a multispecific antibody is a bispecific antibody, a trispecific antibody, or tetraspecific antibody.

[0702] In some embodiments, an encoded multispecific antibody of the payload of an AAV particle described herein is an encoded bispecific antibody. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In some embodiments, the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In some embodiments, the first and second epitopes overlap. In some embodiments, the first and second epitopes do not overlap. In some embodiments, the first and second epitopes are on different antigens, e.g., the different proteins (or different subunits of a multimeric protein).

[0703] An antibody or an antibody binding fragment encoded in a payload region of an AAV particle described herein, may be, but is not limited to, an antibody or antibody fragment that binds to β -amyloid, APOE, tau, SOD1, TDP-43, huntingtin, and/or synuclein. In some embodiments, the encoded payload comprises an antibody or antibody fragment that binds to a neuro-oncology related target, e.g., HER2, EGFR (e.g., EGFRvIII).

Gene Editing System

[0704] In some embodiments, the payload of AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises a gene editing system or one or more components thereof. In some embodiments, the gene editing system comprises nucleic acid sequences that encode proteins having enzymatic activity to (i) selectively induce double or single stranded breaks in a DNA or RNA sequence, or (ii) substitute, insert or delete a particular base or set of bases of a DNA or RNA sequence in the absence of a double or single stranded break in the DNA or RNA. In some embodiments, the gene editing system includes, but is not limited to a CRISPR-Cas

system (including different Cas or Cas-related nucleases), a Zinc finger nuclease, a meganuclease, a TALEN or a base editors. In some embodiments, the gene editing system comprises a chromosomal integration of a transgene, e.g., introduced by a parvovirus vector in the absence of an exogenous nuclease or an enzymatic entity.

RNAi agents

[0705] In some embodiments, the payload of AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises an RNAi agent, e.g., an RNAi agent described herein. 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. RNAi mediated gene silencing can specifically inhibit targeted gene expression. Where the payload region of the viral genome of the AAV particles described herein encodes an RNAi agent, the RNAi agent may be, but is not limited to, dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA. Non-limiting examples of a target gene of an RNAi agent include, SOD1, MAPT, APOE, HTT, C9ORF72, TDP-43, APP, BACE, SNCA, ATXN1, ATXN3, ATXN7, SCN1A-SCN5A, or SCN8A-SCN11A.

[0706] The AAV particles described herein may comprise viral genomes encoding RNAi agents, wherein the RNAi agent targets the mRNA of a gene of interest to interfere with gene expression and/or protein production. Such AAV particles may be used as a therapeutic, a diagnostic, or for research purposes.

[0707] In one embodiment, the RNAi agent may target the gene of interest along any segment of their respective nucleotide sequence.

[0708] In one embodiment, the RNAi agent may target the gene of interest at the location of a single-nucleotide polymorphism (SNP) or variant within the nucleotide sequence.

[0709] In some embodiments, a nucleic acid sequence encoding an RNAi agent, or a single strand of an RNAi agent, is inserted into the viral genome of the AAV particle and introduced into cells, specifically cells in the central nervous system or cells of the DRG.

[0710] The RNAi agent may be an siRNA duplex, wherein the siRNA duplex contains an antisense strand (guide strand) and a sense strand (passenger strand) hybridized together forming a duplex structure, wherein the antisense strand is complementary to the nucleic acid sequence of the targeted gene, and wherein the sense strand is homologous to the nucleic acid sequence of the targeted 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.

[0711] Each strand of an siRNA duplex targeting a gene of interest may be about 19 to 25, 19 to 24 or 19 to 21 nucleotides in length, preferably about 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, or 25 nucleotides in length.

[0712] In one embodiment, an siRNA or dsRNA includes at least two sequences that are complementary to each other. The dsRNA includes a sense strand having a first sequence and an antisense strand having a second sequence. The antisense strand includes a nucleotide sequence that is substantially complementary to at least part of an mRNA encoding the target gene, and the region of complementarity is 30 nucleotides or less, and at least 15 nucleotides in length. Generally, the dsRNA is 19 to 25, 19 to 24 or 19 to 21 nucleotides in length. In some embodiments, the dsRNA is from about 15 to about 25 nucleotides in length, and in other embodiments the dsRNA is from about 25 to about 30 nucleotides in length. In some embodiments, the dsRNA is about 15 nucleotides in length, 16 nucleotides in length, 17 nucleotides in length, 18 nucleotides in length, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides in length, 26 nucleotides in length, 27 nucleotides in length, 28 nucleotides in length, 29 nucleotides in length, or 30 nucleotides in length.

[0713] The dsRNA, whether directly administered or encoded in a viral genome in an AAV particle, upon contacting with a cell expressing the target protein, inhibits the expression of the 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 known in the art.

[0714] In one embodiment, the RNAi agent may be used to reduce the expression of target protein 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%. As a non-limiting example, the expression of target protein expression may be reduced 50-90%.

[0715] In one embodiment, the RNAi agent may be used to reduce the expression of target mRNA 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%. As a non-limiting example, the expression of target mRNA expression may be reduced 50-90%.

[0716] In one embodiment, RNAi agent may be used to reduce the expression of target protein and/or mRNA in at least one region of the CNS. The expression of target protein and/or mRNA is reduced 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% in at least one region of the CNS. As a non-limiting example, the expression of target protein and mRNA in neurons (e.g., cortical neurons) is reduced by 50-90%. As a non-limiting example, the expression of target protein and mRNA in neurons (e.g., cortical neurons) is reduced by 40-50%.

[0717] In some embodiments, the AAV particle described herein, comprising a viral genome encoding at least one RNAi agent targeting a gene of interest is administered to a subject in need for treating and/or ameliorating a disease, e.g., a neurological disorder of any disease associated with the central or peripheral nervous systems.

[0718] In one embodiment, the RNAi agent is an siRNA.

Design of siRNA

[0719] An AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant described herein) may comprise a viral genome encoding one or more siRNA molecules (e.g., siRNA duplexes or encoded dsRNA) that are specifically designed to target a gene of interest and suppress target gene expression and protein production. In some aspects, the siRNA molecules are designed and used to selectively “knock out” target gene variants in cells, e.g., transcripts that are identified in neurological disease. In some aspects, the siRNA molecules are designed and used to selectively “knock down” target gene variants in cells.

[0720] In some embodiments, siRNA molecules targeting a gene of interest may be designed using any available design tools.

[0721] Some guidelines for designing siRNAs (for insertion into a viral genome of the AAV particles described herein) 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 considerations, together with the specific sequence of a target gene, highly

effective siRNA molecules essential for suppressing mammalian target gene expression may be readily designed.

[0722] In one embodiment, the sense and/or antisense strand is designed based on the method and rules outlined in European Patent Publication No. EP1752536, the contents of which are herein incorporated by reference in their entirety. As a non-limiting example, the 3'-terminal base of the sequence is adenine, thymine or uracil. As a non-limiting example, the 5'-terminal base of the sequence is guanine or cytosine. As a non-limiting example, the 3'-terminal sequence comprises seven bases rich in one or more bases of adenine, thymine and uracil.

[0723] In one embodiment, an siRNA molecule 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 target mRNA sequence to direct target-specific RNAi, e.g., the siRNA molecule has a sequence sufficient to trigger the destruction of the target mRNA by the RNAi machinery or process.

[0724] 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. Neither the identity of the sense sequence nor the homology of the antisense sequence need be 100% complementary to the target.

[0725] 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% complementary.

[0726] The siRNA molecule may have a length from about 10-50 or more nucleotides, e.g., 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 complementary to a target region. In one embodiment, the siRNA molecule has a length from about 19 to 25, 19 to 24 or 19 to 21 nucleotides.

[0727] In some embodiments, the siRNA molecule can be a synthetic RNA duplex comprising about 19 nucleotides to about 25 nucleotides, and two overhanging nucleotides at the 3'-end.

[0728] The siRNA molecule may comprise an antisense sequence and a sense sequence, 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% complementary.

[0729] 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% complementary across independently at least 50, 60, 70, 80, 85, 90, 95, or 99% of the length of the strands.

[0730] In some embodiments, the sense and antisense strands of a siRNA duplex are 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.

[0731] In some embodiments, the siRNA molecules, as well as associated spacer and/or flanking regions once designed, can be encoded by the viral genome of the AAV particles described herein, for delivery to a cell.

Molecular Scaffold

[0732] In some embodiments, the siRNA molecules may be encoded in a modulatory polynucleotide which also comprises a molecular scaffold.

[0733] In some embodiments, the modulatory polynucleotide which comprises the payload (e.g., siRNA, miRNA or other RNAi agent described herein) includes a molecular scaffold which comprises at least one 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. A 3' flanking sequence may mirror the 5' flanking sequence in size and origin. Either flanking sequence may be absent. In one embodiment, both the 5' and 3' flanking sequences are absent. The 3' flanking sequence may optionally contain one or more CNNC motifs, where "N" represents any nucleotide.

[0734] In some embodiments the 5' and 3' flanking sequences are the same length.

[0735] In some embodiments the 5' flanking sequence is from 1-10 nucleotides in length, from 5-15 nucleotides in length, from 10-30 nucleotides in length, from 20-50 nucleotides in length, greater than 40 nucleotides in length, greater than 50 nucleotides in length, greater than 100 nucleotides in length or greater than 200 nucleotides in length.

[0736] In some embodiments, the 5' flanking sequence may be 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,

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[0737] 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.

[0738] In some embodiments the 3' flanking sequence is from 1-10 nucleotides in length, from 5-15 nucleotides in length, from 10-30 nucleotides in length, from 20-50 nucleotides in length, greater than 40 nucleotides in length, greater than 50 nucleotides in length, greater than 100 nucleotides in length or greater than 200 nucleotides in length.

[0739] In some embodiments, the 3' flanking sequence may be 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,

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[0740] In some embodiments the 5' and 3' flanking sequences are the same sequence. In some embodiments they differ by 2%, 3%, 4%, 5%, 10%, 20% or more than 30% when aligned to each other.

[0741] Forming the stem of a stem loop structure is a minimum of at least one payload sequence. In some embodiments, the payload sequence comprises at least one nucleic acid sequence which is in part complementary or will hybridize to the target sequence. In some embodiments, the payload is an siRNA molecule or fragment of an siRNA molecule.

[0742] In some embodiments, the 5' arm of the stem loop comprises a sense sequence.

[0743] In some embodiments, the 3' arm of the stem loop comprises an antisense sequence. The antisense sequence, in some instances, comprises a "G" nucleotide at the 5' most end.

[0744] 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.

[0745] Separating the sense and antisense sequence of the stem loop structure is a loop (also known as a loop motif). The loop 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, and/or 12 nucleotides.

[0746] In some embodiments, the loop comprises at least one UGUG motif. In some embodiments, the UGUG motif is located at the 5' terminus of the loop.

[0747] Spacer regions may be present in the modulatory polynucleotide to separate one or more modules from one another. There may be one or more such spacer regions present.

[0748] In one embodiment, a spacer region of between 8-20, e.g., 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 sequence.

[0749] In one embodiment, the spacer is 13 nucleotides and is located between the 5' terminus of the sense sequence and a flanking sequence. In one embodiment, a spacer is of sufficient length to form approximately one helical turn of the sequence.

[0750] In one embodiment, a spacer region of between 8-20, e.g., 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.

[0751] In one embodiment, the spacer sequence is between 10-13, e.g., 10, 11, 12 or 13 nucleotides and is located between the 3' terminus of the antisense sequence and a flanking sequence. In one embodiment, a spacer is of sufficient length to form approximately one helical turn of the sequence.

[0752] In one embodiment, 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 sense sequence and the 3' arm comprises the antisense sequence. In another non-limiting example, the 5' arm comprises the antisense sequence and the 3' arm comprises the sense sequence.

[0753] In one embodiment, the 5' arm, payload (e.g., 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).

[0754] In one embodiment, the molecular scaffold of the modulatory polynucleotides is aligned in order to have the rate of excision of the guide or antisense strand be greater than the rate of excision of the passenger or 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%.

[0755] 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.

[0756] 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%.

[0757] 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.

[0758] In one embodiment, the molecular scaffold comprises a dual-function targeting modulatory polynucleotide.

[0759] 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.

[0760] 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 basal 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.

AAV production

[0761] Viral production disclosed herein describes processes and methods for producing AAV particles (with enhanced, improved and/or increased tropism for a target tissue), e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, that may be used to contact a target cell to deliver a payload.

[0762] In some embodiments, disclosed herein is a method of making AAV particle of the present disclosure, e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, the method comprising: (i) providing a host cell comprising a viral genome described herein and (ii) incubating the host cell under conditions suitable to enclose the viral genome in an AAV capsid variant, e.g., an AAV capsid variant described herein (e.g., an AAV capsid variant listed in Tables 3, 4, or 5), thereby making the AAV particle. In some embodiments, the method comprises prior to step (i), introducing a first nucleic acid comprising the viral genome into a cell. In some embodiments, the host cell comprises a second nucleic acid encoding the AAV capsid variant. In some embodiments, the second nucleic acid is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule. In some embodiments, the AAV particle described herein is an isolated AAV particle. In some embodiments, the AAV particle described herein is a recombinant AAV particle.

[0763] The present disclosure provides methods for the generation of an AAV particle comprising a peptide, e.g., a targeting peptide, (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein). In some embodiments, the AAV particles are prepared by viral genome replication in a viral replication cell. Any method known in the art may be used for the preparation of AAV particles. In some embodiments, AAV particles are produced in mammalian cells (e.g., HEK293). In another embodiment, AAV particles are produced in insect cells (e.g., Sf9).

[0764] Methods of making AAV particles are well known in the art and are described in e.g., U.S. Patent Nos. US6204059, US5756283, US6258595, US6261551, US6270996, US6281010, US6365394, US6475769, US6482634, US6485966, US6943019, US6953690, US7022519, US7238526, US7291498 and US7491508, US5064764, US6194191, US6566118, US8137948; or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597; *Methods In Molecular Biology*, ed. Richard, Humana Press, NJ (1995); O'Reilly et al., *Baculovirus Expression Vectors*, A Laboratory Manual, Oxford Univ. Press (1994); Samulski et al., *J. Vir.* 63:3822-8 (1989); Kajigaya et al., *Proc. Nat'l. Acad. Sci. USA* 88: 4646-50 (1991); Ruffing et al., *J. Vir.* 66:6922-30 (1992); Kimbauer et al., *Vir.*, 219:37-44 (1996); Zhao et al., *Vir.* 272:382-93 (2000); the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, the AAV particles are made using the methods described in International Patent Publication WO2015191508, the contents of which are herein incorporated by reference in their entirety.

Therapeutic Applications

[0765] The present disclosure provides a method for treating a disease, disorder and/or condition in a mammalian subject, including a human subject, comprising administering to the subject an AAV particle described herein, e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant (e.g., an AAV capsid variant described herein), or administering to the subject any of the described compositions, including a pharmaceutical composition, described herein.

[0766] In some embodiments, the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) are administered to a subject prophylactically, to prevent on-set of disease. In another embodiment, the AAV particle (e.g., an AAV particle comprising an AAV capsid variant) of the present disclosure are administered to treat (lessen the effects of) a disease or symptoms thereof. In yet another embodiment, the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) are administered to cure (eliminate) a disease. In another embodiment, the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) of the present disclosure are administered to prevent or slow progression of disease. In yet another embodiment, the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g.,

an AAV capsid variant) of the present disclosure are used to reverse the deleterious effects of a disease. Disease status and/or progression may be determined or monitored by standard methods known in the art.

[0767] In some embodiments, provided herein is method for treating a neurological disorder and/or neurodegenerative disorder in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition described herein or an AAV particle, e.g., a plurality of particles, comprising an AAV capsid variant described herein. In some embodiments, treatment of a neurological disorder and/or neurodegenerative disorder comprises prevention of said neurological disorder and/or neurological disorder.

[0768] In some embodiments, the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) of the disclosure is useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of neurological diseases and/or disorders.

[0769] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of tauopathy.

[0770] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Alzheimer's Disease.

[0771] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Friedreich's ataxia, or any disease stemming from a loss or partial loss of frataxin protein.

[0772] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Parkinson's Disease.

[0773] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Amyotrophic lateral sclerosis.

[0774] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Huntington's Disease.

[0775] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of chronic or neuropathic pain.

[0776] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is useful in the field of medicine for treatment, prophylaxis, palliation or amelioration of a disease associated with the central nervous system.

[0777] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is useful in the field of medicine for treatment, prophylaxis, palliation or amelioration of a disease associated with the peripheral nervous system.

[0778] In some embodiments, the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to a subject having at least one of the diseases or symptoms described herein. In some embodiments, an AAV particle of the present disclosure is administered to a subject having or diagnosed with having a disease or disorder described herein.

[0779] In some embodiments, provided herein is a method for treating a muscular disorder and/or neuromuscular disorder in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition described herein or an AAV particle, e.g., a plurality of particles, comprising an AAV capsid variant described herein. In some embodiments, treatment of a muscular disorder and/or neuromuscular disorder comprises prevention of said muscular disorder and/or neuromuscular disorder.

[0780] In some embodiments, provided herein is a method for treating a neuro-oncological disorder in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition described herein or an AAV particle, e.g., a plurality of particles, comprising an AAV capsid variant described herein. In some embodiments, treatment of a neuro-oncological disorder comprises prevention of said neuro-oncological disorder. In some embodiments, a neuro-oncological disorder comprises a cancer of a primary CNS origin (e.g., a CNS cell, a tissue, or a region), or a metastatic cancer in a CNS cell, tissue, or region.

[0781] Any neurological disease or disorder, neurodegenerative disorder, muscular disorder, neuromuscular disorder, and/or neuro-oncological disorder may be treated with the AAV particles of the disclosure, or pharmaceutical compositions thereof, including but not limited to, Absence of the Septum Pellucidum, Acid Lipase Disease, Acid Maltase Deficiency, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, Attention Deficit-Hyperactivity Disorder (ADHD), Adie's Pupil, Adie's Syndrome, Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, Aicardi-Goutieres Syndrome Disorder, AIDS - Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis (ALS), Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Antiphospholipid Syndrome, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari

Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia Telangiectasia, Ataxias and Cerebellar or Spinocerebellar Degeneration, Atrial Fibrillation and Stroke, Attention Deficit-Hyperactivity Disorder, Autism Spectrum Disorder, Autonomic Dysfunction, Back Pain, Barth Syndrome, Batten Disease, Becker's Myotonia, Bechet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbar palsy, Bulbospinal Muscular Atrophy, Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL), Canavan Disease, Carpal Tunnel Syndrome, Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Central Pontine Myelinolysis, Cephalic Disorders, Ceramidase Deficiency, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysms, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Cavernous Malformation, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Palsy, Cerebro-Oculo-Facio-Skeletal Syndrome (COFS), Charcot-Marie-Tooth Disease, Chiari Malformation, Cholesterol Ester Storage Disease, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIPD), Chronic Orthostatic Intolerance, Chronic Pain, Cockayne Syndrome Type II, Coffin Lowry Syndrome, Colpocephaly, Coma, Complex Regional Pain Syndrome, Concentric sclerosis (Baló's sclerosis), Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Cree encephalitis, Creutzfeldt-Jakob Disease, Chronic progressive external ophthalmoplegia, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Dejerine-Klumpke Palsy, Dementia, Dementia -Multi-Infarct, Dementia - Semantic, Dementia -Subcortical, Dementia With Lewy Bodies, Demyelination diseases, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Distal hereditary motor neuronopathies, Dravet Syndrome, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic Encephalopathy, Empty Sella Syndrome, Encephalitis, Encephalitis Lethargica, Encephaloceles, Encephalomyelitis, Encephalopathy, Encephalopathy (familial infantile), Encephalotrigeminal Angiomatosis, Epilepsy, Epileptic Hemiplegia, Episodic ataxia, Erb's Palsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Essential Tremor, Extrapontine Myelinolysis, Faber's disease, Fabry Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia Calcification, Familial Periodic Paralysis, Familial Spastic Paralysis,

Farber's Disease, Febrile Seizures, Fibromuscular Dysplasia, Fisher Syndrome, Floppy Infant Syndrome, Foot Drop, Friedreich's Ataxia, Frontotemporal Dementia, Gaucher Disease, Generalized Gangliosidoses (GM1, GM2), Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker Disease, Giant Axonal Neuropathy, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Glycogen Storage Disease, Guillain-Barré Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemispheric Continuity, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Hereditary Ataxia Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-I Associated Myelopathy, Hughes Syndrome, Huntington's Disease, Hurler syndrome, Hydranencephaly, Hydrocephalus, Hydrocephalus - Normal Pressure, Hydromyelia, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathies, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaacs' Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lichter's disease, Lipid Storage Diseases, Lipoid Proteinosis, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus - Neurological Sequelae, Lyme Disease - Neurological Complications, Lysosomal storage disorders, Machado-Joseph Disease, Macrencephaly, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini Stroke, Mitochondrial Myopathy, Mitochondrial DNA depletion syndromes, Moebius Syndrome, Monomelic Amyotrophy, Morvan Syndrome, Motor Neuron Diseases, Moyamoya Disease, Mucopolysaccharidoses, Mucopolysaccharidoses, Multi-Infarct Dementia, Multifocal Motor Neuropathy, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia - Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myelitis, Myoclonic Encephalopathy of Infants, Myoclonus, Myoclonus epilepsy, Myopathy, Myopathy - Congenital, Myopathy -Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, NARP (neuropathy, ataxia and retinitis pigmentosa), Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurodegenerative disease, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications of Lyme Disease, Neurological

Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid Lipofuscinosis, Neuronal Migration Disorders, Neuropathic pain, Neuropathy- Hereditary, Neuropathy, Neurosarcoidosis, Neurosyphilis, Neurotoxicity, Nevus Cavemosus, Niemann-Pick Disease, O'Sullivan-McLeod Syndrome, Occipital Neuralgia, Ohtabara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, Overuse Syndrome, Pain -Chronic, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Peroneal muscular atrophy, Periodic Paralysis, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Post-Polio Syndrome, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Postural Hypotension, Postural Orthostatic Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive bulbar palsy, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal Leukoencephalopathy, Progressive Muscular Atrophy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear Palsy, Prosopagnosia, Pseudobulbar palsy, Pseudo-Torch syndrome, Pseudotuberculosis syndrome, Pseudotumor Cerebri, Psychogenic Movement, Ramsay Hunt Syndrome I, Ramsay Hunt Syndrome II, Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease - Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Rheumatic Encephalitis, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Severe Myoclonic Epilepsy of Infancy (SMEI), Shaken Baby Syndrome, Shingles, Shy-Drager Syndrome, Sjögren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Ataxia, Spinocerebellar Atrophy, Spinocerebellar Degeneration, Sporadic ataxia, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, Short-lasting, Unilateral, Neuralgiform (SUNCT) Headache, Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis, Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient

Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Troyer Syndrome, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis Syndromes of the Central and Peripheral Nervous Systems, Vitamin B12 deficiency, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson Disease, Wolman's Disease, X-Linked Spinal and Bulbar Muscular Atrophy.

Pharmaceutical Composition and Formulations

[0782] According to the present disclosure, an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant described herein may be prepared as a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises at least one active ingredients. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient.

[0783] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid polypeptide, e.g., an AAV capsid variant) can be formulated using an excipient to: (1) increase stability; (2) increase cell transfection or transduction; (3) permit the sustained or delayed expression of the payload; (4) alter the biodistribution (e.g., target the viral particle to specific tissues or cell types); (5) increase the translation of encoded protein; (6) alter the release profile of encoded protein; and/or (7) allow for regulatable expression of the payload. Formulations of the present disclosure can include, without limitation, saline, liposomes, lipid nanoparticles, polymers, peptides, proteins, cells transfected with viral vectors (e.g., for transfer or transplantation into a subject) and combinations thereof.

[0784] In some embodiments, the relative amount of the active ingredient (e.g. an AAV particle described herein), a pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% 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.

[0785] In some embodiments, the pharmaceutical composition comprising an AAV particle described herein may comprise an AAV capsid polypeptide, e.g., an AAV capsid variant and a viral genome encoding a payload, e.g., a payload described herein, with or without a pharmaceutically acceptable excipient.

[0786] The present disclosure also provides in some embodiments, a pharmaceutical composition suitable for administration to a subject, e.g., a human. In some embodiments, the pharmaceutical composition is administered to a subject, e.g., a human.

Administration

[0787] In some embodiments, an AAV particle disclosed herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be administered by a to a subject by a delivery route, e.g., a localized delivery route or a systemic delivery route. In some embodiments, the AAV particle is administered to a subject by a delivery route which results in therapeutically effective outcome.

[0788] In some embodiments, an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be administered via such a route that it is able to cross the blood-brain barrier, vascular barrier, or other epithelial barrier. In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) 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. In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be formulated with any appropriate and pharmaceutically acceptable excipient.

[0789] In some embodiments, the AAV particle described herein (e.g., an AAV particle comprising, an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered intramuscularly, intravenously, intracerebrally, intrathecally, intracerebroventricularly, via intraparenchymal administration, or via intra-cisterna magna injection (ICM).

[0790] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be delivered to a subject via a single route administration. In some embodiments, an AAV particle of the present disclosure may be delivered to a subject via a multi-site route of administration. In some embodiments, a subject may be administered at 2, 3, 4, 5, or more than 5 sites.

[0791] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising, an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered via a bolus infusion. In some embodiments, an AAV particle of the present disclosure is administered via sustained delivery over a period of minutes, hours, or days. In some embodiments, the infusion rate may be changed depending on the subject, distribution, formulation, and/or another delivery parameter. In some embodiments, an AAV particle of the present disclosure is administered using a controlled release, e.g., a release profile that conforms to a particular pattern of release to effect a therapeutic outcome. In some embodiments, an AAV particle of the present disclosure is

administered using a sustained release, e.g., a release profile that conforms to a release rate over a specific period of time.

[0792] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be delivered by more than one route of administration. As non-limiting examples of combination administrations, an AAV particle may be delivered by intrathecal and intracerebroventricular, or by intravenous and intraparenchymal administration.

Intravenous administration

[0793] In some embodiments, an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be administered to a subject by systemic administration. In some embodiments, the systemic administration is intravenous administration. In another embodiment, the systemic administration is intraarterial administration. In some embodiments, an AAV particle of the present disclosure may be administered to a subject by intravenous administration. In some embodiments, the intravenous administration may be achieved by subcutaneous delivery. In some embodiments, the AAV particle is administered to the subject via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB) or MRI-guided FUS coupled with intravenous administration, e.g., as described in Terstappen et al. (Nat Rev Drug Discovery, <https://doi.org/10.1038/s41573-021-00139-y> (2021)), the contents of which are incorporated herein by reference in its entirety. In some embodiments, the AAV particle is administered to the subject intravenously. In some embodiments, the subject is a human.

Administration to the CNS

[0794] In some embodiments, an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be delivered by direct injection into the brain. As a non-limiting example, the brain delivery may be by intrahippocampal administration. In some embodiments, an AAV particle of the present disclosure may be administered to a subject by intraparenchymal administration. In some embodiments, the intraparenchymal administration is to tissue of the central nervous system. In some embodiments, an AAV particle of the present disclosure may be administered to a subject by intracranial delivery (See, e.g., US Pat. No. 8119611; the content of which is incorporated herein by reference in its entirety). In some embodiments, an AAV particle described herein may be delivered by injection into the CSF pathway. Non-limiting examples of delivery to the CSF pathway include intrathecal and intracerebroventricular administration.

[0795] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be delivered to the brain by systemic delivery. As a non-limiting example, the systemic delivery may be by intravascular

administration. As a non-limiting example, the systemic or intravascular administration may be intravenous.

[0796] In some embodiments, an AAV particle of the present disclosure may be delivered by an intraocular delivery route. A non-limiting example of an intraocular administration includes an intravitreal injection.

Intramuscular administration

[0797] In some embodiments, an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be delivered by intramuscular administration. Without wishing to be bound by theory, it is believed in some embodiments, that the multi-nucleated nature of muscle cells provides an advantage to gene transduction subsequent to AAV delivery. In some embodiments, cells of the muscle are capable of expressing recombinant proteins with the appropriate post-translational modifications. Without wishing to be bound by theory, it is believed in some embodiments, the enrichment of muscle tissue with vascular structures allows for transfer to the blood stream and whole-body delivery. Examples of intramuscular administration include systemic (e.g., intravenous), subcutaneous or directly into the muscle. In some embodiments, more than one injection is administered. In some embodiments, an AAV particle of the present disclosure may be delivered by an intramuscular delivery route. (See, e.g., U. S. Pat. No. 6506379; the content of which is incorporated herein by reference in its entirety). Non-limiting examples of intramuscular administration include an intravenous injection or a subcutaneous injection.

[0798] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to a subject and transduces the muscle of a subject. As a non-limiting example, an AAV particle is administered by intramuscular administration. In some embodiments, an AAV particle of the present disclosure may be administered to a subject by subcutaneous administration. In some embodiments, the intramuscular administration is via systemic delivery. In some embodiments, the intramuscular administration is via intravenous delivery. In some embodiments, the intramuscular administration is via direct injection to the muscle.

[0799] In some embodiments, the muscle is transduced by administration, e.g., intramuscular administration. In some embodiments, an intramuscular delivery comprises administration at one site. In some embodiments, an intramuscular delivery comprises administration at more than one site. In some embodiments, an intramuscular delivery comprises administration at two, three, four, or more sites. In some embodiments, intramuscular delivery is combined with at least one other method of administration.

[0800] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be administered to a subject by peripheral injections. Non-limiting examples of peripheral injections include intraperitoneal, intramuscular, intravenous, conjunctival, or joint injection. It was disclosed in the art that the peripheral administration of AAV vectors can be transported to the central nervous system, for example, to the motor neurons (e.g., U. S. Patent Publication Nos. US20100240739 and US20100130594; the content of each of which is incorporated herein by reference in their entirety).

[0801] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be administered to a subject by intraparenchymal administration. In some embodiments, the intraparenchymal administration is to muscle tissue. In some embodiments, an AAV particle of the present disclosure is delivered as described in Bright et al 2015 (Neurobiol Aging, 36(2):693-709), the contents of which are herein incorporated by reference in their entirety. In some embodiments, an AAV particle of the present disclosure is administered to the gastrocnemius muscle of a subject. In some embodiments, an AAV particle of the present disclosure is administered to the bicep femorii of the subject. In some embodiments, an AAV particle of the present disclosure is administered to the tibialis anterior muscles. In some embodiments, an AAV particle of the present disclosure is administered to the soleus muscle.

Depot administration

[0802] As described herein, in some embodiments, a pharmaceutical composition and/or an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) are formulated in depots for extended release. Generally, specific organs or tissues are targeted for administration.

[0803] In some embodiments, a pharmaceutical composition and/or an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) are spatially retained within or proximal to target tissues. Provided are methods of providing a pharmaceutical composition, an AAV particle, to target tissues of mammalian subjects by contacting target tissues (which comprise one or more target cells) with the pharmaceutical composition and/or the AAV particle, under conditions such that they are substantially retained in target tissues, e.g., such that at least 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the composition is retained in the target tissues. In some embodiments, retention is determined by measuring the amount of pharmaceutical composition and/or AAV particle, that enter a target cell or a plurality of target cells. For example, at least 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.9%, 99.99%, or greater than 99.99% of a pharmaceutical composition and/or an AAV particle, administered to a subject are present intracellularly at a period of time following administration. For example,

intramuscular injection to a subject may be performed using aqueous compositions comprising a pharmaceutical composition and/or an AAV particle of the present disclosure and a transfection reagent, and retention is determined by measuring the amount of the pharmaceutical composition and/or the AAV particle, present in the muscle cell or plurality of muscle cells.

[0804] In some embodiments, disclosed herein are methods of providing a pharmaceutical composition and/or an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a tissue of a subject, by contacting the tissue (comprising a cell, e.g., a plurality of cells) with the pharmaceutical composition and/or the AAV particle under conditions such that they are substantially retained in the tissue. In some embodiments, a pharmaceutical composition and/or AAV particle described herein comprise a sufficient amount of an active ingredient such that the effect of interest is produced in at least one cell. In some embodiments, a pharmaceutical composition and/or an AAV particle generally comprise one or more cell penetration agents. In some embodiments, the disclosure provides a naked formulations (such as without cell penetration agents or other agents), with or without pharmaceutically acceptable carriers.

Methods of Treatment

AAV particles encoding protein payloads

[0805] Provided in the present disclosure are methods for introducing the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) into cells, the method comprising introducing into said cells any of the vectors in an amount sufficient to modulate, e.g., increase, the production of a target mRNA and/or protein. In some aspects, the cells may be neurons such as but not limited to, motor, hippocampal, entorhinal, thalamic, cortical, sensory, sympathetic, or parasympathetic neurons, and glial cells such as astrocytes, microglia, and/or oligodendrocytes. In other aspects, the cells may be a muscle cell, e.g., a cell of a diaphragm, a quadriceps, or a heart (e.g., a heart atrium or a heart ventricle).

[0806] Disclosed in the present disclosure are methods for treating a neurological disease/disorder or a neurodegenerative disorder, a muscular or neuromuscular disorder, or a neurooncological disorder associated with aberrant, e.g., insufficient or increased, function/presence of a protein, e.g., a target protein in a subject in need of treatment. The method comprises administering to the subject a therapeutically effective amount of a composition comprising AAV particles of the present disclosure. As a non-limiting example, the AAV particles can increase target gene expression, increase target protein production, and thus reduce one or more symptoms of neurological disease in the subject such that the subject is therapeutically treated.

[0807] In some embodiments, the composition comprising the AAV particles of the present disclosure is administered to the central nervous system of the subject via systemic administration. In some embodiments, the systemic administration is intravenous (IV) injection. In some embodiments,

the AAV particle described herein or a pharmaceutical composition comprising an AAV particle described herein is administered by focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB) or MRI-guided FUS coupled with intravenous administration.

[0808] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to the central nervous system of the subject via intraventricular administration. In some embodiments, the intraventricular administration is intra-cisterna magna injection (ICM).

[0809] In some embodiments, the composition comprising an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to the central nervous system of the subject via intraventricular injection and intravenous injection.

[0810] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to the central nervous system of the subject via ICM injection and intravenous injection at a specific dose per subject. As a non-limiting example, the AAV particles are administered via ICM injection at a dose of 1×10^4 VG per subject. As a non-limiting example, the AAV particles are administered via IV injection at a dose of 2×10^{13} VG per subject.

[0811] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to the central nervous system of the subject. In other embodiments, the composition comprising the AAV particles of the present disclosure is administered to a CNS tissue of a subject (e.g., putamen, thalamus or cortex of the subject).

[0812] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to the central nervous system of the subject via intraparenchymal injection. Non-limiting examples of intraparenchymal injections include intraputamenal, intracortical, intrathalamic, intrastriatal, intrahippocampal or into the entorhinal cortex.

[0813] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to the central nervous system of the subject via intraparenchymal injection and intravenous injection.

[0814] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid

variant) is administered to the central nervous system of the subject via intraventricular injection, intraparenchymal injection and intravenous injection.

[0815] In some embodiments, the composition comprising an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) of a plurality of particles of the present disclosure is administered to a muscle of the subject via intravenous injection. In some embodiments, the composition comprising an AAV particle of a plurality of particles of the present disclosure is administered to a muscle of the subject via intramuscular injection.

[0816] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be delivered into specific types of targeted cells, including, but not limited to, thalamic, hippocampal, entorhinal, cortical, motor, sensory, excitatory, inhibitory, sympathetic, or parasympathetic neurons; glial cells including oligodendrocytes, astrocytes and microglia; and/or other cells surrounding neurons such as T cells. In some embodiments, an AAV particle of the present disclosure may be delivered into a muscle cell, e.g., a cell of the quadriceps, diaphragm, liver, and/or heart.

[0817] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be delivered to neurons in the putamen, thalamus and/or cortex.

[0818] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for neurological disease.

[0819] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for tauopathies.

[0820] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Alzheimer's Disease.

[0821] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Amyotrophic Lateral Sclerosis.

[0822] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Huntington's Disease.

[0823] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Parkinson's Disease.

[0824] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Friedreich's Ataxia.

[0825] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for chronic or neuropathic pain.

[0826] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for a muscular disorder or a neuromuscular disorder.

[0827] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) e.g., a plurality of particles, of the present disclosure may be used as a therapy for a neuro-oncological disorder. In some embodiments, the neuro-oncological disorder is a cancer of primary CNS origin (e.g., a cancer of a CNS cell and/or CNS tissue). In some embodiments, the neuro-oncological disorder is metastatic cancer in a CNS cell, CNS region, and/or a CNS tissue.

[0828] In some embodiments, administration of the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a subject may increase target protein levels in a subject. The target protein levels may be increased by 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% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS, or a muscle, a region of a muscle, or a cell of a muscle, of a subject. As a non-limiting example, the AAV particles may increase the protein levels of a target protein by at least 50%. As a non-limiting example, the AAV particles may increase the proteins levels of a target protein by at least 40%. As a non-limiting example, a subject may have an increase of 10% of target protein. As a non-limiting example, the AAV particles may increase the protein levels of a target protein by fold increases over baseline. In some embodiments, AAV particles lead to 5-6 times higher levels of a target protein.

[0829] In some embodiments, administration of the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a subject may increase the expression of a target protein in a subject. The expression of the target protein may be increased by 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% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS or a muscle, a region of a muscle, or a cell of a muscle of a subject. As a non-limiting example, the AAV particles may increase the expression of a target protein by at least 50%. As a non-limiting example, the AAV particles may increase the expression of a target protein by at least 40%.

[0830] In some embodiments, intravenous administration of the AAV particles described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a subject may increase the CNS expression or expression in a muscle, of a target protein in a subject. The expression of the target protein may be increased by 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% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS or a muscle, a region of a muscle, or a cell of a muscle of a subject. As a non-limiting example, the AAV particles may increase the expression of a target protein in the CNS by at least 50%. As a non-limiting example, the AAV particles may increase the expression of a target protein in the CNS by at least 40%. In some embodiments, the AAV particle may increase expression of a target protein in a muscle by at least 50%. In some embodiments, the AAV particle may increase expression of a target protein in a muscle by at least 50%.

[0831] In some embodiments, the AAV particles of the present disclosure (e.g., an AAV particle comprising, an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to increase target protein expression in astrocytes in order to treat a neurological disease. Target protein in astrocytes may be increased 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%.

[0832] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to increase target protein in microglia. The increase of target protein in microglia may be, independently, increased 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%.

[0833] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to increase target protein in cortical neurons. The increase of target protein in the cortical neurons may be, independently, increased 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%.

[0834] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to increase target protein in hippocampal neurons. The increase of target protein in the hippocampal neurons may be, independently, increased 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%.

[0835] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to increase target protein in DRG and/or sympathetic neurons. The increase of target protein in the DRG and/or sympathetic neurons may be, independently, increased 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%.

[0836] In some embodiments, the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to increase target protein in sensory neurons in order to treat neurological disease. Target protein in sensory neurons may be increased 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%.

[0837] In some embodiments, the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to increase target protein and reduce symptoms of neurological disease in a subject. The increase of target protein and/or the reduction of symptoms of neurological disease may be, independently, altered (increased for the production of target protein and reduced for the symptoms of neurological disease) 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%.

[0838] In some embodiments, the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) 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.

[0839] In some embodiments, the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to improve performance on any assessment used to measure symptoms of neurological disease. Such assessments include, but are not limited to ADAS-cog (Alzheimer Disease Assessment Scale – cognitive), MMSE (Mini-Mental State Examination), GDS (Geriatric Depression Scale), FAQ (Functional Activities Questionnaire), ADL (Activities of Daily Living), GPCOG (General Practitioner Assessment of Cognition), Mini-Cog, AMTS (Abbreviated Mental Test Score), Clock-drawing test, 6-CIT (6-item Cognitive Impairment Test), TYM (Test Your Memory), MoCa (Montreal Cognitive Assessment), ACE-R (Addenbrookes Cognitive Assessment), MIS (Memory Impairment Screen), BADLS (Bristol Activities of Daily Living Scale), Barthel Index, Functional Independence Measure, Instrumental Activities of Daily Living, IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly), Neuropsychiatric Inventory, The Cohen-Mansfield Agitation Inventory, BEHAVE-AD, EuroQol, Short Form-36 and/or MBR Caregiver Strain Instrument, or any of the other tests as described in Sheehan B (Ther Adv Neurol Disord. 5(6):349-358 (2012)), the contents of which are herein incorporated by reference in their entirety.

[0840] In some embodiments, the present composition is administered as a solo therapeutic or as combination therapeutic for the treatment of a neurological disease/disorder or a neurodegenerative disorder, a muscular disorder or neuromuscular disorder, and/or a neuro-oncological disorder.

[0841] The AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) encoding the target protein may be used in combination with one or more other therapeutic agents. In some embodiments, 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.

[0842] Therapeutic agents that may be used in combination with the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) can be small molecule compounds which are antioxidants, anti-inflammatory agents, anti-apoptosis agents, calcium regulators, anti-glutamatergic agents, structural protein inhibitors, compounds involved in muscle function, and compounds involved in metal ion regulation. As a non-limiting example, 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 motor neuron degeneration.

[0843] Compounds tested for treating neurological disease which may be used in combination with the AAV particles described herein include, but are not limited to, cholinesterase inhibitors (donepezil, rivastigmine, galantamine), NMDA receptor antagonists such as memantine, anti-psychotics, anti-depressants, anti-convulsants (e.g., sodium valproate and levetiracetam for myoclonus), secretase inhibitors, amyloid aggregation inhibitors, copper or zinc modulators, BACE inhibitors, inhibitors of tau aggregation, such as Methylene blue, phenothiazines, anthraquinones, n-phenylamines or rhodamines, microtubule stabilizers such as NAP, taxol or paclitaxel, kinase or phosphatase inhibitors such as those targeting GSK3 β (lithium) or PP2A, immunization with A β peptides or tau phospho-epitopes, anti-tau or anti-amyloid antibodies, dopamine-depleting agents (e.g., tetrabenazine for chorea), benzodiazepines (e.g., clonazepam for myoclonus, chorea, dystonia, rigidity, and/or spasticity), amino acid precursors of dopamine (e.g., levodopa for rigidity), skeletal muscle relaxants (e.g., baclofen, tizanidine for rigidity and/or spasticity), inhibitors for acetylcholine 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), 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).

[0844] Neurotrophic factors may be used in combination therapy with the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) for treating neurological disease. 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.

[0845] In one aspect, the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be co-administered with AAV particles expressing neurotrophic factors such as AAV-IGF-I (See e.g., Vincent et al., *Neuromolecular medicine*, 2004, 6, 79-85; the contents of which are incorporated herein by reference in their entirety) and AAV-GDNF (See e.g., Wang et al., *J Neurosci.*, 2002, 22, 6920-6928; the contents of which are incorporated herein by reference in their entirety).

[0846] In some embodiments, administration of the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a subject will modulate, e.g., increase or decrease, the expression of a target protein in a subject and the modulation, e.g., increase or decrease of the presence, level, activity, and/or expression of the target protein will reduce the effects and/or symptoms of a neurological disease/disorder or a neurodegenerative disorder, a muscular disorder or neuromuscular disorder, and/or a neuro-oncological disorder in a subject.

[0847] As a non-limiting example, the target protein may be a therapeutic protein or functional variant, or an antibody or antibody binding fragment thereof.

AAV particles comprising RNAi agents or modulatory polynucleotides

[0848] Provided in the present disclosure are methods for introducing the AAV particles of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), comprising a viral genome with a nucleic acid sequence encoding a payload comprising a siRNA molecule into cells, the method comprising introducing into said cells any of the vectors in an amount sufficient for degradation of a target mRNA to occur, thereby activating target-specific RNAi in the cells. In some aspects, the cells may be neurons such as but not limited to, motor, hippocampal, entorhinal, thalamic, cortical, sensory, sympathetic, or parasympathetic neurons, and glial cells such as astrocytes, microglia, and/or oligodendrocytes. In other aspects, the cells may be a muscle cell, e.g., a cell of a diaphragm, a quadriceps, or a heart (e.g., a heart atrium or a heart ventricle).

[0849] Disclosed in the present disclosure are methods for treating a neurological disease/disorder or a neurodegenerative disorder, a muscular or neuromuscular disorder, or a neurooncological disorder associated with dysfunction and/or aberrant, e.g., increased or decreased expression of a target protein in a subject in need of treatment. The method comprises administering to the subject a therapeutically effective amount of a composition comprising AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules. As a non-limiting example, the siRNA molecules can silence target gene expression, inhibit target protein production,

and reduce one or more symptoms of neurological disease in the subject such that the subject is therapeutically treated.

[0850] In some embodiments, the composition comprising the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome encoding one or more siRNA molecules comprise an AAV capsid that allows for enhanced transduction of CNS and/or PNS cells after intravenous administration.

[0851] In some embodiments, the composition comprising the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) with a viral genome encoding at least one siRNA molecule is administered to the central nervous system of the subject. In other embodiments, the composition comprising the AAV particles of the present disclosure is administered to a tissue of a subject (e.g., putamen, thalamus or cortex of the subject).

[0852] In some embodiments, the composition comprising the AAV particles of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules is administered to the central nervous system of the subject via systemic administration. In some embodiments, the systemic administration is intravenous injection. In some embodiments, the AAV particle described herein or a pharmaceutical composition comprising an AAV particle described herein is administered by focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB) or MRI-guided FUS coupled with intravenous administration.

[0853] In some embodiments, the composition comprising the AAV particles of the disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules is administered to the central nervous system of the subject via intraparenchymal injection. Non-limiting examples of intraparenchymal injections include intraputamenal, intracortical, intrathalamic, intrastriatal, intrahippocampal or into the entorhinal cortex.

[0854] In some embodiments, the composition comprising the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules is administered to the central nervous system of the subject via intraparenchymal injection and intravenous injection.

[0855] In some embodiments, the composition comprising an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) of a plurality of particles of the present disclosure is administered to a muscle of the subject via intravenous injection. In some embodiments, the composition comprising an AAV particle of a plurality of particles of the present disclosure is administered to a muscle of the subject via intramuscular injection.

[0856] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be delivered into specific types or targeted cells, including, but not limited to, thalamic, hippocampal, entorhinal, cortical, motor, sensory, excitatory, inhibitory, sympathetic, or parasympathetic neurons; glial cells including oligodendrocytes, astrocytes and microglia; and/or other cells surrounding neurons such as T cells. In some embodiments, an AAV particle of the present disclosure may be delivered into a muscle cell, e.g., a cell of the quadriceps, diaphragm, liver, and/or heart.

[0857] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be delivered to neurons in the putamen, thalamus, and/or cortex.

[0858] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for neurological disease.

[0859] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for tauopathies.

[0860] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Alzheimer's Disease.

[0861] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Amyotrophic Lateral Sclerosis.

[0862] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Huntington's Disease.

[0863] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Parkinson's Disease.

[0864] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Friedreich's Ataxia.

[0865] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for a muscular disorder or a neuromuscular disorder.

[0866] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for a neuro-oncological disorder. In some embodiments, the neuro-oncological disorder is a cancer of primary CNS origin (e.g., a cancer of a CNS cell and/or CNS tissue). In some embodiments, the neuro-oncological disorder is metastatic cancer in a CNS cell, a CNS region, and/or a CNS tissue.

[0867] In some embodiments, the administration of AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules to a subject may lower target protein levels in a subject. The target protein levels may be lowered by 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% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS, or a muscle, a region of a muscle, or a cell of a muscle, of a subject. As a non-limiting example, the AAV particles may lower the protein levels of a target protein by at least 50%. As a non-limiting example, the AAV particles may lower the proteins levels of a target protein by at least 40%.

[0868] In some embodiments, the administration of AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules to a subject may lower the expression of a target protein in a subject. The expression of a target protein may be lowered by 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% in a

subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS, or a muscle, a region of a muscle, or a cell of a muscle, of a subject. As a non-limiting example, the AAV particles may lower the expression of a target protein by at least 50%. As a non-limiting example, the AAV particles may lower the expression of a target protein by at least 40%.

[0869] In some embodiments, the administration of AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules to a subject may lower the expression of a target protein in the CNS of a subject. The expression of a target protein may be lowered by 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% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS, or a muscle, a region of a muscle, or a cell of a muscle, of a subject. As a non-limiting example, the AAV particles may lower the expression of a target protein by at least 50%. As a non-limiting example, the AAV particles may lower the expression of a target protein by at least 40%.

[0870] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein in astrocytes in order to treat neurological disease. Target protein in astrocytes may be 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%. Target protein in astrocytes may be reduced 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%.

[0871] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein in microglia. The suppression of the target protein in microglia 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 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%.

[0872] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress target protein in cortical neurons. The suppression of a target protein in cortical neurons 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 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%.

[0873] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein in hippocampal neurons. The suppression of a target protein in the hippocampal neurons 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 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%.

[0874] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein in DRG and/or sympathetic neurons. The suppression of a target protein in the DRG and/or sympathetic neurons 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 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%.

[0875] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein in sensory neurons in order to treat neurological disease. Target protein in sensory neurons may be 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%. Target protein in the sensory neurons may be reduced 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%.

[0876] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein and reduce symptoms of neurological disease in a subject. The suppression of target protein and/or the reduction of symptoms of neurological disease may be, independently, reduced or 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%.

[0877] In some embodiments, the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules 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.

[0878] In some embodiments, the present composition is administered as a solo therapeutic or as combination therapeutic for the treatment of a neurological disease/disorder or a neurodegenerative disorder, a muscular disorder or neuromuscular disorder, and/or a neuro-oncological disorder.

[0879] The AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used in combination with one or more other therapeutic agents. In some embodiments, 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.

[0880] Therapeutic agents that may be used in combination with the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules 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.

[0881] Compounds tested for treating neurological disease which may be used in combination with the AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules include, but are not limited to, cholinesterase inhibitors (donepezil, rivastigmine, galantamine), NMDA receptor antagonists such as memantine, anti-psychotics, anti-depressants, anti-convulsants (e.g., sodium valproate and levetiracetam for myoclonus), secretase inhibitors, amyloid aggregation inhibitors, copper or zinc modulators, BACE inhibitors, inhibitors of tau aggregation, such as Methylene blue, phenothiazines, anthraquinones, n-phenylamines or rhodamines, microtubule stabilizers such as NAP, taxol or paclitaxel, kinase or phosphatase inhibitors such as those targeting GSK3 β (lithium) or PP2A, immunization with A β peptides or tau phospho-epitopes, anti-tau or anti-amyloid antibodies, dopamine-depleting agents (e.g., tetrabenazine for chorea), benzodiazepines (e.g., clonazepam for myoclonus, chorea, dystonia, rigidity, and/or spasticity), amino acid precursors of dopamine (e.g., levodopa for rigidity), skeletal muscle relaxants (e.g., baclofen, tizanidine for rigidity and/or spasticity), inhibitors for acetylcholine 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), 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).

[0882] Neurotrophic factors may be used in combination therapy with the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules for treating neurological disease. 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.

[0883] In one aspect, the AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) encoding the nucleic acid sequence for the at least one siRNA duplex targeting the gene of interest may be co-administered with AAV particles 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 contents of which are incorporated herein by reference in their entirety).

[0884] In some embodiments, administration of the AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a subject will modulate, e.g., reduce the presence, level, activity, and/or expression of a target gene, mRNA, and/or protein in a subject and the reduction of expression of the target protein will reduce the effects and/or symptoms of a neurological disease/disorder or a neurodegenerative disorder, a muscular disorder or neuromuscular disorder, and/or a neuro-oncological disorder in a subject.

DEFINITIONS

[0885] 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 the invention pertains.

[0886] 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 disclosure 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 disclosure 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.

[0887] 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” and “consisting essentially thereof” is thus also encompassed and disclosed.

[0888] 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 disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0889] *Adeno-associated virus*: As used herein, the term “adeno-associated virus” or “AAV” refers to members of the dependovirus genus or a variant, e.g., a functional variant, thereof. In some embodiments, the AAV is wildtype, or naturally occurring. In some embodiments, the AAV is recombinant.

[0890] *AAV Particle*: As used herein, an “AAV particle” refers to a particle or a virion comprising an AAV capsid, e.g., an AAV capsid variant, and a polynucleotide, e.g., a viral genome or a vector genome. In some embodiments, the viral genome of the AAV particle comprises at least one payload region and at least one ITR. In some embodiments, an AAV particle of the disclosure is an AAV particle comprising an AAV capsid polypeptide, e.g., a parent capsid sequence with at least one peptide, e.g., targeting peptide, insert. In some embodiments, the AAV particle is capable of delivering a nucleic acid, e.g., a payload region, encoding a payload to cells, typically, mammalian, e.g., human, cells. In some embodiments, an AAV particle of the present disclosure may be produced recombinantly. In some embodiments, an AAV particle may be derived from any serotype, described herein or known in the art, including combinations of serotypes (e.g., “pseudotyped” AAV) or from various genomes (e.g., single stranded or self-complementary). In some embodiments, the AAV particle may be replication defective and/or targeted. In some embodiments, the AAV particle may comprise a peptide, e.g., targeting peptide, present, e.g., inserted into, the capsid to enhance tropism for a desired target tissue. It is to be understood that reference to the AAV particle of the disclosure also includes pharmaceutical compositions thereof, even if not explicitly recited.

[0891] *Administering*: As used herein, the term “administering” refers to providing a pharmaceutical agent or composition to a subject.

[0892] *Amelioration*: 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.

[0893] *Amplicon*: As used herein, “amplicon” may refer to any piece of RNA or DNA formed as the product of amplification events, e.g. PCR. In some embodiments, full-length capsid amplicons may be used as templates for next generation sequencing (NGS) library generation. Full-length capsid

amplicons may be used for cloning into a DNA library for any number of additional rounds of AAV selection as described herein.

[0894] *Animal:* As used herein, the term “animal” refers to any member of the animal kingdom. In some embodiments, “animal” refers to humans at any stage of development. In some embodiments, “animal” refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically engineered animal, or a clone.

[0895] *Antisense strand:* 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 a 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.

[0896] *Approximately:* As used herein, the term “approximately” or “about,” as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term “approximately” or “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0897] *Biopanning:* As used herein, the term “biopanning” refers to an AAV capsid library selection process comprising administration of an AAV particle with enhanced tissue- and/or cell type-specific transduction to a cell and/or subject; extraction of nucleotides encoded by said AAV particle from said transduced tissue- and/or cell type-specific; and, use of the extracted nucleotides for cloning into a nucleotide library for the generation of AAV particles for subsequent rounds of the same.

[0898] *Capsid:* As used herein, the term “capsid” refers to the exterior, *e.g.*, a protein shell, of a virus particle, *e.g.*, an AAV particle, that is substantially (*e.g.*, >50%, >60%, >70%, >80%, >90%, >95%, >99%, or 100%) protein. In some embodiments, the capsid is an AAV capsid comprising an AAV capsid protein described herein, *e.g.*, a VP1, VP2, and/or VP3 polypeptide. The AAV capsid protein can be a wild-type AAV capsid protein or a variant, *e.g.*, a structural and/or functional variant from a wild-type or a reference capsid protein, referred to herein as an “AAV capsid variant.” In some embodiments, the AAV capsid variant described herein has the ability to enclose, *e.g.*,

encapsulate, a viral genome and/or is capable of entry into a cell, e.g., a mammalian cell. In some embodiments, the AAV capsid variant described herein may have modified tropism compared to that of a wild-type AAV capsid, e.g., the corresponding wild-type capsid.

[0899] *Complementary and substantially complementary:* 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 pairs 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 adenine. However, when a U is denoted in the context of the present disclosure, 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 a 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 a 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. The term “complementary” as used herein can encompass fully complementary, partially complementary, or substantially complementary. 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. “Fully complementary”, “perfect complementarity”, or “100% complementarity” refers to the situation in which each nucleotide unit of one polynucleotide or oligonucleotide strand can base-pair with a nucleotide unit of a second polynucleotide or oligonucleotide strand.

[0900] *Control Elements:* As used herein, “control elements”, “regulatory control elements” or “regulatory sequences” refers to promoter regions, polyadenylation signals, transcription termination sequences, upstream regulatory domains, origins of replication, internal ribosome entry sites (“IRES”), enhancers, and the like, which provide for the replication, transcription and translation of a coding sequence in a recipient cell. Not all of these control elements need always be present as long as the selected coding sequence is capable of being replicated, transcribed and/or translated in an appropriate host cell.

[0901] *Delivery:* As used herein, “delivery” refers to the act or manner of delivering an AAV particle, a compound, substance, entity, moiety, cargo or payload.

[0902] *Element*: As used herein, the term “element” refers to a distinct portion of an entity. In some embodiments, an element may be a polynucleotide sequence with a specific purpose, incorporated into a longer polynucleotide sequence.

[0903] *Encapsulate*: As used herein, the term “encapsulate” means to enclose, surround or encase. As an example, a capsid protein, e.g., an AAV capsid variant, often encapsulates a viral genome. In some embodiments, encapsulate within a capsid, e.g., an AAV capsid variant, encompasses 100% coverage by a capsid, as well as less than 100% coverage, e.g., 95%, 90%, 85%, 80%, 70%, 60% or less. For example, gaps or discontinuities may be present in the capsid so long as the viral genome is retained in the capsid, e.g., prior to entry into a cell.

[0904] *Engineered*: As used herein, embodiments of the disclosure are “engineered” when they are designed to have a feature or property, whether structural or chemical, that varies from a starting point, wild type or native molecule.

[0905] *Effective Amount*: 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 cancer, an effective amount of an agent is, for example, an amount sufficient to achieve treatment, as defined herein, of cancer, as compared to the response obtained without administration of the agent.

[0906] *Expression*: As used herein, “expression” of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (e.g., by transcription); (2) processing of an RNA transcript (e.g., by splicing, editing, 5' cap formation, and/or 3' end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

[0907] *Formulation*: As used herein, a “formulation” includes at least one AAV particle (active ingredient) and an excipient, and/or an inactive ingredient.

[0908] *Fragment*: A “fragment,” as used herein, refers to a portion. For example, an antibody fragment may comprise a CDR, or a heavy chain variable region, or a scFv, etc.

[0909] *Functional*: As used herein, a “functional” biological molecule is a biological molecule in a form in which it exhibits a property and/or activity.

[0910] *Dual-function targeting*: 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.

[0911] *Gene expression*: The term “gene expression” refers to the process by which a nucleic acid sequence undergoes transcription and/or 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 known in the art.

[0912] *Homology*: As used herein, the term “homology” refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be “homologous” to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term “homologous” necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the disclosure, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. In accordance with the disclosure, two protein sequences are considered to be homologous if the proteins are at least about 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least about 20 amino acids.

[0913] *Identity*: As used herein, the term “identity” refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects,

Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; the contents of each of which are incorporated herein by reference in their entirety. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)).

[0914] *Inhibit expression of a gene:* 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 an RNA 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.

[0915] *Insert:* As used herein the term "insert," when referring to a polypeptide, refers to the addition of one or more amino acids, e.g., a peptide, e.g., targeting peptide, sequence to an amino acid sequence, e.g., a parent AAV capsid sequence. In some embodiments, an insertion may result in the replacement of one or more amino acids of the amino acid sequence, e.g., the parent AAV capsid sequence. In some embodiments, an insertion may result in no changes to the amino acid sequence, e.g., parent AAV capsid sequence, beyond the addition of the one or more amino acids, e.g., a peptide, e.g., targeting peptide sequence.

[0916] *Inverted terminal repeat:* As used herein, the term "inverted terminal repeat" or "ITR" refers to a cis-regulatory element for the packaging of polynucleotide sequences into viral capsids.

[0917] *Isolated:* As used herein, the term "isolated" refers to a substance or entity that is altered or removed from the natural state, e.g., altered or removed from at least some of component with which it is associated in the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not "isolated," but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can

exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature. In some embodiments, an isolated nucleic acid is recombinant, e.g., incorporated into a vector.

[0918] *Library*: As used herein, the term “library” refers to a diverse collection of linear polypeptides, polynucleotides, viral particles, or viral vectors. As examples, a library may be a DNA library or an AAV capsid library.

[0919] *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.

[0920] *Neurological disease*: As used herein, a “neurological disease” is any disease associated with the central or peripheral nervous system and components thereof (e.g., neurons).

[0921] *Naturally Occurring*: As used herein, “naturally occurring” or “wild-type” refers to a substance or entity that has not been altered, e.g., structurally altered, or removed from the natural state, e.g., removed from at least some of component with which it is associated in the natural state. In some embodiments, a naturally occurring when referring to sequence refers to a sequence identical to a wild-type sequence or a naturally occurring variant thereof.

[0922] *Orthogonal evolution*: As used herein, the term “orthogonal evolution” refers to a method wherein AAV particles are administered for a first round of AAV selection as described herein across a set of any number of cell- and/or subject-types that may be from different species and/or strains, and wherein any number of additional, i.e., subsequent, AAV selection rounds are performed either across a set of any number of cell- and/or subject-types that may be from different species and/or strains, or across a set of any number of cell- and/or subject-types that may be from the same species and/or strain.

[0923] *Open reading frame*: As used herein, “open reading frame” or “ORF” refers to a sequence which does not contain a stop codon in a given reading frame.

[0924] *Parent sequence*: As used herein, a “parent sequence” is a nucleic acid or amino acid sequence from which a variant is derived. In some embodiments, a parent sequence is a sequence into which a heterologous sequence is inserted. In other words, a parent sequence may be considered an acceptor or recipient sequence. In some embodiments, a parent sequence is an AAV capsid sequence into which a targeting sequence is inserted.

[0925] *Particle*: As used herein, a “particle” is a virus comprised of at least two components, a protein capsid and a polynucleotide sequence enclosed within the capsid.

[0926] *Patient*: As used herein, “patient” refers to a subject who may seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained professional for a particular disease or condition.

[0927] *Payload region*: As used herein, a “payload region” is any nucleic acid sequence (e.g., within the viral genome) which encodes one or more “payloads” of the disclosure. As non-limiting examples, a payload region may be a nucleic acid sequence within the viral genome of an AAV particle, which encodes a payload, wherein the payload is an RNAi agent or a polypeptide. Payloads of the present disclosure may be, but are not limited to, peptides, polypeptides, proteins, antibodies, RNAi agents, etc.

[0928] *Polypeptide*: As used herein, “polypeptide” means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. In some instances, the polypeptide encoded is smaller than about 50 amino acids and the polypeptide is then termed a peptide. If the polypeptide is a peptide, it will be at least about 2, 3, 4, or at least 5 amino acid residues long. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. They may also comprise single chain or multichain polypeptides and may be associated or linked. The term polypeptide may also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

[0929] *Polypeptide variant*: The term “polypeptide variant” refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. In some embodiments, a variant comprises a sequence having at least about 50%, at least about 80%, or at least about 90%, identical (homologous) to a native or a reference sequence.

[0930] *Peptide*: As used herein, “peptide” is less than or equal to 50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[0931] *Pharmaceutically acceptable*: 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.

[0932] *Preventing*: As used herein, the term “preventing” or “prevention” refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or completely

delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition.

[0933] *Prophylactic*: As used herein, “prophylactic” refers to a therapeutic or course of action used to prevent the spread of disease.

[0934] *Prophylaxis*: As used herein, a “prophylaxis” refers to a measure taken to maintain health and prevent the spread of disease.

[0935] *Region*: As used herein, the term “region” refers to a zone or general area. In some embodiments, when referring to a protein or protein module, a region may comprise a linear sequence of amino acids along the protein or protein module or may comprise a three-dimensional area, an epitope and/or a cluster of epitopes. In some embodiments, regions comprise terminal regions. As used herein, the term “terminal region” refers to regions located at the ends or termini of a given agent. When referring to proteins, terminal regions may comprise N- and/or C-termini.

[0936] In some embodiments, when referring to a polynucleotide, a region may comprise a linear sequence of nucleic acids along the polynucleotide or may comprise a three-dimensional area, secondary structure, or tertiary structure. In some embodiments, regions comprise terminal regions. As used herein, the term “terminal region” refers to regions located at the ends or termini of a given agent. When referring to polynucleotides, terminal regions may comprise 5' and/or 3' termini.

[0937] *RNA or RNA molecule*: 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.

[0938] *RNA interfering or RNAi*: 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).

[0939] *RNAi agent*: As used herein, the term “RNAi agent” refers to an RNA molecule, or its derivative, that can induce inhibition, interfering, or “silencing” of the expression of a target gene and/or its protein product. An RNAi agent may knock-out (virtually eliminate or eliminate) expression, or knock-down (lessen or decrease) expression. The RNAi agent may be, but is not limited to, dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA.

[0940] *miR binding site*: As used herein, a “miR binding site” comprises a nucleic acid sequence (whether RNA or DNA, e.g., differ by “U” of RNA or “T” in DNA) that is capable of binding, or binds, in whole or in part to a microRNA (miR) through complete or partial hybridization. Typically, such binding occurs between the miR and the miR binding site in the reverse complement orientation. In some embodiments, the miR binding site is transcribed from the AAV vector genome encoding the miR binding site.

[0941] In some embodiments, a miR binding site may be encoded or transcribed in series. Such a “miR binding site series” or “miR BSs” may include two or more miR binding sites having the same or different nucleic acid sequence.

[0942] *Spacer*: As used here, a “spacer” is generally any selected nucleic acid sequence of, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive miR binding site sequences. Spacers may also be more than 10 nucleotides in length, e.g., 20, 30, 40, or 50 or more than 50 nucleotides.

[0943] *Sample*: As used herein, the term “sample” or “biological sample” refers to a subset of its tissues, cells, nucleic acids, or component parts (e.g. body fluids, including but not limited to blood, serum, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). A sample further may include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs. A sample further refers to a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins or nucleic acid molecule.

[0944] *Self-complementary viral particle*: As used herein, a “self-complementary viral particle” is a particle comprised of at least two components, a protein capsid and a self-complementary viral genome enclosed within the capsid.

[0945] *Sense Strand:* 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.

[0946] *Similarity:* As used herein, the term “similarity” refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

[0947] *Short interfering RNA or siRNA:* 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 an siRNA duplex.

[0948] *Subject:* As used herein, the term “subject” or “patient” refers to any organism to which a composition in accordance with the disclosure 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, and humans) and/or plants.

[0949] *Substantially*: As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0950] *Targeting peptide*: As used herein, a “targeting peptide” refers to a peptide of 3-20 amino acids in length. These targeting peptides may be inserted into, or attached to, a parent amino acid sequence to alter the characteristics (e.g., tropism) of the parent protein. As a non-limiting example, the targeting peptide can be inserted into an AAV capsid sequence for enhanced targeting to a desired cell-type, tissue, organ or organism. It is to be understood that a targeting peptide is encoded by a targeting polynucleotide which may similarly be inserted into a parent polynucleotide sequence. Therefore, a “targeting sequence” refers to a peptide or polynucleotide sequence for insertion into an appropriate parent sequence (amino acid or polynucleotide, respectively).

[0951] *Target Cells*: As used herein, “target cells” or “target tissue” refers to any one or more cells of interest. The cells may be found *in vitro*, *in vivo*, *in situ* or in the tissue or organ of an organism. The organism may be an animal, preferably a mammal, more preferably a human and most preferably a patient.

[0952] *Therapeutic Agent*: The term “therapeutic agent” refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect.

[0953] *Therapeutically effective amount*: 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. In some embodiments, a therapeutically effective amount is provided in a single dose.

[0954] *Therapeutically effective outcome*: As used herein, the term “therapeutically effective outcome” means an outcome that is sufficient in 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.

[0955] *Treating*: As used herein, the term “treating” refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular infection, disease, disorder, and/or condition. For example, “treating” cancer may refer to inhibiting survival, growth, and/or spread of a tumor. Treatment may be administered to a subject who does not exhibit signs of a

disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0956] *Variant*: As used herein, the term “variant” refers to a polypeptide or polynucleotide that has an amino acid or a nucleotide sequence that is substantially identical, e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity to a reference sequence. In some embodiments, the variant is a functional variant.

[0957] *Functional Variant*: As used herein, the term “functional variant” refers to a polypeptide variant or a polynucleotide variant that has at least one activity of the reference sequence.

[0958] *Insertional Variant*: “Insertional variants” when referring to polypeptides are those with one or more amino acids inserted, e.g., immediately adjacent or subsequent, to a position in an amino acid sequence. “Immediately adjacent” or “immediately subsequent” to an amino acid means connected to either the alpha-carboxy or alpha-amino functional group of the amino acid.

[0959] *Deletional Variant*: “Deletional variants” when referring to polypeptides, are those with one or more amino acids in deleted from a reference protein.

[0960] *Vector*: As used herein, the term “vector” refers to any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule. In some embodiments, vectors may be plasmids. In some embodiments, vectors may be viruses. An AAV particle is an example of a vector. Vectors of the present disclosure may be produced recombinantly and may be based on and/or may comprise adeno-associated virus (AAV) parent or reference sequences. The heterologous molecule may be a polynucleotide and/or a polypeptide.

[0961] *Viral Genome*: As used herein, the terms “viral genome” or “vector genome” refer to the nucleic acid sequence(s) encapsulated in an AAV particle. A viral genome comprises a nucleic acid sequence with at least one payload region encoding a payload and at least one ITR.

Equivalents and Scope

[0962] The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. 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 disclosure described herein. The scope of the present disclosure is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[0963] In addition, it is to be understood that any particular embodiment of the present disclosure 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 disclosure (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.

[0964] 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 disclosure in its broader aspects.

[0965] While the present disclosure 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 disclosure.

[0966] The present disclosure is further illustrated by the following non-limiting examples.

EXAMPLES

Example 1. Peptide display capsid library configuration

[0967] Peptide display capsid libraries are configured by insertion of randomized n-mer amino acids such as, but not limited to, 5-mer, 6-mer, 7-mer and/or 9-mer amino acids, into the surface-exposed hypervariable loop I, loop IV, loop VI, and/or loop VIII region of any AAV capsid serotype, including AAV5, AAV6, or AAV-DJ8, as well as AAV9 capsids, and/or variants thereof. The genes encoding the peptide display capsid library are under the control of any promoter, depending on the desired tropism, e.g., a neuron-specific synapsin promoter (SYN or Syn), or an astrocyte-specific GFAP promoter.

[0968] Peptide display capsid libraries are further configured such that the n-mer peptide insertion(s) follows a contiguous (or continuous) design and/or a noncontiguous (or noncontinuous), or split design, or combination thereof, with insertion position(s) mapped using a sliding window algorithm. As a non-limiting example, the peptide insertion may be an AAV9 6-mer contiguous peptide insertion with a sliding window originating at any amino acid position, e.g., amino acids 454-461. As another non-limiting example, the peptide insertion may be an AAV9 3-mer peptide split design or contiguous peptide insertion with a sliding window originating at any amino acid position, e.g., amino acids 586-588. As yet another non-limiting example, the peptide insertion may be an AAV9 6-mer and/or 7-mer peptide contiguous peptide insertion with a sliding window originating at any amino acid position, e.g., amino acids 585-590.

[0969] Any number of such configured peptide display capsid libraries may be pooled in a cell and/or subject, including a non-human primate (NHP) cell and/or subject, and administered to any tissue (e.g., central nervous system tissue) via any route, including but not limited to IV and/or ICM injection, at any VG/cell and/or VG/subject dose. As a non-limiting example, six configured peptide

display capsid libraries are pooled and administered to the central nervous system of an NHP via intravenous administration of dose 1×10^{14} VG/NHP. As another non-limiting example, six libraries are pooled and administered to the central nervous system of NHP via an intraventricular administration, such as, but not limited to intraventricular administration that is an intra-cisterna magna injection (ICM) of dose 2×10^{13} a VG/NHP.

Example 2. Identification and design of non-human primate AAV capsid libraries

[0970] A TRACER RNA-driven library selection for increased nervous system tissue transduction in a non-human primate (NHP) is developed and carried out in accordance with methods similar, or equivalent, to those described in WO2020072683, the contents of which are herein incorporated by reference in their entirety, particularly as pertains to the TRACER method.

[0971] AAV libraries, e.g., AAV9 libraries, generated are administered by any route to NHPs at a given VG dose(s) per animal. A number of groups of NHPs are administered promoter-driven (e.g., SYN-driven or GFAP-driven) libraries derived from wild-type AAV9 flanking sequences, while other groups receive pooled libraries containing wild-type, PHP.eB-derived, or other AAV serotype sequences. After a period, RNA is extracted from a tissue, such as but not limited to spinal cord and brain tissue. The RNA preparation is subjected to mRNA enrichment. The enriched mRNA is reverse transcribed to cDNA. The cDNA is amplified. This method allows recovery of abundant amplicons from tissue samples.

[0972] Full-length capsid amplicons are used as templates for NGS library generation, as well as cloning into a DNA library for the next, or subsequent, round(s) of biopanning (FIG. 1A and FIG. 1B). Any number of rounds of AAV selection may be performed. The total number of unique capsid variants may drop by a fold amount across AAV selection rounds. Capsid libraries may be pooled or combined at any step with any other capsid libraries described herein.

[0973] Following RNA recovery and PCR amplification, a systematic enrichment analysis by NGS is performed. Capsids enrichment ratio including comparison to a benchmark and sequence convergence is evaluated.

[0974] Peptide library candidates are evaluated and optimized using any of the methods described herein and are carried out, e.g., using methods similar, or equivalent, to those described in WO2020072683, the contents of which are herein incorporated by reference in their entirety, particularly the subject matter of Examples, 8, 9, and 10. The top-ranking peptide variants are generated and transduction efficacy evaluated as described in WO2020072683, the contents of which are herein incorporated by reference in their entirety, particularly the subject matter of Examples 10, 12 and 13.

Example 3. Identification and design of orthogonal evolution AAV capsid libraries

[0975] This study involves the use of orthogonal evolution wherein AAV particles may be administered for a first round of AAV selection across a set of any number of cell- and/or subject-

types that may be from different species and/or strains; and, wherein any number of additional, i.e., subsequent, AAV selection rounds are performed either across a set of any number of cell- and/or subject-types that may be from different species and/or strains, or across a set of any number of cell- and/or subject-types that may be from the same species and/or strains, as represented in FIG 2.

[0976] ATRACER based RNA-driven library selection for increased nervous system tissue transduction a set of any number of cell- and/or subject-types that may be from different species and/or strain is developed and carried out in accordance with methods similar, or equivalent, to those described in WO2020072683, the contents of which are herein incorporated by reference in their entirety, particularly the subject matter of Example 7. AAV libraries, e.g., AAV9 libraries, generated are administered for a first round of AAV selection (biopanning) by any route to a non-human primate (NHP), a rodent (e.g., a rat), and/or a cell (e.g., a human brain microvascular endothelial cell, or hBMVEC) at a given VG dose(s) per subject and/or cell. A number of groups of NHPs, rodents, and/or cells are administered promoter-driven (e.g., SYN-driven or GFAP-driven) libraries derived from wild-type AAV9 sequences, while other groups receive pooled libraries containing wild-type, PHP.eB-derived, or other AAV serotype sequences. After a period, RNA is extracted from a tissue, such as but not limited to spinal cord and brain tissue. The RNA preparation is subjected to mRNA enrichment. The enriched mRNA is reverse transcribed to cDNA. The cDNA is amplified. This method allows recovery of abundant amplicons from tissue samples.

[0977] Full-length capsid amplicons are used as templates for NGS library generation, as well as cloning into DNA libraries for the next, or subsequent round(s) of biopanning. Subsequent rounds of biopanning are performed either across a set of any number of cell- and/or subject-types that may be from different species and/or strain as used in the above-described first round, or across a set of any number of cell- and/or subject-types that may be from the same species and/or strain as used in the above-described first round. Any number of rounds of selection is performed. The total number of unique capsid variants may drop by a fold amount across AAV selection rounds. Capsid libraries may be pooled or combined at any step with any other capsid libraries described herein (FIG. 2)

[0978] Following RNA recovery and PCR amplification, a systematic enrichment analysis by NGS is performed. Capsids enrichment ratio including comparison to a benchmark and sequence convergence is evaluated.

[0979] Peptide library candidates are evaluated and optimized using any of the methods described herein and are carried out, e.g., using methods similar, or equivalent, to those described in WO2020072683, the contents of which are herein incorporated by reference in their entirety. The top-ranking peptide variants are generated and transduction efficacy evaluated as in WO2020072683.

Example 4. NHP high-throughput screen of TRACER AAV libraries

[0980] A TRACER based method as described in WO2020072683, the contents of which are herein incorporated by reference in their entirety, was adapted for use in non-human primates (NHP). An orthogonal evolution approach as exemplified in FIG. 2 (e.g., NHP and BMVEC) was combined with a high throughput screening by NGS in NHP as shown in FIG. 3. Briefly, AAV9/AAV5 starting libraries, driven by synapsin or GFAP promoters as shown in FIG. 4 were administered to non-human primate (NHP) intravenously for *in vivo* AAV selection (biopanning), performed iteratively. All libraries were injected intravenously at a dose of 1e14VG per animal (approximately 3e13 VG/kg). Orthogonally, biopanning was conducted in hBMVEC cells using the same starting libraries. In the second round of biopanning in NHP, only libraries driven by the synapsin promoter were used. After a period, (e.g., 1 month) RNA was extracted from nervous tissue, e.g., brain and spinal cord. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed and the targeting peptides shown in Table 1 identified. Capsids enrichment ratio, including calculating the ratio of, e.g., P2/P1 reads and comparison to a benchmark (e.g., AAV9) was evaluated.

[0981] Candidate library enrichment data in P3 NHP brain for the targeting peptides of Table 1, over benchmark AAV9, are shown in Table 7. Data are provided as fold enrichment. Fifty-one variants showed greater than 10-fold enrichment over AAV9. Variants with 0.0 enrichment over AAV9 are not included in Table 7.

Table 7. NHP NGS AAV9 Enrichment

Peptide Sequence	SEQ ID NO:	Fold enrichment over AAV9	Peptide Sequence	SEQ ID NO:	Fold enrichment over AAV9
PLNGAVHLYA	1725	473.7	AQAQPPSARY	2280	0.7
AQARDSPEGW	1726	214	AQAGLQGTAA	2281	0.7
LTNGAVRDRP	1727	134.4	AQPQGSSTFA	2282	0.7
VQAFTHDSRG	1728	88.6	TQYRAVEGQA	2283	0.7
AQAYSTDVRM	1729	84.8	AQAISTQLAG	2284	0.7
AQAYSTDVRI	1730	83.8	AQLGSNISHA	2285	0.7
AQAFTAAERM	1731	74.9	AQTGLSGTVA	2286	0.7
AQTHLQIGVA	1732	54.6	AQRVDSSGRA	2287	0.7
AQSNVLSLA	1733	51.6	AQAGLALNPN	2288	0.7
AQAYSTDERM	1734	41.4	AQFYSDNSLA	2289	0.7
AQAYSTDVRL	1735	31.7	AQAVGAPQRL	2290	0.7
AQATVSTLRM	1736	31.5	AQASYDDGRA	2291	0.7
AQAYSTDERK	1737	31.2	SSFAAVATAA	2292	0.6
AQAYSTDMRM	1738	30.4	AQSTLSMPLA	2293	0.6
VVNGAVLHVA	1739	29.8	AQASLHAPRP	2294	0.6
AQAYSTDVTM	1740	29.7	HAVAASVYPY	2295	0.6
AQAHLQIGVA	1741	23	AQTSPVMVQA	2296	0.6
FLDPAVSSKA	1742	22.6	AQADITSTIS	2297	0.6

AQAYVSTLRM	1743	21.9	AQAAGVAMLY	2298	0.6
AQAQTGPPLK	1744	20.1	AQASVSTLRK	2299	0.6
EQASRLPTPG	1745	20	MDLKAVSSRA	2300	0.6
AQASVSTMRM	1746	19.7	AQASLSTLRM	2301	0.6
TDYSAVRLGA	1747	18	AQPRSPLPMA	2302	0.6
TQAYSTDVRM	1748	17.9	GQYADVSSYA	2303	0.6
AQALPSNERL	1749	17.4	LVGGAVVPPA	2304	0.6
AQAYSTDVRT	1750	16.4	AQAQ SARPLA	2305	0.6
AQSSLP EMVA	1751	16.2	AQSLHPSTTA	2306	0.6
AQAGEQSTRL	1752	16.1	AQFQTDLSRA	2307	0.6
AQASNDVGRA	1753	15.4	RTLAVGLSA	2308	0.6
AQATFTASEY	1754	15.3	AQVVDNSPLA	2309	0.6
AKAHAGTIYS	1755	14.9	AQAVSSDSMH	2310	0.6
AQARTIDQCC	1756	14.8	AQASPALHTL	2311	0.6
AQEYNSNPKA	1757	14.5	GQYAAVASYA	2312	0.6
AQVVDNSTHA	1758	14.5	AQLWQSRVDA	2313	0.6
AQATLSVPLK	1759	14.4	GTFSVQSTA	2314	0.6
AQIVMNSLKA	1760	12.5	AQAILSTIEV	2315	0.6
AQATMSQTMA	1761	12.5	AQNVVSTLRA	2316	0.6
AQALTQDERW	1762	12	AQAMLAVSPG	2317	0.6
AQAQLSTLRP	1763	11.6	AQATDSLVAR	2318	0.6
AQVVMGISVA	1764	11.4	AQASPQSSHG	2319	0.6
AQAYTTDVRM	1765	11.4	AQATPVHDTL	2320	0.6
AQHIDSMRPP	1766	11.3	LRSSAVGTAA	2321	0.6
AQASTGT LRL	1767	11.1	MGRGAVLDTA	2322	0.6
AQHRALDYA	1768	11	AQSHLIPTPA	2323	0.6
AQARESPRGL	1769	10.9	AQAVLKAPIN	2324	0.6
AQALLAGTRV	1770	10.7	AQKIAPAFLA	2325	0.6
TKIQAVPWNA	1771	10.7	AGNVAVLPHA	2326	0.6
AQASLSSTRP	1772	10.6	AQSLGTGLHD	2327	0.6
AQAMGSRSDQ	1773	10.4	AQAHAMSSRP	2328	0.6
AQAAQGT YRG	1774	10.3	AQQGKFDMRA	2329	0.6
SQENAVFSKA	1775	10.3	AQALSGDGTR	2330	0.6
AQALSLSTRP	1776	9.8	AQTHLQIAVA	2331	0.6
AQAAAAGTLRD	1777	9.7	AQRTQGSSWA	2332	0.6
AQASRLPTPG	1778	9.5	AIGSAVDLRA	2333	0.6
AQAGSLSERG	1779	9.5	AQAQLASGTL	2334	0.6
AQSKGDGFTA	1780	9.4	AQALVSAGAL	2335	0.6
GAGTAVTATA	1781	9.3	AQATESVPLK	2336	0.6
AQAQGSSSVG	1782	8.8	AQVYNSNPKA	2337	0.6
AQAYSTDARM	1783	8.8	AQRTTYPSSA	2338	0.6
ERAHAVTG LA	1784	8.5	AQAMFQCAST	2339	0.6
AQAYGLPKGP	1785	8.4	AQPDALVIRA	2340	0.6

AQAYSTEVRM	1786	8.4	AQARDISMRG	2341	0.6
AQAGVSTALH	1787	8.2	AQMSFGSTLA	2342	0.6
AQSYSTDVRM	1788	8.1	RLLSAVDQQA	2343	0.6
AQPLMSHTDA	1789	7.9	AQTTRSIENA	2344	0.6
AQAAALASRP	1790	7.9	AQVSDFSSRA	2345	0.5
AQAAITSTIS	1791	7.8	AQAHSRVNTE	2346	0.5
AQPANDGLRA	1792	7.5	AQAYSTDLRM	2347	0.5
AQDYSTDVRM	1793	7.4	AQALNGSAYS	2348	0.5
AQATLGYSTA	1794	7.4	TQYGAVEAQA	2349	0.5
AQATLGIRV	1795	7.3	AQAHAGTIYS	2350	0.5
AQAGASDMVH	1796	7	AQDPHSMRPA	2351	0.5
AQAVSGTVRS	1797	6.9	AQASANIHSS	2352	0.5
GGTLAVVSLA	1798	6.9	AQASLQAVSM	2353	0.5
AQAYSADVRM	1799	6.8	AQSSHAPMVA	2354	0.5
AQAFAMPKGL	1800	6.6	AQANLQPRGA	2355	0.5
AQALVSTSRP	1801	6.6	AQAVGSSPRG	2356	0.5
AQASFQAST	1802	6.6	AQTSAPSALA	2357	0.5
AQAMTGNDRS	1803	6.3	AQAVQLQNRG	2358	0.5
AQASTQSPPG	1804	6.1	AQAQSGGMVS	2359	0.5
NARSAVESLA	1805	6.1	AQAYPSSKSG	2360	0.5
AQITVSHTTA	1806	6	AQAVSDYGRG	2361	0.5
AQALAGYDKA	1807	6	AQMSLGATRA	2362	0.5
AQSTSHDTRA	1808	5.9	AQAFNLNSASA	2363	0.5
AQAIQDRTVV	1809	5.8	AQALPSNARL	2364	0.5
AQSKTTLTLA	1810	5.7	AQANVSVRRE	2365	0.5
AQASMGTVRL	1811	5.7	AQAGASVMVH	2366	0.5
AQHSDTLTRA	1812	5.5	AQSLAKDQSA	2367	0.5
AQKEMYTSVA	1813	5.5	AQILSALSSA	2368	0.5
AQASPSQPLL	1814	5.4	AQSVHLSLAA	2369	0.5
AQAYAGTIYS	1815	5.3	AQALSASSFL	2370	0.5
AQARSLEPVI	1816	5.3	AQTSQLNQTA	2371	0.5
TQAGVSTAVH	1817	5.2	AQSNLFPTPA	2372	0.5
AQNTLSLSLA	1818	5.2	AQAHGRSFDT	2373	0.5
AQAYVSSVKM	1819	5.2	AQLGSNTILA	2374	0.5
AQAATSPRLG	1820	5.1	AQASMNSAKA	2375	0.5
GYLTAVQPQA	1821	5	AQRQAVEQSA	2376	0.5
LNNLAVGMTA	1822	5	AQASTGTLRH	2377	0.5
AQTVSVHVRA	1823	5	AQGPTYPNVA	2378	0.5
AQINGLVTTA	1824	4.9	AQAGPTTSKA	2379	0.5
AQAAITTTIS	1825	4.8	AQATTYRGMA	2380	0.5
AQASTFVTI	1826	4.7	AQVTNRGMPA	2381	0.5
AQALYDNVPL	1827	4.6	AQAISGQAAW	2382	0.5
AQAAAGTWKG	1828	4.6	AQAFRGEDKG	2383	0.5

AQATTGTLRS	1829	4.6	AQQSMPRFVA	2384	0.5
GQYAADSSYA	1830	4.5	AQAGVKSTRL	2385	0.5
AQAGIATVRT	1831	4.5	AQATGSILLA	2386	0.5
AQALGHELRA	1832	4.5	AQASGHSSFS	2387	0.5
AQAREAIPOG	1833	4.4	AQTANDGLRA	2388	0.5
AQAMSGTLRM	1834	4.4	AQASQLALLA	2389	0.5
AQAVDRVRPP	1835	4.4	AQLVDRVPRA	2390	0.5
AQAPVNNDRG	1836	4.3	AQHSNGYVHA	2391	0.5
AQAQQVAGTM	1837	4.3	AQAAPSSSDS	2392	0.5
AQAEPRDTRA	1838	4.3	AQAMQRSSSA	2393	0.5
AQRLSEQGVA	1839	4.2	AQAASGRPTC	2394	0.5
AQASEGIQLS	1840	4.1	AQPRPGDSRA	2395	0.5
AQRQGPDPPLA	1841	4.1	AQRDRANGIA	2396	0.5
AQVTLGSAKA	1842	4.1	AQVLAISLSA	2397	0.5
AQAGASLGLA	1843	4	AQAGMRDPRM	2398	0.5
AQFTQDERW	1844	4	AQASSNSSRA	2399	0.5
AQASQTTVRS	1845	4	MHRDAVSGVA	2400	0.5
AQARVSSNGV	1846	3.9	AQAEMKNMPP	2401	0.5
AQGPLSGLRA	1847	3.9	AQSGSLLASA	2402	0.5
AQAYGGQSLG	1848	3.9	AQAFASQSRG	2403	0.5
AQANLGTVRQ	1849	3.9	AQALHLP TLQ	2404	0.5
AQARSDTRGL	1850	3.8	AQAKTGGMNT	2405	0.5
AQAGSDGPRL	1851	3.8	ISLNAVSGKA	2406	0.5
TDGA AVVMRA	1852	3.8	AQGVHGHYVA	2407	0.5
SGITAVPLHA	1853	3.8	AQAYSKDVRM	2408	0.5
AQAAAVGHLP	1854	3.7	VPSIAVSSHA	2409	0.5
AQRVEPKWIA	1855	3.7	AQSSRHDDLA	2410	0.5
AQAVASSPYA	1856	3.7	AQANGSGSRG	2411	0.5
TQYGAVEGQD	1857	3.7	AQVGIADRRRA	2412	0.5
AQAKSHTLEG	1858	3.6	AQARGMESML	2413	0.5
AQTHLQIVVA	1859	3.6	AQAGVSTAGH	2414	0.5
AQKNEHGMLA	1860	3.6	AQVSTRNLIA	2415	0.5
AQITVSHTRA	1861	3.6	AQAVPRLTAG	2416	0.5
AQARLAPKGL	1862	3.6	AQRHMEQEA	2417	0.5
KTPGAVSTTA	1863	3.6	SQSRVAVWEA	2418	0.5
AQAFSGTIKS	1864	3.6	QSHTAVSSLA	2419	0.5
PLNGAVNLYA	1865	3.5	AKASVSTLRM	2420	0.5
AQALTQDERC	1866	3.5	AQASGSSQWA	2421	0.5
AQATAQVQRS	1867	3.4	AQPNAQYMKA	2422	0.5
AQTPALINLA	1868	3.4	AQAMGTGSSL	2423	0.5
AQASDRSPLL	1869	3.4	AQAFSTSQLT	2424	0.5
AQITVSHTMA	1870	3.3	AQAKDQSQRL	2425	0.4
AQATGTHLMG	1871	3.3	AQVGNGSRA	2426	0.4

LDGGAVVVTA	1872	3.3	AQANGASRAV	2427	0.4
LTNGAVRDRA	1873	3.2	QVNKAVLDFA	2428	0.4
AQARGSDLRD	1874	3.2	AQETLSSTRA	2429	0.4
AQATFGTQRI	1875	3.2	GVYGAVHSSA	2430	0.4
AQALPQTNRP	1876	3.1	AQTITIENVA	2431	0.4
AQARSNDPVL	1877	3.1	AQALMKIADG	2432	0.4
AQAYLAVQNG	1878	3.1	AQANVSLQAA	2433	0.4
AQATQSTLRP	1879	3.1	AQSTTSHLRA	2434	0.4
AQALGGFGPQ	1880	3.1	AQLSNLVSVV	2435	0.4
LVGQAVGSRA	1881	3.1	AQANSTPTRQ	2436	0.4
AQSIANVVVA	1882	3	AQQRGDRAAA	2437	0.4
AQASPSVSRP	1883	3	AQARLGQSVG	2438	0.4
AQTVVVSTTA	1884	3	AQQLTYGSSA	2439	0.4
VKEQAVSVMA	1885	3	AQPAEKQYSA	2440	0.4
AQQATGTFR	1886	3	AQAMPSTRGD	2441	0.4
AQAQGSSSGG	1887	3	AQGLSGRALA	2442	0.4
AQAHAVGPQG	1888	3	AQARVTAVDA	2443	0.4
AQRLETKETA	1889	3	AQVGVSATA	2444	0.4
AQLAQGIGVA	1890	3	AQTGVTSAQA	2445	0.4
AQAVQSSFTI	1891	3	AQALVTSSEK	2446	0.4
AQATYTASEY	1892	2.9	AQASPHSSMA	2447	0.4
AQTSSQNLKA	1893	2.9	AQALTQDEMW	2448	0.4
AQLVPSVAMA	1894	2.9	AQAFSTQQRL	2449	0.4
AQASPSAFAG	1895	2.9	AQAGSQVTQA	2450	0.4
AQALALVSAS	1896	2.9	AQQSTLALKA	2451	0.4
AQASVGTTYT	1897	2.9	AQALNGSHAA	2452	0.4
AQARVSSSGT	1898	2.9	AQATEGHLRS	2453	0.4
NSMGAUVA	1899	2.9	AQPMANMLMA	2454	0.4
AQHTDTLTRA	1900	2.9	PSTSAVSQKA	2455	0.4
AQPNLQPRGA	1901	2.8	AQAPPSSTEM	2456	0.4
AQADRHSSIV	1902	2.8	AQRERVDLAA	2457	0.4
SPSVAVPSQA	1903	2.8	AQASVTLPR	2458	0.4
AQPGIVSTIA	1904	2.8	AQAYPSSSKA	2459	0.4
AQAQHSVGLP	1905	2.7	AQAHSGSAIP	2460	0.4
AQTNNGAILA	1906	2.7	AQSPSQSLKA	2461	0.4
AQDSYDVGRA	1907	2.7	AQATPPATSP	2462	0.4
EAQAGSSSVG	1908	2.7	CLGAAVNQCA	2463	0.4
AQAGVSTAVQ	1909	2.7	VLGQAVRDKA	2464	0.4
AQARDMLPLQ	1910	2.7	AQAQKANNVG	2465	0.4
AQAMVGTLRG	1911	2.7	AQTLLPVNGA	2466	0.4
AQPNVVSTLA	1912	2.7	AQAHGTIQRG	2467	0.4
AQAGHVVTSD	1913	2.7	TVYTAVGVSA	2468	0.4
AQAYTTDERM	1914	2.7	LGRGAVLDMA	2469	0.4

TAVSAVQVMA	1915	2.6	AQANVRSDQM	2470	0.4
AQAAAGTLRV	1916	2.6	AQARDSQKGW	2471	0.4
VSNEAVHARA	1917	2.6	AQTPGSRSA	2472	0.4
AQVLPQSLSA	1918	2.6	AQALPSNARQ	2473	0.4
AQASVSTLRM	1919	2.6	AQASATSVVH	2474	0.4
AQAGLLLSVA	1920	2.5	AQINLGMTMA	2475	0.4
AQANLVTGPL	1921	2.5	AQVYNNTSAA	2476	0.4
AQASQHSSMA	1922	2.5	AQASANLTRG	2477	0.4
GYSSAVSSVA	1923	2.5	AQLRTDYTRA	2478	0.4
AQVGVSPAVA	1924	2.5	AQAYSTDVKM	2479	0.4
DGTLAVPFKA	1925	2.5	AQTSQLYQPA	2480	0.4
AQAPPTSTAM	1926	2.5	AQALTQEERW	2481	0.4
AQATPANVRG	1927	2.5	LPNGAVRDRA	2482	0.4
AQAGSSNFLS	1928	2.5	VTGSAVAGIA	2483	0.4
AQLLAQDIRA	1929	2.5	AQAFSTDVRM	2484	0.4
AQPSSDGYRA	1930	2.5	AQAHGPTSGV	2485	0.4
AQALIGTLRT	1931	2.5	AQAGVGLPIA	2486	0.4
SVHGAVGILA	1932	2.5	AQVNSGQARA	2487	0.4
AQPYVVSGAA	1933	2.4	AQAQTGPPMK	2488	0.4
AQWTHNITAA	1934	2.4	AQARLAPVAC	2489	0.3
PTNAAVRTNA	1935	2.4	LSIGAVASMA	2490	0.3
AHAYSTDVRM	1936	2.4	AQAQDLGVMR	2491	0.3
PLAAAVGMKA	1937	2.4	PTGLAVTSPA	2492	0.3
AQARDNSVML	1938	2.4	AQSASTSWSA	2493	0.3
AQAQFPRNGG	1939	2.4	AQNGSNVRNA	2494	0.3
GALNAVNGVA	1940	2.4	AQASISSSAT	2495	0.3
AQASHQQGV	1941	2.4	AQNSHAHLAA	2496	0.3
SYQSAVVPQA	1942	2.3	AQAVGVKQFF	2497	0.3
AQSIMGTIRA	1943	2.3	AQAHLSPHTA	2498	0.3
AQAYVSQAQG	1944	2.3	AQPAYGSSYA	2499	0.3
AQATGNQAHF	1945	2.3	AQAHQARSGS	2500	0.3
AQVTVGTPIA	1946	2.3	AQAHTSPTQR	2501	0.3
AQAQTSTFRG	1947	2.3	AQAATPSSSR	2502	0.3
SVHMAVTVSA	1948	2.2	AQAHNSYPKV	2503	0.3
AQAQSTLNLG	1949	2.2	AQSSLGSSLA	2504	0.3
AQDQTGPPLK	1950	2.2	AQALSRNVG	2505	0.3
HLAHAVSTAA	1951	2.2	AQASLSSLSG	2506	0.3
AQALARDSSF	1952	2.2	AQHGSSEFTA	2507	0.3
AQLLSGTLKA	1953	2.2	AQSALVAGVA	2508	0.3
AQASLLPTPG	1954	2.2	AQASSSLRP	2509	0.3
AQPMAGQSTA	1955	2.2	AQTARDTGFA	2510	0.3
AQARSLEPDI	1956	2.2	KSVQAVRDPA	2511	0.3
AQFVTGNQDA	1957	2.2	AQAGSHSSVS	2512	0.3

AQATFKTSVP	1958	2.1	VRAHAVTGLA	2513	0.3
LNARAVEGPA	1959	2.1	ASHTAVGEFA	2514	0.3
AQALPNSGRP	1960	2.1	AQIRSEWRDA	2515	0.3
AQALNGSPEA	1961	2.1	AQQLARVSGA	2516	0.3
AQATSLHPLP	1962	2	AQAAITSTNS	2517	0.3
AQAVQPPLKN	1963	2	AQARDAVQLP	2518	0.3
AQAMLSGTRI	1964	2	AQAKELVSTS	2519	0.3
AQHVDLASKA	1965	2	AQGIAETLSA	2520	0.3
AQASFATMRP	1966	2	AQLGSGFSTA	2521	0.3
AQAMPLNARS	1967	2	AQNAKELERA	2522	0.3
AQALVGQMRG	1968	2	AQTHLQNGVA	2523	0.3
VVNGAVLHLA	1969	2	SGNLAVGTPA	2524	0.3
AQAQTAPPLK	1970	2	AQSPGTSVA	2525	0.3
AQGHGDLHRA	1971	2	AQSSAAAAGRA	2526	0.3
AQAADRSPVH	1972	2	AQAGISAAIM	2527	0.3
GALNAVTVGA	1973	2	AQALGYHQTG	2528	0.3
AQAERMASLG	1974	1.9	NAGQAVAARA	2529	0.3
AQAPTTTRL	1975	1.9	AQPFGGSGYA	2530	0.3
AQAAVQGTLA	1976	1.9	AQAGSPSRLC	2531	0.3
AQSLGTGMHA	1977	1.9	AQARTIGTIA	2532	0.3
AQSLGSPALA	1978	1.9	AQVVSVSRA	2533	0.3
AQASVSVTRP	1979	1.9	AQAGQARSMG	2534	0.3
AQATMSHTMA	1980	1.9	AQATRGVTAG	2535	0.3
AQAVQSLTVG	1981	1.9	AQQSNGYGRA	2536	0.3
AQSQTGTYRA	1982	1.9	AQASLAPLKS	2537	0.3
AQSLASVYAA	1983	1.9	AQPGANHNGA	2538	0.3
STKLAVHEQA	1984	1.9	LGRGAVPDTA	2539	0.3
AQSHLFPTPA	1985	1.9	AQHFTASLA	2540	0.3
AQGTWSSSEA	1986	1.9	AQAPAGHHTR	2541	0.3
AQTPQGLTKA	1987	1.9	AQPSVQNSMA	2542	0.3
AQVSLGTQYA	1988	1.9	AQAKLSGHVS	2543	0.3
AQDSRLPTPG	1989	1.8	AQFGTSSPSA	2544	0.3
ASIQAVGVKA	1990	1.8	AQASHISSVR	2545	0.3
AQATMSEQRL	1991	1.8	AQALSRNGIG	2546	0.3
TAQAAVQGMA	1992	1.8	AQASAVQORS	2547	0.3
AQAFNAAERM	1993	1.8	AQGGPHLQAA	2548	0.3
AQINFLSGVA	1994	1.8	AQAQSDSAFR	2549	0.3
PQHLAVSSEA	1995	1.8	AQTYSTDVVRM	2550	0.3
AQALGNFPAV	1996	1.8	LARGAVLDTA	2551	0.3
AQANASTVRV	1997	1.8	AQASPHTLRS	2552	0.3
AQRIVDLTTA	1998	1.8	AQHSDTQTRA	2553	0.3
VRQVAVEGVA	1999	1.8	AQATPSPSAS	2554	0.3
AQAPASSQKL	2000	1.8	AQNQVTYSKA	2555	0.3

AQQIDSMRPA	2001	1.7	AQHTSVVYGA	2556	0.3
AQAHGTSSLF	2002	1.7	AQAQVSQMSH	2557	0.3
AQVNSGIALA	2003	1.7	SFLRAVKNDA	2558	0.3
AQLHLAETRA	2004	1.7	AQAYSTDVGM	2559	0.3
AQALTHDERW	2005	1.7	AKTPALINLA	2560	0.3
NTVRVIMEA	2006	1.7	VSTAAVSSAA	2561	0.3
AQAYVAGSRP	2007	1.7	AQAPITSTIS	2562	0.3
AQDRAFFVSA	2008	1.7	AQTNLQTRGA	2563	0.3
AQAQEKQVFS	2009	1.7	AQATRLPTPG	2564	0.3
AQACVSTAVH	2010	1.7	PQHLLAVSSAA	2565	0.2
AQAFTHDSRG	2011	1.7	AQASPHPSRP	2566	0.2
AQASHQGTVG	2012	1.7	AQAQPAQQRG	2567	0.2
AQAVLVTEQG	2013	1.7	AQPQRQGVQA	2568	0.2
AQAVVSTAVH	2014	1.7	AQHVAGSSNA	2569	0.2
AQATSRETKG	2015	1.7	AQVPIQMGVA	2570	0.2
YQPAVSSRA	2016	1.6	AQATVSVPLK	2571	0.2
AQANMGLSLS	2017	1.6	AQISVSHTRA	2572	0.2
AQWTSSMSEA	2018	1.6	SLVGPVAQMA	2573	0.2
AQASISIMST	2019	1.6	AQPRLNLTEA	2574	0.2
AQASVAPLTC	2020	1.6	AQASQEYSRL	2575	0.2
AQLVTVEKQA	2021	1.6	AQKSLAFDSA	2576	0.2
AQAATAGEKL	2022	1.6	AQALGHSHHC	2577	0.2
AQALSHGPGG	2023	1.6	AQAAQTGRPI	2578	0.2
AQSNAHIEIA	2024	1.6	AQASGTSVRQ	2579	0.2
AQARSSSTGI	2025	1.6	AQAMGTASYC	2580	0.2
AQAVGGDVTR	2026	1.6	AQISHNHPQA	2581	0.2
AQAPRTVYQG	2027	1.6	AQAYSTYVRM	2582	0.2
AQALHNLGPA	2028	1.6	AQVGKLDIRA	2583	0.2
VRMGAUSDNA	2029	1.6	AQLKQGGINA	2584	0.2
AQAFRTSQFT	2030	1.6	AQASAHFREP	2585	0.2
AQSSATMQRA	2031	1.5	AQALDTVLSA	2586	0.2
AQTLAETYRA	2032	1.5	GAGTAVGNIA	2587	0.2
AQANGSIVLN	2033	1.5	AQANGSATYA	2588	0.2
AQARVADQLP	2034	1.5	AQTQLAQQKA	2589	0.2
AQAVKQGLYE	2035	1.5	AQYVTVVSPA	2590	0.2
AQAFSDGLKS	2036	1.5	SQFSAVTVTA	2591	0.2
AQVSVTPVKA	2037	1.5	AQAASDSFRY	2592	0.2
VNGRAVSMMA	2038	1.5	AQASPASVTR	2593	0.2
SLVGAVAQMA	2039	1.5	AQARDSGMFL	2594	0.2
AQARVSPVGL	2040	1.5	AQSKTTLTSL	2595	0.2
AQSNITTLTA	2041	1.5	AQLVQESLSA	2596	0.2
AQTSTEHLRA	2042	1.5	AQAALKSLAG	2597	0.2
AQAGMGINLP	2043	1.5	AQAVPNQGQK	2598	0.2

AQANAHSRTL	2044	1.5	AQALSRSSLG	2599	0.2
AQARFTTTEM	2045	1.5	AQAGSVMSRV	2600	0.2
AQLGYQEVKA	2046	1.4	AQMATVTPMA	2601	0.2
AQAGQHASFV	2047	1.4	AQARTASGID	2602	0.2
AQATGSNPRG	2048	1.4	SHSSAVSHPA	2603	0.2
AQAPVSPSIP	2049	1.4	AQADRMRTTA	2604	0.2
AQTTLGVGTA	2050	1.4	AQNAQNRALA	2605	0.2
AQASHLVSLA	2051	1.4	AQAASNAYSS	2606	0.2
AQAPLTGLSV	2052	1.4	AQATFQCAST	2607	0.2
AQVSTSTLRA	2053	1.4	AQVYTISTPA	2608	0.2
AQVQLGTLKA	2054	1.4	AQTVIAGVVA	2609	0.2
AQAHVSVSER	2055	1.4	LARGAVPPTA	2610	0.2
AQLLLSGQTA	2056	1.4	AQMLQTSVLA	2611	0.2
TTSSAVLTPA	2057	1.4	AQARQVSPLL	2612	0.2
AQFGADTVNA	2058	1.4	AQAGQMSNAR	2613	0.2
AQTFSSDNLA	2059	1.4	AQTPALIKLA	2614	0.2
AQIHPANSRA	2060	1.4	AQAYTTDVRK	2615	0.2
AQSIGQFPVA	2061	1.3	VVKGAVLHVA	2616	0.2
AQVISPENLA	2062	1.3	AQDTSVSVPLK	2617	0.2
AQALSAISAT	2063	1.3	AQKGAPSLQA	2618	0.2
AQAGVSASQM	2064	1.3	AQASYDVGRA	2619	0.2
AQASTKTPLP	2065	1.3	AQGPLSGMRA	2620	0.2
AQAPPSTTAM	2066	1.3	AQALGTSVPA	2621	0.2
AQAVSSDRMH	2067	1.3	AQVNEKGASTA	2622	0.2
AQAGSVTMRL	2068	1.3	AQLTRTSPVA	2623	0.2
AQAVLLGGAV	2069	1.3	AQADAALRFS	2624	0.2
AQAQRDMVTT	2070	1.3	AQVQLVVSPA	2625	0.2
AQAHHGSSLG	2071	1.3	AQAYSSDVRM	2626	0.2
VLSSAVGQRA	2072	1.3	AQARSGLSLP	2627	0.2
AQAAGSVLLG	2073	1.3	AQNGHKFTAA	2628	0.2
AQAYPTDVRM	2074	1.3	AQGLSSATKA	2629	0.2
AQWSRDAQSA	2075	1.3	AQGTWSTVKA	2630	0.2
AQQGLDMGRA	2076	1.3	AQASGVGGRI	2631	0.2
AQAAQNHALV	2077	1.3	AQTSYPAQKA	2632	0.2
AQRSQIVEVA	2078	1.3	AQNAVPTHSA	2633	0.2
AQMSDVSGRA	2079	1.3	AQSYPEITRA	2634	0.2
AKALTQDERW	2080	1.3	AQTGLSTSSA	2635	0.2
AQAVSSSTLT	2081	1.3	AQYDTHNFAA	2636	0.2
AQPSRLPTPG	2082	1.3	AQAVLSSVIQ	2637	0.2
RTSTAVLDFA	2083	1.3	AQDSAVALMA	2638	0.2
AQDLSSSIRA	2084	1.3	AQATGKGALP	2639	0.2
AQLLDGLTSA	2085	1.3	AQNSRSGHDA	2640	0.2
AQALIGLSKP	2086	1.3	AQAFQKEPSV	2641	0.2

AQASGTVRPP	2087	1.2	AQAGSTSGKM	2642	0.2
AQLLDTRYKA	2088	1.2	AQRDQAHSQA	2643	0.2
AQAPNTSFTA	2089	1.2	AQAASALSGR	2644	0.2
AQTHLQIGVD	2090	1.2	AQARHSSLLP	2645	0.2
AQRLDTSQVA	2091	1.2	AQGPQTSYLA	2646	0.2
AQRTQDTLSA	2092	1.2	FLAPAVSSKA	2647	0.2
AQADIQSHAL	2093	1.2	AQAGPQCSSC	2648	0.2
PNMNAVGIKA	2094	1.2	AQALTQHERW	2649	0.2
AQAGVSTAVH	2095	1.2	AQAIRSSERV	2650	0.2
AQASGKTFIG	2096	1.2	AQAVHSSSVY	2651	0.2
AQAGVQSTRL	2097	1.2	AQSSRTALAA	2652	0.2
AQAQGAYPLV	2098	1.2	AQITFSHTRA	2653	0.2
AQPYSTDVRLM	2099	1.2	AQALTLGGGL	2654	0.2
SSSVAVVTLA	2100	1.2	AQAGKTLVL	2655	0.2
AQTYNGLNKA	2101	1.2	AQASRSNLDN	2656	0.2
AQASVSKLRM	2102	1.2	AQGSLSHTA	2657	0.2
AQRGSENEKA	2103	1.2	AQQSVAYNVA	2658	0.2
PITNAVLKTA	2104	1.2	AQHTLRLSSA	2659	0.2
TNSYAVSSPA	2105	1.2	AQAGGTPNKL	2660	0.2
PYQTAVAGAA	2106	1.1	AQAFQSLTLA	2661	0.2
GPALAVLGRA	2107	1.1	AQAVALSHQE	2662	0.2
LSISAVPAKA	2108	1.1	AQMLASGIPA	2663	0.2
AQTLGPLPHA	2109	1.1	AQNRALDSYA	2664	0.2
AQAQOPLAHV	2110	1.1	AQASGSTTRN	2665	0.2
AQTDGAWSKA	2111	1.1	AQARGDGYVA	2666	0.2
AQALSGPPSI	2112	1.1	DARVAVLDFA	2667	0.2
AQASSPSTRG	2113	1.1	AQAVASQVSR	2668	0.2
AQASLASNRP	2114	1.1	AQARGPSPAT	2669	0.2
AQNMALSTVA	2115	1.1	AQHRLALSYD	2670	0.2
AQHSMTMTRA	2116	1.1	AQLIDSTSRA	2671	0.2
AQAMPYPPL	2117	1.1	AQAQTLRGS	2672	0.2
AQHDSMSPA	2118	1.1	AQFRSAITSA	2673	0.2
AQALPGTSRV	2119	1.1	AQANMTKQSL	2674	0.2
AQAKSTQDVQ	2120	1.1	AQNAGSTSRA	2675	0.2
AQPLVSASKA	2121	1.1	VLGSAVTGRA	2676	0.2
AQAMSGTLRK	2122	1.1	AQPMLQSSSA	2677	0.2
AQTLILGAHA	2123	1.1	AQLGTPSLSA	2678	0.2
AQAGQARSQG	2124	1.1	AQATAHTGVP	2679	0.2
AQRKDLSLVA	2125	1.1	AQAVGRDNRL	2680	0.2
AQALSAPMSL	2126	1.1	AQATSASVWA	2681	0.2
TNSLAVGMRA	2127	1.1	AQAGSEASLR	2682	0.2
AQAPIGTVRP	2128	1.1	AQANQNRTAF	2683	0.2
FIQAAVSSSA	2129	1.1	AQASAQVKRS	2684	0.2

AQAEKPTHLL	2130	1.1	AQATSGVHHP	2685	0.2
AQALSGDTTR	2131	1.1	AQTHMQIGVA	2686	0.2
AQAYIASGGT	2132	1.1	AQSHIFPTPA	2687	0.2
QLNQAVGTLA	2133	1.1	AQLFHTGSPA	2688	0.2
AQASGALDRP	2134	1.1	LASRAVVGTA	2689	0.2
AQAQDTALRA	2135	1.1	AQALLRVGVG	2690	0.2
AQAQAGMARG	2136	1.1	AQITLPSGTA	2691	0.2
AQAQGSSAVG	2137	1.1	AQAEKSLGRQ	2692	0.2
AQLLRDIGPA	2138	1.1	AQTSNTTTRA	2693	0.2
VDRGAVTQMA	2139	1.1	AQAHTQASYM	2694	0.2
AQAVNVSKGS	2140	1.1	AQERGASSSA	2695	0.2
SVNTAVESLA	2141	1.1	AQATPSSTAM	2696	0.2
AQARLPHTSS	2142	1.1	AQSTVNRTYA	2697	0.2
AQRNGSEVVA	2143	1.1	AQAGHGPSTR	2698	0.2
AQATDRVDRP	2144	1.1	AQLSLVPLQA	2699	0.2
AQASLSRERT	2145	1.1	AQLHSPIPSA	2700	0.2
AQAYSTHVRM	2146	1.1	AQSLARDGLA	2701	0.2
AQHLSAGPTA	2147	1.1	AQAPPSSPAM	2702	0.2
LNGGAVSLRA	2148	1	TQYGAVERQA	2703	0.1
AQAYGVSSVT	2149	1	AQAGQARSLA	2704	0.1
AQFGSAVQLA	2150	1	AQPVGRVPPA	2705	0.1
AQAPPTSTRL	2151	1	AQAREQRGPV	2706	0.1
AQVSTNWPKA	2152	1	AQKTSLLWEA	2707	0.1
AQTSTDLRA	2153	1	AQSGGKNLIA	2708	0.1
AQAHSTDVRM	2154	1	AQASEGHQLS	2709	0.1
AQATLTGHVS	2155	1	AQALHAGHHP	2710	0.1
AQATTQGALT	2156	1	AQSKRDDPSA	2711	0.1
AQAAKASDRT	2157	1	AQTSRELMA	2712	0.1
AQAGNEHGGRA	2158	1	AQALPASGAR	2713	0.1
AQALSTSLLL	2159	1	AQSNALLSLA	2714	0.1
AQASLGSTYL	2160	1	AQASPVVGVS	2715	0.1
AQAFSTVGAV	2161	1	AQARGDSYMA	2716	0.1
AQLNGLVTTA	2162	1	AQAGASSLTV	2717	0.1
AQASVRTLRM	2163	1	AQALRPVNGT	2718	0.1
AQATMSRPWQ	2164	1	AQVRSGPTLA	2719	0.1
AQSSLPAMVA	2165	1	AQFPPLSRSA	2720	0.1
RETVAVGQYA	2166	1	AQVARGTVQA	2721	0.1
AQAFGSEGRS	2167	1	AQTSTQSPPG	2722	0.1
SSGTAVEHRA	2168	1	AQARDGMNVR	2723	0.1
FGTNAVIPRA	2169	1	AQAVSRNVVV	2724	0.1
AQAGQARSLG	2170	1	AQHTATRSVA	2725	0.1
AQSFSSDNMA	2171	1	AQAVREDGHA	2726	0.1
AQMNGLTGKA	2172	1	TNSSAVAASA	2727	0.1

AQQNGKQHLA	2173	1	AQATFQLAST	2728	0.1
AQHIDSIRPA	2174	1	AQAHHQQTSL	2729	0.1
AQAADRLSTL	2175	1	AQQQHAHMMA	2730	0.1
AQFGLKDIRA	2176	1	AQATSSLHVL	2731	0.1
AQAHQGGATL	2177	1	AQAPNSGLAM	2732	0.1
AQATYNPKP	2178	1	SASRAVL DFA	2733	0.1
AQAMSNMLRN	2179	0.9	AQARGEQRFV	2734	0.1
VPISAVMSTA	2180	0.9	AQTHLQIRVA	2735	0.1
AQHSLGNTVA	2181	0.9	AQAPPSSKAM	2736	0.1
AQATSALSRL	2182	0.9	AQIVSKAMPA	2737	0.1
AQADRQTFPV	2183	0.9	AQASVRNNPS	2738	0.1
AQAVNSMSIG	2184	0.9	AQAESRVAAL	2739	0.1
AQALAIVSKN	2185	0.9	LTNGAVRDRT	2740	0.1
AQQQLQERFA	2186	0.9	AQGRLAGSLA	2741	0.1
AQFNGASAHA	2187	0.9	AQAGQDSARR	2742	0.1
AQLGGQSPVA	2188	0.9	AQAASRLGAV	2743	0.1
AQANGAYTDN	2189	0.9	AQALARGMAS	2744	0.1
AQNLSSSEPA	2190	0.9	AQASRGLSMG	2745	0.1
AQSAIVLTTA	2191	0.9	AQAQASSYGS	2746	0.1
ITRSVPDVA	2192	0.9	AKASRLPTPG	2747	0.1
GALKAVTGVA	2193	0.9	AQSLSRATA	2748	0.1
AQAVGQDYLR	2194	0.9	AQASTFVQTI	2749	0.1
AQVTNLTPLA	2195	0.9	AQASSKVAAA	2750	0.1
AQALTQDDRW	2196	0.9	AQAYRNGEAA	2751	0.1
AQAYSTNVRM	2197	0.9	AQAYSTGV RM	2752	0.1
AQAVAAPASL	2198	0.9	AQAVSSRSMG	2753	0.1
AQANPVSIMS	2199	0.9	AQARGGLATP	2754	0.1
AQASMQAVKD	2200	0.9	AQAGHSGVRA	2755	0.1
AQAVGGHSVA	2201	0.9	AQPSYHGGAA	2756	0.1
AQAVAASTRL	2202	0.9	AQRVNQVSTA	2757	0.1
GGTHAVSSFA	2203	0.9	AQAAFQQAST	2758	0.1
AQAADSSGFR	2204	0.9	AQAVPGSPRA	2759	0.1
AQQSHVPQTA	2205	0.9	AQLSLSPLAA	2760	0.1
AQARVGNTNV	2206	0.9	AQANMTVRVS	2761	0.1
AQTVSYSDLA	2207	0.9	AQATRSSGDP	2762	0.1
AQAEHGLARS	2208	0.9	AQVASNATRA	2763	0.1
AQASNYPVAA	2209	0.9	AQTNQQPRGA	2764	0.1
VLLSAVGMAA	2210	0.9	AQRLQNDHLA	2765	0.1
AQALSGQNRG	2211	0.9	AQAPVQLGRP	2766	0.1
AQAWGQETRQ	2212	0.9	AQRQGPDTLA	2767	0.1
AQGYSTDVRM	2213	0.9	AQHTLSNHMA	2768	0.1
AQAGSVMSRE	2214	0.8	AQLSGMVNRA	2769	0.1
AQAGSLSARG	2215	0.8	AQDRQVSSRA	2770	0.1

AQATALAPKS	2216	0.8	AQRQLSTSLA	2771	0.1
AQAIRQNGSS	2217	0.8	AQQRPTVSFA	2772	0.1
AQLQDNLQLA	2218	0.8	AQAKPHSQLD	2773	0.1
AKAYSTDVRM	2219	0.8	AQAGRVNHPP	2774	0.1
AQSVDRTLLA	2220	0.8	AQAINSQSMR	2775	0.1
AQAGQNSRLP	2221	0.8	AQYSTAVMSA	2776	0.1
AQTNLQPRGA	2222	0.8	SQARAVERSA	2777	0.1
PNTIAVGQRA	2223	0.8	AQAYKSSSVG	2778	0.1
AQAHATLSLS	2224	0.8	AQASTPGLYP	2779	0.1
NHLRAVGSPA	2225	0.8	AQSRTSMLAA	2780	0.1
AQETDRNLRA	2226	0.8	AQLFSSNMPA	2781	0.1
AQARAETSGS	2227	0.8	AQAYCTDVRM	2782	0.1
AQHRELD SYA	2228	0.8	AQTMSRGFVA	2783	0.1
AQRHTSDVLA	2229	0.8	AQALNGYPAA	2784	0.1
AQVGQTSSWA	2230	0.8	AQAQTGHPLK	2785	0.1
AQANSAALLM	2231	0.8	AQASSNSQYR	2786	0.1
AQAIERTAT	2232	0.8	AQAAIKSTIS	2787	0.1
AQSSRYEKA	2233	0.8	AQSTLNLRPA	2788	0.1
QATGAVNPRA	2234	0.8	AQATLSPGSG	2789	0.1
AQASYSVSVG	2235	0.8	AQANGSGTGR	2790	0.1
AQQGHTVNNA	2236	0.8	STSLAVAGRA	2791	0.1
AQASLPISTR	2237	0.8	AQASNLSAYR	2792	0.1
AQHIDSMRPT	2238	0.8	AQASRQVLVA	2793	0.1
AQAQDTENMR	2239	0.8	NEVRAVFFEA	2794	0.1
RTGA AVTGAA	2240	0.8	AKAQGSSSVG	2795	0.1
AQASSVRGMG	2241	0.8	ARGSAVQSQA	2796	0.1
AQPGIESTIA	2242	0.8	AVRVAVSSSA	2797	0.1
AQHVDLDSKA	2243	0.8	AQAFSTSQFK	2798	0.1
AQATTVPALG	2244	0.8	AQGTSSQRTA	2799	0.1
AQVNPTPQKA	2245	0.8	AQATMSQTIA	2800	0.1
AQAGYISSAS	2246	0.8	AQSANRSTLA	2801	0.1
AQTLILGDPA	2247	0.8	AQRDLAHSKA	2802	0.1
AQAASGLTMM	2248	0.8	AQASKVGLYA	2803	0.1
AQALERPPSG	2249	0.8	AQAYYTDVRM	2804	0.1
TTYDAVHSKA	2250	0.8	AQAGLRDPRA	2805	0.1
AQAMLDSANG	2251	0.7	AQAFSQATGA	2806	0.1
AQAMHQTDKF	2252	0.7	AQVAGMSVRA	2807	0.1
KSTVAVQSVA	2253	0.7	AQAGQSSFTI	2808	0.1
AQATAGTLIG	2254	0.7	AQKEMRSQGA	2809	0.1
GLKSAVTHVA	2255	0.7	AQNYSSGVRA	2810	0.1
AQAHSAYQGA	2256	0.7	AQITVSYTRA	2811	0.1
AQSFSSDNLA	2257	0.7	AQAQQPRSSI	2812	0.1
AQLNMAASVA	2258	0.7	WTSGAVPGKA	2813	0.1

AQFSQAYNAA	2259	0.7	AQFKPSQVIA	2814	0.1
AQHLTAGLRA	2260	0.7	RQQQAVGSSA	2815	0.1
AQAHTVSPHL	2261	0.7	AQSISPHYAA	2816	0.1
GILGAVLPRA	2262	0.7	AQARSLNEYK	2817	0.1
AQHNSSSLAA	2263	0.7	AQAASSRLMA	2818	0.1
AQAPQVAGTM	2264	0.7	AQAYSTDGRM	2819	0.1
AQHQDSRPMA	2265	0.7	AQASVPRVMG	2820	0.1
AQRFQETGLA	2266	0.7	AQQQMPRYPA	2821	0.1
AQLTVSHTRA	2267	0.7	AQASSGMKPC	2822	0.1
AQANLRTTMG	2268	0.7	AQPLRSSLSA	2823	0.1
AQAGLRDPRM	2269	0.7	AQNSASQSQA	2824	0.1
AQHLLHGTA	2270	0.7	AQGHLGSLRA	2825	0.1
RNQGAVASLA	2271	0.7	AQRAQSGVAA	2826	0.1
AQAGSSSVTW	2272	0.7	AQANPRLQDK	2827	0.1
AQPHLQIGVA	2273	0.7	AQAPRTATLG	2828	0.1
AQANSQAVLA	2274	0.7	AQRTASLSQA	2829	0.1
AQLLGDAVKA	2275	0.7	AQGNPGLLRA	2830	0.1
SSGNAVSSLA	2276	0.7	MSSHAVGNRA	2831	0.1
AQVSVTMALA	2277	0.7	AQLAPKASPA	2832	0.1
AQYHTRGFAA	2278	0.7	AQTTQGRERA	2833	0.1
AQSTTKGTLA	2279	0.7	AQASGKSTSS	2834	0.1
			AQAPHQHSMK	2835	0.1

[0982] A subset of the targeting peptide variants from the NHP biopanning showed a very strong and consistent enrichment over AAV9 and PHP.B controls. Further, the targeting peptide of SEQ ID NO: 1725 not only showed a strong enrichment over AAV9 in the brain, but also in the spinal cord, as it led to a 125.6 fold enrichment over AAV9 in the spinal cord. Following the removal of the least reliable variants, a set of 22 variants with enrichment factors ranging from 7-fold to >400-fold over AAV9 was identified. These were cross-referenced to a non-synthetic PCR-amplified library screened in parallel and 12 candidates showed reliable enrichment and high consistency in both assays. Of these, 5 candidates with the highest enrichment scores in both assays and the highest consistency across animals and tissues were retained for individual evaluation. Candidate capsids were labeled TTD-001, TTD-002, TTD-003, TTD-004 and TTD-005 as shown in Table 3 above.

[0983] After 3 rounds of screening of AAV9 peptide insertion library in NHP, many capsids outperformed their parental capsid AAV9 in penetration of the blood brain barrier (BBB). Some of the capsids comprising a targeting peptide showed high enrichment scores and high consistency both across different brain tissue samples from the same animal and across different animals. Consistency in both NNK and NNM codons was also observed. 22 capsid variants exhibited enrichment factors ranging from 7-fold to >400-fold over AAV9 in the brain tissues. A majority of these variants also

demonstrated high enrichment factors up to 125-fold over AAV9 in the spinal cord. Of these, 5 candidates with diverse inserted sequences were selected for further evaluation as individual capsids.

Example 5. Individual Capsid Characterization

[0984] The goal of these experiments was to determine the transduction level and the spatial distribution of each of the 5 capsid candidates selected from the study described in Example 4 relative to AAV9 following intravascular infusion in NHPs (cynomolgus macaque). The 5 selected capsid candidates were TTD-001 (SEQ ID NO: 3623 and 3636, comprising targeting peptide SEQ ID NO: 1725 or 3648), TTD-002 (SEQ ID NO: 3623, 3625, and 3637, comprising targeting peptide SEQ ID NO: 1726 or 3649), TTD-003 (SEQ ID NO: 3626 and 3638, comprising targeting peptide SEQ ID NO: 1729 or 3650), TTD-004 (SEQ ID NO: 3627 and 3639, comprising targeting peptide SEQ ID NO: 1760 or 3651) and TTD-005 (SEQ ID NO: 3629 and 3641, comprising targeting peptide SEQ ID NO: 1769 or 3652) as outlined in Table 3 above.

[0985] AAV particles were generated with each of these 5 capsids encapsulating a transgene encoding a payload fused to an HA tag (payload-HA) and driven by a full-length CMV/chicken beta actin promoter by triple transfection in HEK293T cells and formulated in a pharmaceutically acceptable solution.

[0986] Each test capsid and AAV9 control were tested by intravenously providing two (2) NHP females the AAV particle formulation at a dose of 2×10^{13} VG/kg. The in-life period was 14 days and then a battery of CNS and peripheral tissues were collected for quantification of transgene mRNA, transgene protein and viral DNA (biodistribution). Samples were also collected, fixed and paraffin embedded for immunohistochemical stainings.

[0987] In a first pass screening of RNA quantification by qRT-PCR and RT-ddPCR, total RNA was extracted from 3-mm punches from various areas of the brain (cortex, striatum, hippocampus, cerebellum), spinal cord sections, liver and heart, and analyzed by qRT-PCR using a proprietary Taqman set specific for the synthetic CAG exon-exon junction. Cynomolgus TBP (TATA box-binding protein) was used as a housekeeping gene. Data are shown in FIG. 6A, FIG. 6B, and FIG. 6C.

[0988] TRACER capsids showed an increase in RNA expression in all brain regions relative to AAV9 in at least one animal. The highest and most consistent increase in brain transduction was observed with capsids TTD-003 and TTD-004 (8- to 200-fold depending in various anatomical locations). In this initial screening TTD-001 was not assessed due to staggered animal dosing. An approximate 10- to 12-fold increase was consistently observed in whole brain slices (equivalent to an average of multiple regions), which was consistent with the values indicated in a next-generation sequencing (NGS) assay. In order to increase data robustness, droplet digital RT-PCR (ddPCR) was performed in parallel to qRT-PCR and confirmed the trends indicated by the qPCR data as shown in FIG. 7.

[0989] Interestingly, RNA quantification performed in the spinal cord and dorsal root ganglia indicated important differences between the capsid variants. The spinal cord transduction profile was consistent with the brain, with a strong and consistent increase with TTD-003 and TTD-004 capsids, but interestingly the DRG transduction suggested a substantial detargeting of the TTD-004 capsid, whereas the TTD-003 capsid showed a strongly increased RNA expression as shown in FIG. 8.

[0990] Total DNA was extracted from the same brain tissues as RNA, and biodistribution was measured by ddPCR using a Taqman set specific for the CMV promoter sequence. The RNaseP gene was used as a copy number reference. Vector genome (VG) per cell values were determined both by qPCR and ddPCR. Increased biodistribution was observed for the TTD-004 capsid in most brain regions, but surprisingly none of the other candidates showed a significant increase by comparison with AAV9. This apparent contradiction with the RNA quantification data could suggest that some capsids may present improved properties over AAV9 in post-attachment mechanisms rather than strict vector translocation in CNS parenchyma. Interestingly, DNA analysis confirmed the substantial detargeting of TTD-004 capsid from the DRG (FIG. 9A-9D).

[0991] To further explore the behavior of capsid variant TTD-004, viral genome (VG) quantification was completed from tissues collected from heart atrium, heart ventricle, quadriceps muscle, liver (left and right) and diaphragm and compared to vector genome presence as delivered by AAV9 in the same tissues. The data are shown in FIG. 10A and B.

[0992] For TTD-003 and TTD-004 initial immunohistochemical analyses demonstrated the presence of payload-HA to a greater extent than seen with AAV9 delivery in cerebellar tissue, including in the dentate nucleus. Immunohistochemistry confirmed the de-targeting of the dorsal root ganglia for capsid variant TTD-004 as compared to TTD-003 and AAV9.

[0993] Data for each of the variants were compiled as an average mRNA (fold over TBP) or DNA (VG per cell) quantification per capsid variant per tissue as shown in Table 8 below and FIG. 11A-11B and FIG. 12A-12B, respectively.

Table 8. Characterization of exemplary capsid variants

Measure	Tissue	AAV9	TTD-001	TTD-002	TTD-003	TTD-004	TTD-005
mRNA	Frontal Cortex	0.000325065	2.7232575	0.000768179	0.006268831	0.007076252	0.002204024
mRNA	Sensory Cortex	0.001486245	3.400055	0.00417739	0.006788644	0.010976612	0.004139604
mRNA	Motor Cortex	0.00063318	9.00819	0.001050247	0.009954825	0.010522399	0.002942249
mRNA	Putamen	0.000612759	3.557205	0.001395549	0.011832671	0.011476176	0.001150153
mRNA	Thalamus	0.002610992	2.863635	0.013937891	0.101411445	0.07565653	0.01100289
mRNA	Cerebellar Cortex	0.00133497	1.3439	0.008517779	0.006396677	0.012964181	0.004382119
mRNA	Dentate Nucleus	0.001364954	0.963955	-	-	-	-
mRNA	Caudate	0.000352281	1.3026	-	0.003259804	0.00634117	-
mRNA	Hippocampus	0.000311824	0.407015	-	-	-	-
mRNA	SC-cervical	0.012205449	11.877762	0.022004264	0.026994764	0.088316491	0.005773054

mRNA	SC-Thoracic	0.048833465	2.9974295	0.004360318	0.035118928	0.020543776	0.005629959
mRNA	SC-Lumbar	0.029887407	7.969603	0.056231995	0.016033388	0.047713563	0.026324154
mRNA	DRG-cervical	0.74570895	9.274951	0.007897714	2.47872652	0.280868887	0.008122233
mRNA	DRG-Thoracic	0.5559061	5.22606	0.006456564	8.721845271	0.104701895	-
mRNA	DRG-Lumbar	1.089758	17.308436	0.008247771	2.271300217	0.426704698	0.119974244
mRNA	Lung	0.004807149	0.000546842	-	-	0.013744781	-
mRNA	Pancreas	-	-	-	-	-	-
mRNA	Colon	0.017962678	0.005041385	-	-	0.183862903	-
mRNA	Kidney	0.043825993	0.006649157	-	-	0.041254576	-
mRNA	Liver	0.674478605	0.253188648	-	-	2.578654807	-
mRNA	Adrenal	-	-	-	-	-	-
mRNA	Spleen	0.014066875	0.000955981	-	-	0.013435626	-
mRNA	Heart	1.323389668	0.132477314	-	-	5.587929805	-
mRNA	Quadriceps	0.116623509	-	-	-	4.527799743	-
mRNA	Diaphragm	0.250001109	-	-	-	1.936435215	-
DNA	Frontal Cortex	0.07713	2.104843	0.10252	0.068367	0.380429	0.1257545
DNA	Sensory Cortex	0.093003	2.679886	0.07443	0.034016	0.2670975	0.132503
DNA	Motor Cortex	0.08796	4.3437625	0.0913085	0.094401	0.318999	0.1110695
DNA	Putamen	0.0581365	3.07904	0.12326	0.1497635	0.2731175	0.0715295
DNA	Thalamus	0.0524055	2.076863	0.0664225	0.090511	0.214999	0.086863
DNA	Cerebellar Cortex	0.014238	0.186361	0.0092915	0.009578	0.0356345	0.0128655
DNA	Dentate Nucleus	0.025042	0.1861975	0.210238	0.041906	0.106107	0.055287
DNA	Caudate	0.079294	3.9433175	-	0.0529005	0.2451035	-
DNA	Hippocampus	0.095436	1.760891	0.205433	0.368645	1.335324	0.432829
DNA	SC-cervical	0.0376	1.143863	0.061085	0.061535	0.07573	0.05885
DNA	SC-Thoracic	0.02692	0.933734	0.025955	0.05011	0.064915	0.0355
DNA	SC-Lumbar	0.03615	0.992728	0.019125	0.034175	0.085165	0.051475
DNA	DRG-cervical	0.0765	0.14319	0.08196	0.13722	0.04115	0.071625
DNA	DRG-Thoracic	0.165865	0.172363	0.07202	0.133455	0.04444	0.03139
DNA	DRG-Lumbar	0.218725	0.385712	0.146115	0.153205	0.032875	0.12034
DNA	Lung	1.085639916	3.72	0.958576278	0.700015423	1.22442329	0.919823152
DNA	Pancreas	0.256670617	20.535	0.320558325	0.240633195	0.067860607	0.004802583
DNA	Colon	0.053867646	3.405	1.179065405	0.348969617	0.116867365	0.015288464
DNA	Kidney	0.896656371	26.635	4.861362029	0.532746958	0.386522209	7.973793288
DNA	Liver	207.332334	217.64	111.910319	193.8349405	448.5980021	213.0317219
DNA	Adrenal	1.647725996	0.69	1.561129869	1.871878	1.269473156	0.847293047
DNA	Spleen	14.93815481	20.43565	51.70294001	22.79095714	6.514778227	45.91987284
DNA	Heart	2.012377817	14.49	0.757528914	1.780956673	3.814571986	0.44694144
DNA	Quadriceps	0.724278943	1.285	0.476250457	1.366015493	5.611203726	0.646197937
DNA	Diaphragm	-	1.06	-	-	-	-

[0994] When calculated as fold over AAV9 the data were as shown in Table 9 below and FIG. 13A-13B and FIG. 14A-14B.

Table 9. Characterization of exemplary capsid variants

Measure	Tissue	AAV9	TTD-001	TTD-002	TTD-003	TTD-004	TTD-005
mRNA	Frontal Cortex	1.0	8378	2.4	19.3	21.8	6.8
mRNA	Sensory Cortex	1.0	2288	2.8	4.6	7.4	2.8
mRNA	Motor Cortex	1.0	14227	1.7	15.7	16.6	4.6
mRNA	Putamen	1.0	5805	2.3	19.3	18.7	1.9
mRNA	Thalamus	1.0	1097	5.3	38.8	29.0	4.2
mRNA	Cerebellar Cortex	1.0	1007	6.4	4.8	9.7	3.3
mRNA	Dentate Nucleus	1.0	706	-	-	-	-
mRNA	Caudate	1.0	3698	-	-	-	-
mRNA	Hippocampus	1.0	1305	-	-	-	-
mRNA	SC-cervical	1.0	973	1.8	2.2	7.2	0.5
mRNA	SC-Thoracic	1.0	61	0.1	0.7	0.4	0.1
mRNA	SC-Lumbar	1.0	267	1.9	0.5	1.6	0.9
mRNA	DRG-cervical	1.0	12	0.0	3.3	0.4	0.0
mRNA	DRG-Thoracic	1.0	9	0.0	15.7	0.2	-
mRNA	DRG-Lumbar	1.0	16	0.0	2.1	0.4	0.1
mRNA	Lung	1.0	0.11	-	-	2.9	-
mRNA	Pancreas	-	-	-	-	-	-
mRNA	Colon	1.0	0.28	-	-	10.2	-
mRNA	Kidney	1.0	0.15	-	-	0.9	-
mRNA	Liver	1.0	0.38	-	-	3.8	-
mRNA	Adrenal	-	-	-	-	-	-
mRNA	Spleen	1.0	0.07	-	-	1.0	-
mRNA	Heart	1.0	0.10	-	-	4.2	-
mRNA	Quadriceps	1.0	-	-	-	38.8	-
mRNA	Diaphragm	1.0	-	-	-	7.7	-
DNA	Frontal Cortex	1.0	27.29	1.3	0.9	4.9	1.6
DNA	Sensory Cortex	1.0	28.82	0.8	0.4	2.9	1.4
DNA	Motor Cortex	1.0	49.38	1.0	1.1	3.6	1.3
DNA	Putamen	1.0	52.96	2.1	2.6	4.7	1.2
DNA	Thalamus	1.0	39.63	1.3	1.7	4.1	1.7
DNA	Cerebellar Cortex	1.0	13.09	0.7	0.7	2.5	0.9
DNA	Dentate Nucleus	1.0	7.44	8.4	1.7	4.2	2.2
DNA	Caudate	1.0	49.73	-	0.7	3.1	-
DNA	Hippocampus	1.0	18.45	2.2	3.9	14.0	4.5
DNA	SC-cervical	1.0	30.42	1.6	1.6	2.0	1.6
DNA	SC-Thoracic	1.0	34.69	1.0	1.9	2.4	1.3
DNA	SC-Lumbar	1.0	27.46	0.5	0.9	2.4	1.4
DNA	DRG-cervical	1.0	1.87	1.1	1.8	0.5	0.9
DNA	DRG-Thoracic	1.0	1.04	0.4	0.8	0.3	0.2
DNA	DRG-Lumbar	1.0	1.76	0.7	0.7	0.2	0.6
DNA	Lung	1.0	3.43	0.9	0.6	1.1	0.8
DNA	Pancreas	1.0	80.01	1.2	0.9	0.3	0.0
DNA	Colon	1.0	63.21	21.9	6.5	2.2	0.3
DNA	Kidney	1.0	29.70	5.4	0.6	0.4	8.9
DNA	Liver	1.0	1.05	0.5	0.9	2.2	1.0
DNA	Adrenal	1.0	0.42	0.9	1.1	0.8	0.5
DNA	Spleen	1.0	1.37	3.5	1.5	0.4	3.1
DNA	Heart	1.0	7.20	0.4	0.9	1.9	0.2
DNA	Quadriceps	1.0	1.77	0.7	1.9	7.7	0.9
DNA	Diaphragm	-	-	-	-	-	-

[0995] Capsid variant TTD-001 showed greater than 5,000 fold increase in payload-HA levels delivered to the brain as compared to AAV9 and measured by qRT-PCR and normalized to TBP. In all CNS tissues measured, TTD-001 showed dramatically enhanced delivery of payload-HA as compared to AAV9.

[0996] Graphical representations of the spinal cord and dorsal root ganglia measurements outlined in Tables 8 and 9 are shown in FIG. 15A-15B, FIG. 16A-16B, FIG. 17A-17B, and FIG. 18A-18B.

[0997] Immunohistochemistry of fixed brain tissues revealed dramatic transduction in both NHP tested by TTD-001 of the dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus and putamen. AAV9 transduction of the dentate nucleus, cerebellar cortex, cerebral cortex, hippocampus, thalamus and putamen appeared negligible in comparison. TTD-001 therefore demonstrated broad and robust expression and distribution in the brain following intravenous administration in NHPs. In the dorsal root ganglia, both TTD-001 and AAV9 showed similar IHC patterns. Images of these stainings are shown in FIG. 19A-19E.

[0998] Immunohistochemical support for the DRG de-targeting nature of capsid variant TTD-004 (as noted above) is shown in FIG. 20A-20B.

[0999] Graphical representations of the biodistribution of viral genomes delivered by variant capsids or AAV9 to peripheral tissues is shown in FIG. 21A-21B.

Example 6. Individual Capsid Characterization in the Heart

[1000] This Example characterized the transduction level and the spatial distribution the TTD-001 (SEQ ID NO: 3623 and 3636, comprising targeting peptide SEQ ID NO: 1725 or 3648) and TTD-004 (SEQ ID NO: 3627 and 3639, comprising targeting peptide SEQ ID NO: 1760 or 3651) capsid variants in the heart muscle.

[1001] AAV particles were generated with each of a TTD-001 and TTD-004 capsid variant or a wild-type AAV9 capsid polypeptide control, encapsulating a transgene encoding a payload fused to an HA tag (payload-HA) and driven by a full-length CMV/chicken beta actin promoter. The AAV particles comprising the TTD-001 or TTD-004 capsid variant or the wild-type AAV9 capsid control, were administered intravenously to 2 female NHPs at a dose of 2e13 VG/kg. At day 14 post-administration of the AAV particles, the heart tissue was collected, fixed, and paraffin embedded for immunohistochemical staining. An anti-HA antibody (Cell Signal Technology) was used for staining the heart tissue for visualization of the transduction and distribution of the AAV capsid variants investigated. Both left and right heart ventricle samples were collected and analyzed.

[1002] As shown in FIG. 22A-22C, immunohistochemistry of the fixed heart tissue and cardiomyocytes, demonstrated transduction by both TTD-001 and TTD-004, in the left ventricle (FIG. 22B) and right ventricle (FIG. 22C). However, TTD-004 led to the greatest transduction in the left and right ventricle regions of the heart (FIG. 22B-22C), as compared to TTD-001 and the wild-type

AAV9 control, as evidenced by increased IHC staining. TTD-001 and the wild-type AAV9 control demonstrated similar levels of transduction in both regions of the heart, as evidenced by similar IHC staining patterns. These data demonstrate that both the TTD-001 and TTD-004 capsid variants can be utilized to transduce and/or deliver a payload, e.g., a payload described herein, to a heart muscle.

We claim:

1. An AAV capsid variant, comprising:

(a) the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or

(b) at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659;

optionally, wherein the capsid variant comprises:

(i) the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto; and/or

(ii) an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 138.

2. The AAV capsid variant of claim 1, wherein the amino acid sequence is present immediately subsequent to position 586, 588, or 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138

3. The AAV capsid variant of claim 1 or 2, wherein:

(i) the 5 consecutive amino acids comprise PLNGA (SEQ ID NO: 3679);

(ii) the 6 consecutive amino acids comprise PLNGAV (SEQ ID NO: 3680);

(iii) the 7 consecutive amino acids comprise PLNGAVH (SEQ ID NO: 3681);

(iv) the 8 consecutive amino acids comprise PLNGAVHL (SEQ ID NO: 3682); and/or

(v) the 9 consecutive amino acids comprise PLNGAVHLY (SEQ ID NO: 3648);

optionally wherein the amino acid sequence of (i), (ii), (iii), (iv), or (v) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

4. The AAV capsid variant of claim 1 or 2, wherein:

(i) the 5 consecutive amino acids comprise YSTDE (SEQ ID NO: 3691) or YSTDV (SEQ ID NO: 3700);

(ii) the 6 consecutive amino acids comprise YSTDER (SEQ ID NO: 3692) or YSTDVR (SEQ ID NO: 3701); and/or

(iii) the 7 consecutive amino acids comprise YSTDVRM (SEQ ID NO: 3650), YSTDERM (SEQ ID NO: 3657), or YSTDERK (SEQ ID NO: 3658);

optionally wherein the amino acid sequence of (i), (ii), or (iii) is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

5. The AAV capsid variant of claim 1 or 2, wherein:

- (i) the 5 consecutive amino acids comprise IVMNS (SEQ ID NO: 3694);
- (ii) the 6 consecutive amino acids comprise IVMNSL (SEQ ID NO: 3695); and/or
- (iii) the 7 consecutive amino acids comprise IVMNSLK (SEQ ID NO: 3651),

optionally wherein the amino acid sequence of (i), (ii), or (iii) is present immediately subsequent to position 588, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

6. The AAV capsid variant of any one of the preceding claims, comprising:

(i) the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), wherein the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138;

(ii) the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654), wherein the amino acid sequence of GGTLAVVSL (SEQ ID NO: 3654) is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138;

(iii) the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), wherein the amino acid sequence of IVMNSLK (SEQ ID NO: 3651) is present immediately subsequent to position 588, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138;

or

(iv) the amino acid sequence of any of SEQ ID NOs: 3649, 3650, 3652, 3653, or 3655-3659, wherein the amino acid sequence of any of the aforesaid sequences is present immediately subsequent to position 589, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

7. The AAV capsid variant of any one of the preceding claims, wherein:

(i) the capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 3660-3671, or a nucleotide sequence having at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(ii) the capsid variant comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequences of any of SEQ ID NOs: 3660-3671;

(iii) the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of any one of SEQ ID NOs: 3660-3671, or a nucleotide sequence having at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or

(iv) the nucleotide sequence encoding the capsid variant comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of the nucleotide sequence of any of SEQ ID NOs: 3660-3671.

8. The AAV capsid variant of any one of the preceding claims, wherein:

(i) the capsid variant further comprises a substitution at position K449, e.g., a K449R substitution, numbered according to SEQ ID NO: 138;

(ii) the capsid variant further comprises a modification, e.g., an insertion, substitution, and/or deletion, in loop I, II, IV and/or VI;

(iii) the capsid variant comprises an amino acid residue other than "A" at position 587 and/or an amino acid residue other than "Q" at position 588, numbered according to SEQ ID NO: 138;

(iv) the capsid variant comprises an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 138;

(v) the capsid variant comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto;

(vi) the capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto; and/or

(vii) the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto.

9. The AAV capsid variant of any one of the preceding claims, which comprises:

(i) a VP1 protein, a VP2 protein, a VP3 protein, or a combination thereof;

(ii) the amino acid sequence corresponding to positions 138-743, e.g., a VP2, of any one of SEQ ID NOs: 3636-3647, or a sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto;

(iii) the amino acid sequence corresponding to positions 203-743, e.g., a VP3, of any one of SEQ ID NOs: 3636-3647, or a sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto;

(iv) the amino acid sequence of any one of SEQ ID NOs: 3636-3647, or an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto;

(v) an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any one of SEQ ID NOs: 3636-3647;

(vi) an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto.

10. The AAV capsid variant of any one of the preceding claims, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto, optionally wherein the nucleotide sequence encoding the capsid variant is codon optimized.

11. An AAV capsid variant comprising:

(i) the amino acid sequence of any one of claims 1-3, or 6-10, and further comprising an amino acid sequence at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) identical to SEQ ID NO: 3636; or

(ii) the amino acid sequence of SEQ ID NO: 3636.

12. An AAV capsid variant comprising:

(i) the amino acid sequence of any one of claims 1, 2, 4, or 6-10, and further comprising an amino acid sequence at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) identical to SEQ ID NO: 3638 or 3645-3646; or

(ii) the amino acid sequence of SEQ ID NO: 3638 or 3645-3646.

13. An AAV capsid variant comprising:

(i) the amino acid sequence of any one of claims 1, 2, 5-10, and further comprising an amino acid sequence at least 90% identical (e.g., at least about 95, 96, 97, 98, or 99%) to SEQ ID NO: 3639; or

(ii) the amino acid sequence of SEQ ID NO: 3639.

14. The AAV capsid variant of any one of the preceding claims, comprising the amino acid sequence of any one of SEQ ID NO: 3636-3647, or an amino acid sequence at least 95% identical thereto.

15. An AAV capsid variant comprising a parental amino acid sequence having an insert, e.g., a targeting peptide, wherein the insert comprises:

(a) the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or

(b) at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659.

16. The AAV capsid variant of claim 15, wherein:

(i) the parental sequence comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(ii) the parental sequence comprises an amino acid sequence comprising at least one, two, or three modifications, but no more than 30, 20 or 10 modifications, e.g., substitutions, to the amino acid sequence of SEQ ID NO: 138;

(iii) the parental sequence comprises a substitution at position K449, e.g., a K449R substitution;

(iv) the parental sequence comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or

(v) the nucleotide sequence encoding the parental sequence comprises the nucleotide sequence of SEQ ID NO: 137, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

17. The AAV capsid variant of claim 15 or 16, wherein the insert comprises the amino acid sequence chosen from PLNGAVHLY (SEQ ID NO: 3648), GGTLAVVSL (SEQ ID NO: 3654), IVMNSLK (SEQ ID NO: 3651), RDSPKGW (SEQ ID NO: 3649), YSTDVRM (SEQ ID NO: 3650), RESPRGL (SEQ ID NO: 3652), SFNDTRA (SEQ ID NO: 3653), YGLPKGP (SEQ ID NO: 3655), or STGTLRL (SEQ ID NO: 3656), optionally wherein the insert is inserted immediately subsequent to position 586, 588, or 589 in the parental amino acid sequence.

18. The AAV capsid variant of any one of claims 15-17, which comprises:

(i) an amino acid other than "A" at position 587 and/or an amino acid other than "Q" at position 588 of the parental sequence; or

(ii) a deletion at position 587 and/or a deletion at position 588 of the parental amino acid sequence.

19. The AAV capsid variant of any one of claims 15-18, comprising:

(i) an insert comprising the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), which is inserted immediately subsequent to position 586 of the parental amino acid sequence, and a deletion of the amino acids "AQ" at positions 587-588 of the parental amino acid sequence;

(ii) an insert comprising the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), which is inserted immediately subsequent to position 588 of the parental amino acid sequence;

(iii) an insert comprises an amino acid sequence chosen from RDSPKGW (SEQ ID NO: 3649), YSTDVRM (SEQ ID NO: 3650), RESPRGL (SEQ ID NO: 3652), SFNDTRA (SEQ ID NO: 3653), YGLPKGK (SEQ ID NO: 3655) or STGTLRL (SEQ ID NO: 3656), which is inserted immediately subsequent to position 589 of the parental amino acid sequence.

20. The AAV capsid variant of any one of the preceding claims, which has an increased tropism for a CNS cell or tissue (e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue), and/or a muscle cell or tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138, optionally wherein:

- (i) the brain cell or tissue is a cell or tissue of a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus;
- (ii) the spinal cord cell or tissue is a cell or tissue of a cervical, thoracic, and/or lumbar region; and/or
- (iii) the muscle cell or tissue is a cell or tissue of a heart muscle (e.g., a heart atrium muscle region or a heart ventricle muscle region), quadriceps muscle, and/or a diaphragm muscle.

21. The AAV capsid variant of any one of the preceding claims, wherein the capsid variant:

- (i) is enriched at least about 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 100, 200, 300, or 400-fold, in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4;
- (ii) transduces a brain region, e.g., selected from dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus and putamen, wherein the level of transduction is at least 5, 10, 50, 100, 200, 500, 1,000, 2,000, 5,000, or 10,000-fold greater as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay, a qRT-PCR, or a RT-ddPCR assay, e.g., as described in Example 5;
- (iii) delivers an increased level of a payload to a brain region, optionally wherein the level of the payload is increased by at least 500, 1,000, 2,000, 5,000, or 10,000-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5), optionally wherein the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus;
- (iv) delivers an increased level of a payload to a spinal cord region, optionally wherein the level of the payload is increased by at least 10, 20, 50, 100, 200, 300, 400, 500, 600, 700, 800 or 900-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR assay (e.g., as described in Example 5), optionally wherein the spinal cord region comprises a cervical, thoracic, and/or lumbar region; and/or

(v) delivers an increased level of viral genomes to a brain region, optionally wherein the level of viral genomes is increased by at least 5, 10, 20, 30, 40 or 50-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5), optionally wherein the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

22. The AAV capsid variant of any one of claims 1-2, 5, 6-10, 13-17, or 19-21, which shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG).

23. The AAV capsid variant of any one of claims 1-3, 6-11, 14-21, wherein the capsid variant:

(i) is enriched at least about 300 or 400-fold compared, in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4;

(ii) transduces a brain region, e.g., selected from dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus and putamen, wherein the level of transduction is at least 500, 1,000, 2,000, 5,000, or 10,000-fold greater as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay, a qRT-PCR, or a RT-ddPCR assay, e.g., as described in Example 5;

(iii) delivers an increased level of a payload to a brain region, optionally wherein the level of the payload is increased by at least 500, 1,000, 2,000, 5,000, or 10,000-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5), optionally wherein the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus;

(iv) delivers an increased level of a payload to a spinal cord region, optionally wherein the level of the payload is increased by at least 50, 100, 200, 300, 400, 500, 600, 700, 800 or 900-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR assay (e.g., as described in Example 5), optionally wherein the spinal cord region comprises a cervical, thoracic, and/or lumbar region; and/or

(v) delivers an increased level of viral genomes to a brain region, optionally wherein the level of viral genomes is increased by at least 5, 10, 20, 30, 40 or 50-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a RT-ddPCR assay (e.g., as described in Example 5), optionally wherein the brain region comprises a frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

24. The AAV capsid variant of any one of claims 1, 2, 5, 6-10, 13-17, or 19-22, wherein:

(i) the AAV capsid variant has an increased tropism for a muscle cell or tissue, e.g., a heart tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138; and/or

(ii) delivers an increased level of a payload to a muscle region, optionally wherein the level of the payload is increased by at least 10, 15, 20, 30, or 40-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an IHC assay or a RT-ddPCR assay (e.g., as described in Example 5), optionally wherein the muscle region comprises a heart muscle (e.g., a heart atrium muscle region or a heart ventricle muscle region), quadriceps muscle, and/or a diaphragm muscle region.

25. A polynucleotide encoding the polypeptide, e.g., the AAV capsid variant of any one of claims 1-24.

26. The polynucleotide of claim 25, which comprises the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto.

27. A peptide, e.g., a targeting peptide, comprising:

(i) the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or

(ii) at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659.

28. A peptide, e.g., a targeting peptide, comprising:

(i) the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), or at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648);

(ii) the amino acid sequence of IVMNSLK (SEQ ID NO: 3651), or at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of IVMNSLK (SEQ ID NO: 3651);

(iii) the amino acid sequence of YSTDVRM (SEQ ID NO: 3650), YSTDERM (SEQ ID NO: 3657), or YSTDERK (SEQ ID NO: 3658), or at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of YSTDVRM (SEQ ID NO: 3650), YSTDERM (SEQ ID NO: 3657), or YSTDERK (SEQ ID NO: 3658); or

(iv) the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659, or at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659.

29. A polynucleotide encoding an AAV capsid variant, comprising:

- (a) the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659; or
- (b) at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any of SEQ ID NO: 1725-3622 or 3648-3659.

30. The polynucleotide of claim 29, wherein:

- (i) the AAV capsid variant comprises the amino acid sequence of any one of SEQ ID NOs: 3636-3647, or an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto;
- (ii) the AAV capsid variant comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of any one of SEQ ID NOs: 3636-3647; and/or
- (iii) the polynucleotide comprises the nucleotide sequence of any one of SEQ ID NOs: 3623-3635, or a nucleotide sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity thereto.

31. An AAV particle comprising the AAV capsid variant of any one of claims 1-24, an AAV capsid variant encoded by the polynucleotide of any one of claims 25-26 or 29-30, or an AAV capsid variant comprising the peptide, e.g., targeting peptide, of any one of claims 27-28.

32. The AAV particle of claim 31, which comprises a nucleotide sequence encoding a payload, optionally wherein the encoded payload comprises a therapeutic protein or functional variant thereof; an antibody or antibody fragment; an enzyme; a component of a gene editing system; an RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA); or a combination thereof.

33. The AAV particle of claim 32, wherein:

- (i) the therapeutic protein or functional variant thereof, e.g., a recombinant protein, is associated with (e.g., aberrantly expressed in) a neurological or neurodegenerative disorder, a muscular or neuromuscular disorder, or a neuro-oncological disorder, optionally wherein the therapeutic protein or functional variant thereof is chosen from apolipoprotein E (APOE) (e.g., ApoE2, ApoE3 and/or ApoE4); human survival of motor neuron (SMN) 1 or SMN2; glucocerebrosidase (GBA1); aromatic L-amino acid decarboxylase (AADC); aspartoacylase (ASPA); tripeptidyl peptidase I (CLN2); beta-galactosidase (GLB1); N-sulphoglucosamine sulphohydrolase

(SGSH); N-acetyl- α -glucosaminidase (NAGLU); iduronate 2-sulfatase (IDS); intracellular cholesterol transporter (NPC1); gigaxonin (GAN); or a combination thereof;

(ii) the antibody or antibody binding fragment binds to

(a) a CNS related target, e.g. an antigen associated with a neurological or neurodegenerative disorder, e.g., β -amyloid, APOE, tau, SOD1, TDP-43, huntingtin (HTT), and/or synuclein;

(b) a muscular or neuromuscular related target, e.g., an antigen associated with a muscular or neuromuscular disorder; or

(c) a neuro-oncology related target, e.g., an antigen associated with a neuro-oncological disorder, e.g., HER2, or EGFR (e.g., EGFRvIII);

(iii) the enzyme comprises a meganuclease, a zinc finger nuclease, a TALEN, a recombinase, integrase, a base editor, a Cas9, or a fragment thereof;

(iv) the component of a gene editing system comprises one or more components of a CRISPR-Cas system, optionally wherein the one or more components of the CRISPR-Cas system comprises a Cas9, e.g., a Cas9 ortholog or a Cpf1, and a single guide RNA (sgRNA), wherein:

(a) the sgRNA is located upstream (5') of the cas9 enzyme; and/or

(b) the sgRNA is located downstream (3') of the cas9 enzyme; and/or

(v) the RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA), modulates, e.g., inhibits, expression of, a CNS related gene, mRNA, and/or protein, optionally wherein the CNS related gene is chosen from SOD1, MAPT, APOE, HTT, C9ORF72, TDP-43, APP, BACE, SNCA, ATXN1, ATXN3, ATXN7, SCN1A-SCN5A, SCN8A-SCN11A, or a combination thereof.

34. The AAV particle of any one of claims 31-33, which comprises a viral genome comprising a promoter operably linked to the nucleic acid sequence encoding the payload, optionally wherein, the promoter is chosen from human elongation factor 1 α -subunit (EF1 α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β -actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC), neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF- β), intercellular adhesion molecule 2 (ICAM-2), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β -globin minigene β 2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), a cardiovascular promoter (e.g., α MHC, cTnT, and CMV-MLC2k), a liver promoter (e.g.,

hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512) or a fragment, e.g., a truncation, or a functional variant thereof.

35. The AAV particle of claim 34, wherein the viral genome further comprises:

- (i) a polyA signal sequence;
- (ii) an inverted terminal repeat (ITR) sequence, optionally wherein the ITR sequence is positioned 5' relative to the encoded payload and/or the ITR sequence is positioned 3' relative to the encoded payload;
- (iii) an enhancer, a Kozak sequence, an intron region, and/or an exon region;
- (iv) a miR binding site, e.g., a miR binding site that modulates, e.g., reduces, expression of the payload encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed; and/or
- (v) a nucleotide sequence encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein, optionally wherein the Rep78 protein, the Rep68 protein, the Rep52 protein, and/or the Rep40 protein are encoded by at least one Rep gene.

36. The AAV particle of claim 34 or 35, wherein the viral genome comprises:

- (i) at least 1-5 copies of a miR binding site, e.g., at least 1, 2, 3, 4, or 5 copies;
- (ii) at least 3 copies of a miR binding site, optionally wherein all three copies comprise the same miR binding site, or at least one, two, or all of the copies comprise a different miR binding site; and/or
- (iii) at least 4 copies of a miR binding site, optionally wherein all four copies comprise the same miR binding site, or at least one, two, three, or all of the copies comprise a different miR binding site.

37. The AAV particle of claim 36, wherein the miR binding site comprises a miR122 binding site, a miR183 binding site, a miR-142-3p, or a combination thereof, optionally wherein:

- (i) the miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 3672, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 3672;
- (ii) the miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 3675, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two,

three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 3675; and/or

(iii) the miR-142-3p binding site comprises the nucleotide sequence of SEQ ID NO: 3674, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 3674.

38. The AAV particle of any one of claims 34-37, wherein the viral genome:

(i) is single stranded; and/or

(ii) further comprises a nucleic acid sequence encoding the AAV capsid variant of any one of claims 1-24.

39. The AAV capsid variant, polynucleotide, peptide, or AAV particle of any one of the preceding claims which is isolated, e.g., recombinant.

40. A vector comprising a polynucleotide encoding the AAV capsid variant of any one of claims 1-24 or 39, the polynucleotide of any one of claims 25-26, 29-30, or 39, or a polynucleotide encoding the peptide, e.g., targeting peptide, of any one of claims 27-28 or 39.

41. A cell, e.g., a host cell, comprising the AAV capsid variant of any one of claims 1-24 or 39, the polynucleotide of any one of claims 25-26, 29-30, or 39, the peptide of any one of claims 27-28 or 39, the AAV particle of any one of claims 31-39, or the vector of claim 40, optionally wherein:

(i) the cell is a mammalian cell or an insect cell;

(ii) the cell is a cell of a brain region or a spinal cord region, optionally a cell of the frontal cortex, sensory cortex, motor cortex, caudate, dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus, putamen, cervical spinal cord region, thoracic spinal cord region, and/or lumbar spinal cord region; and/or

(iii) a neuron, a sensory neuron, a motor neuron, an astrocyte, or a muscle cell (e.g., a cell of the heart, diaphragm, or quadriceps).

42. A method of making an AAV particle, comprising

(i) providing a host cell comprising a viral genome; and

(ii) incubating the host cell under conditions suitable to enclose the viral genome in the AAV capsid variant of any one of claims 1-24 or 39, an AAV capsid variant encoded by the polynucleotide of any one of claims 25-26, 29-30, or 39, or an AAV capsid variant comprising the peptide, e.g., targeting peptide, of any one of claims 27-28 or 39;

thereby making the AAV particle.

43. A pharmaceutical composition comprising the AAV particle of any one of claims 31-39, an AAV particle comprising the capsid variant of any one of claims 1-24 or 39, or an AAV particle comprising the peptide of any one of claims 27-28 or 39, and a pharmaceutically acceptable excipient.

44. A method of delivering a payload to a cell or tissue (e.g., a CNS cell, a CNS tissue, a muscle cell, or a muscle tissue), comprising administering an effective amount of the pharmaceutical composition of claim 43, the AAV particle of any one of claims 31-39, an AAV particle comprising the capsid variant of any one of claims 1-24 or 39, or an AAV particle comprising the peptide of any one of claims 27-28 or 39.

45. The method of claim 44, wherein:

(i) the cell or tissue is a cell or tissue of a brain region or a spinal cord region, optionally a cell or tissue of the frontal cortex, sensory cortex, motor cortex, caudate, dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus, putamen, cervical spinal cord region, thoracic spinal cord region, and/or lumbar spinal cord region;

(ii) the cell is a neuron, a sensory neuron, a motor neuron, an astrocyte, or a muscle cell (e.g., a cell of the heart, diaphragm, or quadriceps); and/or

(iii) the cell or tissue is within a subject, optionally wherein the subject has, has been diagnosed with having, or is at risk of having a neurological disorder, a neurodegenerative disorder, a muscular disorder, a neuromuscular disorder, or a neuro-oncological disorder.

46. A method of treating a subject having or diagnosed with having a neurological disorder, a neurodegenerative disorder, a muscular disorder, a neuromuscular disorder, or a neuro-oncological disorder comprising administering to the subject an effective amount of the pharmaceutical composition of claim 43, the AAV particle of any one of claims 31-39, an AAV particle comprising the capsid variant of any one of claims 1-24 or 39, or an AAV particle comprising the peptide of any one of claims 27-28 or 39.

47. The method of claim 46, where treating comprises prevention of progression of the disease or disorder in the subject, optionally wherein the subject is a human.

48. The method of any one of claims 45-47, wherein the AAV particle is administered to the subject:

(i) intramuscularly, intravenously, intracerebrally, intrathecally, intracerebroventricularly, via intraparenchymal administration, or via intra-cisterna magna injection (ICM);

(ii) via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or via MRI-guided FUS coupled with intravenous administration; and/or
(iii) intravenously.

49. The pharmaceutical composition of claim 43, the AAV particle of any one of claims 31-39, an AAV particle comprising the capsid variant of any one of claims 1-24 or 39, or an AAV particle comprising the polypeptide of any one of claims 27-28 or 39, for use in a method of delivering a payload to a cell or tissue.

50. The pharmaceutical composition of claim 43, the AAV particle of any one of claims 31-39, an AAV particle comprising the capsid variant of any one of claims 1-24 or 39, or an AAV particle comprising the polypeptide of any one of claims 27-28 or 39, for use in a method of treating a neurological disorder, a neurodegenerative disorder, a muscular disorder, a neuromuscular disorder, or a neuro-oncological disorder.

51. The pharmaceutical composition of claim 43, the AAV particle of any one of claims 31-39, an AAV particle comprising the capsid variant of any one of claims 1-24 or 39, or an AAV particle comprising the polypeptide of any one of claims 27-28 or 39, for use in the manufacture of a medicament.