We claim:

1. An adeno-associated virus (AAV) capsid variant, comprising:

(a) the amino acid sequence of any of SEQ ID NO: 3648-3659 or 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: 3648-3659 or 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. An adeno-associated virus (AAV) capsid variant comprising the amino acid sequence of:

(a) PLNGAVHLY (SEQ ID NO: 3648);

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

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

wherein (a), (b), or (c) are present in hypervariable loop VIII of the AAV capsid variant, and wherein the AAV capsid variant has increased tropism for a brain cell or tissue relative to wild-type AAV9.

~~2~~3. The AAV capsid variant of claim 1 or 2, wherein the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648) is present immediately subsequent to ~~position~~ amino acid 586~~, 588, or 589~~ of the AAV capsid variant, numbered according to SEQ ID NO: 3636~~relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138~~.

~~3~~4. The AAV capsid variant of any one of claims 1 ~~or 2~~3, 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)~~;~~.

5. The AAV capsid variant of any one of claims 2-4, which comprises an amino acid sequence at least 95% identical to amino acids 203-743 of SEQ ID NO: 3636.

6. The AAV capsid variant of any one of claims 2-5, which comprises an amino acid sequence at least 98% identical to amino acids 203-743 of SEQ ID NO: 3636.

7. The AAV capsid variant of any one of claims 2-6, which comprises the amino acid sequence of amino acids 203-743 of SEQ ID NO: 3636.

8. The AAV capsid variant of any one of claims 2-7, which comprises an amino acid sequence at least 95% identical to amino acids 138-743 of SEQ ID NO: 3636.

9. The AAV capsid variant of any one of claims 2-8, an amino acid sequence at least 98% identical to amino acids 138-743 of SEQ ID NO: 3636.

10. The AAV capsid variant of any one of claims 2-9, which comprises the amino acid sequence of amino acids 138-743 of SEQ ID NO: 3636.

11. The AAV capsid variant of any one of claims 1-10, which comprises an amino acid sequence having no more than 20 modifications of the amino acid sequence of SEQ ID NO: 3636.

12. The AAV capsid variant of any one of claims 1-11, which comprises an amino acid sequence at least 95% identical to SEQ ID NO: 3636.

13. The AAV capsid variant of any one of claims 1-12, which comprises an amino acid sequence at least 98% identical to SEQ ID NO: 3636.

14. The AAV capsid variant of any one of claims 1-13, which comprises the amino acid sequence of SEQ ID NO: 3636.

15. An adeno-associated virus (AAV) capsid variant comprising:

(a) the amino acid sequence of amino acids 203-743 of SEQ ID NO: 3636;

(b) the amino acid sequence of amino acids 138-743 of SEQ ID NO: 3636; or

(c) the amino acid sequence of SEQ ID NO: 3636.

16. A polynucleotide encoding the AAV capsid variant of any one of claims 1-15.

17. The polynucleotide of claim 16, which comprises the nucleotide sequence of SEQ ID NO: 3623, or a nucleotide sequence with at least 95% sequence identity thereto.

18. A peptide comprising:

(i) the amino acid sequence of any one of SEQ ID NOs: 3648-3659 or 1725-3622; or

(ii) at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of any one of SEQ ID NOs: 3648-3659 or 1725-3622.

19. An adeno-associated virus (AAV) capsid variant comprising the peptide of claim 9.

20. An adeno-associated virus (AAV) particle comprising the AAV capsid variant of any one of claims 1-15 or 19, an AAV capsid variant encoded by the polynucleotide of claim 16 or 17, or an AAV capsid variant comprising the peptide of claim 18.

21. The AAV particle of claim 20, which when administered intravenously to a subject as an AAV particle comprising the AAV capsid variant and a viral genome:

(i) delivers at least a 5-fold increased level of the viral genome to a brain region, as compared to an AAV particle comprising the amino acid sequence of SEQ ID NO: 138;

(ii) is enriched at least about 300-fold in the brain compared to an AAV particle comprising the amino acid sequence of SEQ ID NO: 138; and/or

(iii) transduces a brain region selected from dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus and putamen, wherein the level of transduction is at least 500-fold greater as compared to an AAV particle comprising the amino acid sequence of SEQ ID NO: 138.

~~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), 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.

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~~22. The AAV particle of claim ~~31~~20 or 21, which comprises a nucleotide sequence encoding a payload~~, optionally wherein the encoded payload~~ comprisinges a therapeutic protein or functional variant thereof; an antibody or antibody fragment; an enzyme; a component of a gene editing system; or an RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA)~~; or a combination thereof~~.

~~33~~23. The AAV particle of claim ~~32~~22, wherein:

(i) the encoded therapeutic protein or functional variant thereof~~, e.g., a recombinant protein,~~ increases the presence, level, and/or activity of a gene, mRNA, or protein, which is aberrantly expressed in~~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 encoded 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); or 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, or ~~(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 functional 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, or SCN8A-SCN11A~~, or a combination thereof~~.

~~34~~24. The AAV particle of any one of claims ~~31~~20-~~33~~23, 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 1α-subunit (EF1α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β-actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC), 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 nβ2, 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., αMHC, 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~~25. The AAV particle of claim ~~34~~24, 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) at least 1-5 copies of a microRNA (miR) binding site~~, e.g., a miR binding site that modulates, e.g.,~~ that reduces~~,~~ expression of the payload encoded by the viral genome of the AAV particle 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~~26. The AAV particle of claim ~~36~~25, 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~~27. A vector comprising a polynucleotide encoding the AAV capsid variant of any one of claims 1-15 or 19~~1-24 or 39~~, the polynucleotide of ~~any one of~~ claim~~s 25-26, 29-30, or 39~~16 or 17, or a polynucleotide encoding the peptide~~, e.g., targeting peptide,~~ of ~~any one of~~ claim~~s 27-28 or 39~~18.

~~41~~28. A cell~~, e.g., a host cell,~~ comprising the AAV capsid variant of any one of claims 1-~~24~~ 15 or ~~39~~19, the polynucleotide ~~of any one~~ of claim~~s 25-26, 29-30,~~16 or ~~39~~17, the peptide of ~~any one of~~ claim~~s 27-28 or 39~~18, the AAV particle of any one of claims ~~31~~20-~~39~~26, or the vector of claim ~~40~~27, 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)~~.

29~~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~~ 15 or ~~39~~19, an AAV capsid variant encoded by the polynucleotide ~~of any one~~ of claim~~s 25-26, 29-30, or 39~~16 or 17, or an AAV capsid variant comprising the peptide~~, e.g., targeting peptide, of any one~~ of claim~~s 27-28 or 39~~18;

thereby making the AAV particle.

~~43~~30. A pharmaceutical composition comprising the AAV particle of any one of claims ~~31~~20-~~39~~26, an AAV particle comprising the capsid variant of any one of claims 1-~~24~~15 or ~~39~~19, or an AAV particle comprising the peptide ~~of any one of~~ claim~~s 27-28 or 39~~18, and a pharmaceutically acceptable excipient.

~~44~~31. Use of the AAV particle of any one of claims 20-26, an AAV particle comprising the capsid variant of any one of claims 1-15 or 19, an AAV particle comprising the peptide claim 18, or the pharmaceutical composition of claim 30, in the manufacture of a medicament for ~~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) in a subject~~, 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~~32. The ~~method~~ use of claim ~~44~~31, 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~~33. Use of the AAV particle of any one of claims 20-26, an AAV particle comprising the capsid variant of any one of claims 1-15 or 19, an AAV particle comprising the peptide claim 18, or the pharmaceutical composition of claim 30, in the manufacture of a medicament for~~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~~34. The ~~method~~ use of any one of claims ~~45~~31-~~47~~33, wherein the AAV particle or pharmaceutical composition is formulated for~~ administered to the subject~~:

(i) intramuscular administration~~ly~~, intravenous~~ly~~ administration, intracerebral administration~~ly~~, ~~intrathecally~~intrathecal administration, intracerebroventricular administration~~ly~~, ~~via~~ intraparenchymal administration, or ~~via~~ intra-cisterna magna injection (ICM); or

(ii) administration 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.~~