## SUMMARY

**[0006]** Provided herein are recombinant AAV vectors which evade antibody recognition and/or selectively target tissues of the CNS.

**[0007]** In one aspect, the present disclosure refers to an adeno-associated virus (AAV) vector comprises (i) a recombinant capsid protein and (ii) a cargo nucleic acid encapsidated by the capsid protein, wherein the capsid protein comprises a peptide having the sequence of any one of SEQ ID NO: 12-20.

**[0008]** In some examples, an adeno-associated virus (AAV) vector comprises (i) a mutant AAV9 capsid protein and (ii) a cargo nucleic acid encapsidated by the capsid protein, wherein the capsid protein comprises a peptide having the sequence $X^1$-$X^2$-$X^3$-$X^4$-$X^5$-$X^6$-$X^7$-$X^8$ (SEQ ID NO: 158) at amino acids 451-458 of the native AAV9 capsid protein sequence, wherein the peptide does not occur in the native AAV9 capsid protein sequence.

**[0009]** In some examples, an adeno-associated virus (AAV) vector comprises (i) a mutant AAV9 capsid protein and (ii) a cargo nucleic acid encapsidated by the capsid protein, wherein the capsid protein comprises a peptide having the sequence $X^1$-$X^2$-$X^3$-$X^4$-$X^5$-$X^6$-$X^7$-$X^8$ (SEQ ID NO: 158) at amino acids 587-594 of the native AAV9 capsid protein sequence, wherein the peptide does not occur in the native AAV9 capsid protein sequence.

**[0010]** In another aspect, the present disclosure refers to an adeno-associated virus (AAV) vector comprises (i) a recombinant capsid protein and (ii) a cargo nucleic acid encapsidated by the capsid protein, wherein the capsid protein comprises an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 165-187.

**[0011]** In another aspect, the present disclosure refers to a nucleic acid sequence encoding the recombinant capsid protein of the AAV vector as disclosed herein. In another aspect, the present disclosure refers to an expression vector comprising the nucleic acid sequence. Also provided herein are nucleic acid sequences encoding a recombinant capsid protein, and expression vectors comprising the same.

**[0012]** In another aspect, the present disclosure refers to a cell comprising the nucleic acid sequence as disclosed herein, or the expression vector as disclosed herein. Also provided are cells comprising a nucleic acid, an expression vector, an AAV vector, or an AAV capsid described herein.

**[0013]** In another aspect, the present disclosure refers to a pharmaceutical composition comprising the AAV vector as disclosed herein, or the cell as disclosed herein. Also provided are pharmaceutical compositions comprising a nucleic acid, an expression vector, an AAV vector, an AAV capsid, or a cell described herein.

**[0014]** In another aspect, the present disclosure refers to the AAV vector as disclosed herein for use in therapy. In another aspect, the present disclosure refers to the use of the AAV vector as disclosed herein in the manufacture of a medicament for treating a disease or disorder of the central nervous system in a subject in need thereof. Also provided are methods for treating a subject in need thereof comprising administering to the subject a therapeutically effective amount of an AAV vector described herein.

**[0015]** In another aspect, the present disclosure refers to an *in vitro* method of introducing a nucleic acid molecule into a cell, the methods comprising contacting the cell with an AAV vector described herein.

**[0016]** Also provided is an AAV vector described herein for use as a medicament.

**[0017]** Also provided is an AAV vector described herein for use in a method of treatment of a subject in need thereof.

**[0018]** In yet another aspect, the present disclosure refers to the use of an AAV vector as disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder of the CNS in a subject in need thereof. Also provided is an AAV vector described herein for use in a method of treating or preventing a disease or disorder of the CNS in a subject in need thereof.

**[0019]** These and other examples are described in more detail below.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0020]** **FIG. 1A-1C**. Bubble plots showing analysis of library diversity, directed evolution and enrichment of novel antigenic footprints. Parental (FIG. 1A) and evolved libraries from a first round (FIG. 1B) and a second round (FIG. 1C) of evolution were subjected to high-throughput sequencing using the Illumina MiSeq platform. Following analysis with a custom Perl script, enriched amino acid sequences were plotted. Each bubble represents a distinct capsid amino acid sequence with the radius of the bubble proportional to the number of reads for that variant in the respective library. The y-axis represents the percentage of total reads from the sequencing run. Data are spread along the x-axis for ease of visualization. The percent reduction in unique clones (96.5%) directly demonstrates that numerous “un-fit” sequences were removed after a first and second round of evolution. Dominant isolates were selected for further analysis.

**[0021]** **FIG. 2.** Volumetric yield of AAV vectors comprising AAV capsid variants STRD.101 and STRD.102, as compared to wildtype AAV9. Bars represent mean +/- 95% confidence interval.

**[0022]** **FIG. 3.** Infectivity values of AAV-STRD.101 and wildtype AAV9 determined using a standard TCID50 assay. Data are graphed as the natural log of the number of particles required to generate an infectious unit (P:I Ratio). Error bars represent standard deviation.

## CLAIMS

What is claimed is:

1. An adeno-associated virus (AAV) vector comprising (i) a recombinant capsid protein and (ii) a cargo nucleic acid encapsidated by the capsid protein, wherein the capsid protein comprises a peptide having the sequence of any one of SEQ ID NO: 12-20.

2. The AAV vector of claim 1, wherein the cargo nucleic acid comprises 5' and 3' AAV inverted terminal repeats.

3. The AAV vector of claim 1 or 2, wherein the cargo nucleic acid comprises a transgene.

4. The AAV vector of claim 3, wherein the transgene encodes a therapeutic protein or RNA.

5. The AAV vector of any one of claims 1-4, wherein the recombinant capsid protein has at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the native sequence of the AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAVrh.8, AAVrh.10, AAVrh32.33, AAVrh74, bovine AAV or avian AAV capsid.

6. The AAV vector of any one of claims 1-5, wherein the recombinant capsid protein comprises:

a) a first peptide having a sequence of any one of SEQ ID NO: 12-18 located at the amino acid positions corresponding to amino acids 451-458 of the native AAV9 capsid, or the equivalent amino acid residues in AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV10, AAV11, AAV12, AAVrh.8, AAVrh.10, AAVrh32.33, AAVrh74, bovine AAV or avian AAV; and/or

b) a second peptide having a sequence of any one of SEQ ID NO: 19-20 located at the amino acid positions corresponding to amino acids 587-594 of the native AAV9 capsid, or the equivalent amino acid residues in AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV10, AAV11, AAV12, AAVrh.8, AAVrh.10, AAVrh32.33, AAVrh74, bovine AAV or avian AAV.

7. The AAV vector of any one of claims 1-6, wherein the peptide inhibits binding of at least one antibody to the capsid protein.

8. The AAV vector of claim 7, wherein the peptide inhibits neutralization of infectivity of the AAV vector by the antibody.

9. The AAV vector of any one of claims 1-8, wherein the capsid protein further comprises a peptide that modifies the HI loop of the capsid.

10. An adeno-associated virus (AAV) vector comprising (i) a recombinant capsid protein and (ii) a cargo nucleic acid encapsidated by the capsid protein, wherein the capsid protein comprises an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 165-187.

11. The AAV vector of claim any one of claims 1-10, wherein the capsid protein comprises an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 165-187.

12. The AAV vector of any one of claims 1-11, wherein the capsid protein comprises the amino acid sequence of SEQ ID NO: 175.

13. The AAV vector of any one of claims 1-11, wherein the capsid protein comprises the amino acid sequence of SEQ ID NO: 180.

14. The AAV vector of any one of claims 1-13, wherein the AAV vector selectively delivers the cargo nucleic acid to a cell or tissue of the central nervous system.

15. The AAV vector of claim 14, wherein the tissue of the central nervous system is the premotor cortex, the thalamus, the cerebellar cortex, the dentate nucleus, the spinal cord, or the dorsal root ganglion.

16. The AAV vector of any one of claims 1-15, wherein the AAV vector delivers the cargo nucleic acid to the brain, but does not deliver the AAV vector to the heart.

17. The AAV vector of any one of claims 1-15, wherein the AAV vector delivers the cargo nucleic acid to the brain and to the heart.

18. The AAV vector of claim 17, wherein delivery of the cargo nucleic acid is greater to the brain than to the heart.

19. The AAV vector of claim 17, wherein delivery of the cargo nucleic acid is approximately equal in the brain and in the heart.

20. A nucleic acid sequence encoding the recombinant capsid protein of the AAV vector of any one of claims 1 to 19.

21. The nucleic acid sequence of claim 20, wherein the nucleic acid sequence is a DNA sequence or an RNA sequence.

22. An expression vector comprising the nucleic acid sequence of claim 20 or claim 21.

23. A cell comprising the nucleic acid sequence of claim 20 or claim 21, or the expression vector of claim 22.

24. A pharmaceutical composition comprising the AAV vector of any one of claims 1-19, or the cell of claim 23.

25. The pharmaceutical composition of claim 24, wherein the composition further comprises a pharmaceutically acceptable carrier.

26. The AAV vector of any one of claims 1-19 for use in therapy.

27. Use of the AAV vector of any one of claims 1-19 in the manufacture of a medicament for treating a disease or disorder of the central nervous system in a subject in need thereof.

28. The use of claim 26 or 27, wherein the subject is a mammal.

29. The use of claim 28, wherein the subject is a human.

30. An *in vitro* method of introducing a nucleic acid molecule into a cell, comprising contacting the cell with the AAV vector of any one of claims 1-19.

31. Use of an AAV vector of any one of claims 1-19 in the manufacture of a medicament for treating or preventing a disease or disorder of the CNS in a subject in need thereof.