We claims:

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

(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;

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.

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 amino acid 586 of the AAV capsid variant, numbered according to SEQ ID NO: 3636.

4. The AAV capsid variant of any one of claims 1-3, 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.

22. The AAV particle of claim 20 or 21, which comprises a nucleotide sequence encoding a payload comprising 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).

23. The AAV particle of claim 22, wherein:

(i) the encoded therapeutic protein or functional variant thereof increases the presence, level, and/or activity of a gene, mRNA, or protein, which is 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);

(ii) the antibody or antibody fragment binds to

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

(b) an antigen associated with a muscular or neuromuscular disorder; or

(c) an antigen associated with a neuro-oncological disorder, e.g., HER2, EGFR, or 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; or

(v) the RNAi agent 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.

24. The AAV particle of any one of claims 20-23, which comprises a viral genome comprising a promoter operably linked to the nucleic acid sequence encoding the payload, 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, a liver promoter , a skeletal muscle promoter, or a functional variant thereof.

25. The AAV particle of claim 24, wherein the viral genome further comprises:

(i) a polyA signal sequence;

(ii) an inverted terminal repeat (ITR) sequence, 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 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

26. The AAV particle of claim 25, wherein the miR binding site comprises a miR122 binding site, a miR183 binding site, a miR-142-3p, or a combination thereof, wherein:

(i) the miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 3672, or a nucleotide sequence at least 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 at least 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 at least 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.

27. A vector comprising a polynucleotide encoding the AAV capsid variant of any one of claims 1-15 or 19, the polynucleotide of claim 16 or 17, or a polynucleotide encoding the peptide of claim 18.

28. A cell comprising the AAV capsid variant of any one of claims 1-15 or 19, the polynucleotide of claim 16 or 17, the peptide of claim 18, the AAV particle of any one of claims 20-26, or the vector of claim 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.

29. 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 1-15 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;

thereby making the AAV particle.

30. A pharmaceutical composition comprising 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, or an AAV particle comprising the peptide claim 18, and a pharmaceutically acceptable excipient.

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 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.

32. The use of claim 31, wherein:

(i) the cell or tissue is 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; 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.

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 treating a neurological disorder, a

neurodegenerative disorder, a muscular disorder, a neuromuscular disorder, or a neuro-oncological disorder.

34. The use of any one of claims 31-33, wherein the AAV particle or pharmaceutical composition is formulated for:

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

(ii) administration via focused ultrasound (FUS), coupled with the intravenous administration of microbubbles (FUS-MB); or MRI-guided FUS coupled with intravenous administration.