SUMMARY

[0005] Described herein are viral vectors each comprising a modified capsid, wherein the modified capsid comprises at least one amino acid sequence that targets the viral vector to a distinct brain structure.

[0006] In one aspect, the present disclosure refers to a modified adeno-associated virus (AAV) capsid protein comprising a targeting peptide that targets a viral vector comprising the modified AAV capsid protein to a distinct brain structure, wherein the targeting peptide comprises SEQ ID NO: 110 and is a sequence up to ten amino acids in length, wherein the modified AAV capsid protein is a modified AAV9 capsid protein derived from an AAV9 capsid protein having the amino acid sequence of SEQ ID NO: 140 and wherein the targeting peptide is inserted after residue 588 of the modified AAV9 capsid protein.In one example, modified adeno-associated virus (AAV) capsid proteins are described comprising a targeting peptide that targets a viral vector comprising the modified AAV capsid protein to a distinct organ or brain structure, and the targeting peptide is three to ten amino acids in length. In some examples, the modified AAV capsid proteins are modified AAV1 capsid proteins, modified AAV2 capsid proteins, or modified AAV9 capsid proteins.

[0007] In some examples, the modified AAV capsid proteins are derived from an AAV1 capsid protein (see SEQ ID NO: 138), and the targeting peptide is inserted after residue 590 of the AAV1 capsid protein. In some examples, the targeting peptide is flanked by linker sequences, and the linker sequences on each side of the targeting peptides are two or three amino acids long. In some examples, the linker sequences are SSA on the N-terminal side of the targeting peptide and AS on the C-terminal side of the targeting peptide. In some examples, the modified AAV1 capsid proteins have a sequence at least 95% identical to SEQ ID NO: 141.

[0008] In some examples, the modified AAV capsid proteins are derived from an AAV2 capsid protein (see SEQ ID NO: 139), and the targeting peptide is inserted after residue 587 of the AAV2 capsid protein. In some examples, the targeting peptide is flanked by linker sequences, and the linker sequences on each side of the targeting peptides are two or three amino acids long. In some examples, the linker sequences are AAA on the N-terminal side of the targeting peptide and AA on the C-terminal side of the targeting peptide. In some examples, the modified AAV2 capsid proteins have a sequence at least 95% identical to SEQ ID NO: 142.

[0009] In some examples, the modified AAV capsid proteins are derived from an AAV9 capsid protein (see SEQ ID NO: 140), and the targeting peptide is inserted after residue 588 of the AAV9 capsid protein. In some examples, the targeting peptide is flanked by linker sequences, and the linker sequences on each side of the targeting peptides are two or three amino acids long. In some examples, the linker sequences are AAA on the N-terminal

side of the targeting peptide and AS on the C-terminal side of the targeting peptide. In some examples, the modified AAV9 capsid proteins have a sequence at least 95% identical to SEQ ID NO: 143.

[0010] In some examples, the target peptide comprises a sequence up to ten amino acids in length having therein an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-137 and 144. In some examples, the targeting peptide is seven amino acids in length.

[0011] In some examples, the distinct brain structure is the brainstem, caudate, cerebellar cortex, cerebral cortex, ependyma, globus pallidus, hippocampus, meninges, optic nerve, putamen, spinal cord, substantia nigra, subthalamic nuclei, or thalamus. In certain examples, the modified AAV capsid protein is a modified AAV1 capsid protein, and the targeting peptide is selected from those listed in Table 1 in order to target a corresponding brain structure. In certain examples, the modified AAV capsid protein is a modified AAV2 capsid protein, and the targeting peptide is selected from those listed in Table 2 in order to target a corresponding brain structure. In certain examples, the modified AAV capsid protein is a modified AAV9 capsid protein, and the targeting peptide is selected from those listed in Table 3 in order to target a corresponding brain structure.

[0012] In some examples, the distinct organ is the brain, kidney, heart, liver, gonad, spleen, or liver. In certain examples, the modified AAV capsid protein is a modified AAV1 capsid protein, and the targeting peptide is selected from those listed in Table 4 in order to target a corresponding organ. In certain examples, the modified AAV capsid protein is a modified AAV2 capsid protein, and the targeting peptide is selected from those listed in Table 5 in order to target a corresponding organ. In certain examples, the modified AAV capsid protein is a modified AAV9 capsid protein, and the targeting peptide is selected from those listed in Table 6 in order to target a corresponding organ.

[0013] In one example, nucleic acids are described herein comprising a sequence encoding the modified capsid protein of any one of the present examples.

[0014] In one example, recombinant adeno-associated viruses (rAAV) are described herein comprising the modified capsid protein of any one of the present examples. In some examples, combinations of rAAVs are described. For example, the combination of an rAAV having a modified AAV1 capsid protein and a targeting peptide of SEQ ID NO: 21, an rAAV having a modified AAV2 capsid protein and a targeting peptide of SEQ ID NO: 53, an

rAAV having a modified AAV2 capsid protein and a targeting peptide of SEQ ID NO: 80, and an rAAV having a modified AAV9capsid protein and a targeting peptide of SEQ ID NO: 113 is provided.

[0015] In one example, viral vectors are described comprising a nucleic acid encoding the modified capsid protein of any one of the present examples. In some examples, the viral vectors further comprise a nucleic acid sequence encoding a nucleic acid of interest. In some examples, the nucleic acid of interest is a therapeutic agent. In some examples, the therapeutic agent is an enzyme or an RNAi molecule.

[0016] In one example, cells are described herein comprising the viral vector of any one of the present examples. In some examples, the cell is a mammalian cell, such as a human cell. In some examples, the cell is in vitro or in vivo.

[0017] In one aspect, the present disclosure refers to pharmaceutical compositions comprising the viral vector as disclosed herein and a pharmaceutically acceptable carrier.

[0018] In one aspect, the present disclosure refers to the use of the viral vector disclosed herein in the manufacture of a medicament for treating a neurodegenerative disease in a mammal. In another aspect, the present disclosure refers to the use of the rAAV as disclosed herein in the manufacture of a medicament for delivering an agent to a distinct brain structure of a subject. In one example, methods to deliver an agent to a distinct brain structure of a subject are described, comprising administering a virus of the present examples to the subject. In some examples, the distinct brain structure is the brainstem, caudate, cerebellar cortex, cerebral cortex, ependyma, globus pallidus, hippocampus, meninges, optic nerve, putamen, spinal cord, substantia nigra, subthalamic nuclei, or thalamus. In certain examples, an rAAV having a modified AAV1 capsid protein is used, and the targeting peptide is selected from those listed in Table 1 in order to target a corresponding brain structure. In certain examples, an rAAV having a modified AAV2 capsid protein is used, and the targeting peptide is selected from those listed in Table 2 in order to target a corresponding brain structure. In certain examples, an rAAV having a modified AAV9 capsid protein is used, and the targeting peptide is selected from those listed in Table 3 in order to target a corresponding brain structure. In various examples, combinations of any of the rAAVs are used. For example, the combination of an rAAV having a modified AAV1 capsid protein and a targeting peptide of SEQ ID NO: 21, an rAAV having a modified AAV2 capsid protein and a targeting peptide of SEQ ID NO: 53, an rAAV having a modified AAV2 capsid protein and a targeting peptide of SEQ ID NO: 80, and an rAAV having a modified AAV9capsid protein and a targeting peptide of SEQ ID NO: 113 is used.

[0019] In one example, methods to deliver an agent to a distinct organ of a subject are described herein, comprising administering a virus of the present examples to the subject. In some examples, the organ is the brain, kidney, heart, liver, gonad, spleen, or liver. In certain examples, an rAAV having a modified AAV1 capsid protein is used, and the targeting peptide is selected from those listed in Table 4 in order to target a corresponding organ. In certain examples, an rAAV having a modified AAV2 capsid protein is used, and the targeting peptide is selected from those listed in Table 5 in order to target a corresponding organ. In certain examples, an rAAV having a modified AAV9 capsid protein is used, and the targeting peptide is selected from those listed in Table 6 in order to target a corresponding organ. In various examples, combinations of any of the rAAVs are used.

[0020] In some examples, the agent is an siRNA, shRNA, miRNA, non-coding RNA, lncRNA, therapeutic protein, or CRISPR system. In some examples, the administration is to the central nervous system. In some examples, the administration is to a cisterna magna, an intraventricular space, an ependyma, a brain ventricle, a subarachnoid space, and/or an intrathecal space. In some examples, the brain ventricle is the rostral lateral ventricle, and/or the caudal lateral ventricle, and/or the right lateral ventricle, and/or the left lateral ventricle, and/or the right rostral lateral ventricle, and/or the left rostral lateral ventricle, and/or the right caudal lateral ventricle, and/or the left caudal lateral ventricle.

[0021] In some examples, a plurality of viral particles is administered. In some examples, the virus is administered at a dose of about 1×10^{6} to about 1×10^{18} vector genomes per kilogram (vg/kg). In some examples, the virus is administered at a dose from about $1x10^{7}$-$1x10^{17}$, about $1x10^{8}$-$1x10^{16}$, about $1x10^{9}$-$1x10^{15}$, about $1x10^{10}$-$1x10^{14}$, about $1x10^{10}$-$1x10^{13}$, about $1x10^{10}$-$1x10^{13}$, about $1x10^{10}$-$1x10^{11}$, about $1x10^{11}$-$1x10^{12}$, about $1x10^{12}$-$x10^{13}$, or about $1x10^{13}$-$1X10^{14}$ vg/kg of the patient. In some examples, the subject is human.

[0022] In one example, methods of treating a disease in a mammal are described comprising administering the virus of the present examples to the mammal. In some examples, the disease is a neurodegenerative disease. In some examples, the neurodegenerative disease is Huntington's disease, ALS, hereditary spastic hemiplegia, primary lateral sclerosis, spinal muscular atrophy, Kennedy's disease, Alzheimer's disease, a polyglutamine repeat disease, or Parkinson's disease. In some examples, the mammal is human.

WHAT IS CLAIMED IS:

1. A modified adeno-associated virus (AAV) capsid protein comprising a targeting peptide that targets a viral vector comprising the modified AAV capsid protein to a distinct brain structure, wherein the targeting peptide comprises SEQ ID NO: 110 and is a sequence up to ten amino acids in length, wherein the modified AAV capsid protein is a modified AAV9 capsid protein derived from an AAV9 capsid protein having the amino acid sequence of SEQ ID NO: 140 and wherein the targeting peptide is inserted after residue 588 of the modified AAV9 capsid protein.

2. The modified AAV capsid protein of claim 1, wherein the targeting peptide is flanked by linker sequences, wherein the linker sequences on each side of the targeting peptide are two or three amino acids long.

3. The modified AAV capsid protein of claim 2, wherein the linker sequences are AAA on the N-terminal side of the targeting peptide and AS on the C-terminal side of the targeting peptide.

4. The modified AAV capsid protein of claim 3, wherein the modified AAV9 capsid protein has a sequence at least 95% identical to SEQ ID NO: 143.

5. The modified AAV capsid protein of claim 4, wherein the targeting peptide consists of SEQ ID NO: 110.

6. The modified AAV capsid protein of claim 4, wherein the targeting peptide is at amino acid residues 592-598 of SEQ ID NO: 143.

7. The modified AAV capsid protein of claim 1, wherein the distinct brain structure is the brainstem, caudate, cerebellar cortex, cerebral cortex, ependyma, globus pallidus, hippocampus, meninges, optic nerve, putamen, spinal cord, substantia nigra, subthalamic nuclei, or thalamus.

8. A recombinant adeno-associated virus (rAAV) comprising the modified capsid protein of any one of claims 1-7.

9. A viral vector comprising a nucleic acid encoding the modified capsid protein of any one of claims 1-7.

10. The viral vector of claim 9, further comprising a nucleic acid sequence encoding a nucleic acid of interest, wherein the nucleic acid of interest is a therapeutic agent.

11. The viral vector of claim 9 or 10, wherein the therapeutic agent is an enzyme or an RNAi molecule.

12. An *in vitro* cell comprising the viral vector of any one of claims 9-11.

13. A pharmaceutical composition comprising the viral vector of any one of claims 9-11 and a pharmaceutically acceptable carrier.

14. Use of the viral vector of claim 10 in the manufacture of a medicament for treating a neurodegenerative disease in a mammal.

15. The use of claim 14, wherein the neurodegenerative disease is Huntington's disease, ALS, hereditary spastic hemiplegia, primary lateral sclerosis, spinal muscular atrophy, Kennedy's disease, Alzheimer's disease, a polyglutamine repeat disease, or Parkinson's disease.

16. The use of any one of claims 14 or 15, wherein the mammal is a human.

17. Use of the rAAV of claim 8 in the manufacture of a medicament for delivering an agent to a distinct brain structure of a subject.

18. The use of claim 17, wherein the agent is an siRNA, shRNA, miRNA, non-coding RNA, lncRNA, therapeutic protein, or CRISPR system.

19. The use of claim 17, wherein the distinct brain structure of the subject is a brainstem;
wherein the distinct brain structure of the subject is a caudate;
wherein the distinct brain structure of the subject is a cerebellar cortex;
wherein the distinct brain structure of the subject is a cerebral cortex;
wherein the distinct brain structure of the subject is an ependyma;
wherein the distinct brain structure of the subject is a globus pallidus;
wherein the distinct brain structure of the subject is a hippocampus;
wherein the distinct brain structure of the subject is meninges;
wherein the distinct brain structure of the subject is an optic nerve;
wherein the distinct brain structure of the subject is a putamen;

wherein the distinct brain structure of the subject is a spinal cord;

wherein the distinct brain structure of the subject is a substantia nigra;

wherein the distinct brain structure of the subject is subthalamic nuclei; or

wherein the distinct brain structure of the subject is a thalamus.

20. The use of any one of claims 17-19, wherein the medicament is formulated as a plurality of viral particles.

21. The use of claim 20, wherein a dosage of the plurality of viral particles comprises about $1x10^{6}$ to about $1x10^{18}$ vector genomes per kilogram (vg/kg).